A CanVasc project

CAVALI

CAnadian VAsculitis Learning Initiative

THIRD EDITION



An approach to vasculitis through interactive clinical cases

Corisande Baldwin, MD · Joanne Jiang, MD · Frédéric Lefebvre, MD · Medha Soowamber, MD

Christian Pagnoux, MD, senior co-author and editor

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List of commonly used abbreviations

ACR: American College of Rheumatology

ANA: Antinuclear antibody

ANCA: Antineutrophil cytoplasm(ic) antibodies

AZA: Azathioprine

BVAS: Birmingham vasculitis activity score

CD: Cluster of differentiation (e.g. CD4+ T cell, CD19+ B cells)

COVID-19: Coronavirus disease 2019

CRP: C-reactive protein

CT (scan): Computerized tomography (scanner)

CYC: Cyclophosphamide

DADA2: Deficiency of adenosine deaminase 2

DCVAS: Diagnostic and classification criteria for primary systemic vasculitis

EBV: Epstein-Barr virus

EGPA: Eosinophilic granulomatosis with polyangiitis

ELISA: Enzyme-linked immunosorbent assay

ENA: Extractable nuclear antigens

ENT: Ear, nose and throat

EULAR: European League Against Rheumatism

ESR: Erythrocyte sedimentation rate

GBM: Glomerular basal membrane (such as anti-GBM antibody)

G6PD: Glucose-6-phosphate dehydrogenase

GC: Glucocorticoid(s)

GCA: Giant cell arteritis

GPA: Granulomatosis with polyangiitis

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

HLA: Human leukocyte antigen

KD: Kawasaki disease

IgA: Immunoglobulin A

IgG4-RD: Immunoglobulin G4-related disease

IL: Interleukin (such as IL-6, IL-5)

(I)IF: (indirect) Immunofluorescence (study)

IV: Intravenous

IVIg: Intravenous immunoglobulins

LCV: Leukocytoclastic vasculitis

LEF: Leflunomide

MIS-C: Multisystem inflammatory syndrome in children

MMF: Mycophenolate mofetil

MPA: Microscopic polyangiitis

MPO: Myeloperoxidase (such as MPO-ANCA)

MRA: Magnetic resonance angiography

MRI: Magnetic resonance imaging

MTX: Methotrexate

PAN: Polyarteritis nodosa

(18F-FDG-)PET: (18-fluorodeoxyglucose) Positron emission tomography

PLEX: Plasma exchange (therapy)

PR3: Proteinase 3 (such as PR3-ANCA)

RA: Rheumatoid arthritis

RPC: Relapsing polychondritis

RCT: Randomized controlled trial

RF: Rheumatoid factor

RTX: Rituximab

SSc: Systemic scleroderma

TAK: Takayasu arteritis

TCZ: Tocilizumab

TNF-alpha: Tumour necrosis factor-alpha

TPMT: Thiopurine methyltransferase

VDI: Vasculitis damage index

Introduction to the 1st Edition

Christian Pagnoux

Cavali, First edition, February 2017

The Canadian Vasculitis Network (CanVasc) was founded in November 2010. Its core committee includes more than 20 physicians from various medical specialties across Canada, with expertise and interest in vasculitis, and many more collaborators (updated list on the CanVasc website – https://canvasc.ca/). CanVasc ultimately aims at optimizing the management of vasculitis patients in Canada, throughout the development of (or assistance with the development of) guidelines, educational and awareness programs for health care providers, and studies on vasculitides.

Since its creation, CanVasc core members have initiated and achieved several important projects. The first CanVasc/Canadian recommendations, for the diagnosis and management of ANCA-associated vasculitis, have been published (McGeoch et al. J Rheumatol 2016;43:97-120). Work is in progress to develop similar recommendations for other vasculitides. Several descriptive studies have also been completed and published, and projects for prospective studies and cohorts are underway.

In parallel, several tools have been developed to provide and help disseminate continuous, up-to-date educational materials to physicians who manage patients with vasculitides, and increase awareness on these rare and potentially life-threatening diseases. The CanVasc website offers practical information and resources. Conferences and presentations during sessions organized with Vasculitis Foundation Canada, the Canadian patients' support group, helped to reach more diversified audiences, including patients of course, but also their health care allied professionals and general practitioners.

The development of 'Cavali, a CAnadian VAsculitis Learning Initiative: An approach to vasculitis through interactive clinical cases' aims to further support the continuous learning of physicians and health care providers managing vasculitis patients and training residents. Cavali is the result of hundreds of hours of work to develop practical cases and have them reviewed by CanVasc core physicians. It would not have been possible and this book would not be in your hands today without the contribution or support of several individuals, listed in the Contributors' page, and the educational grants obtained from the Canadian Initiative for Outcomes in Rheumatology cAre (CIORA) and Hoffmann-La Roche. Corisande Baldwin, Raphael Rush and Medha Soowamber helped develop several cases, at the time they were (outstanding!) vasculitis and/or rheumatology fellows in the Vasculitis clinic at Mount Sinai Hospital (Toronto, ON). Of course, as new studies will come up, Cavali will need some periodical updates.

There are multiple aspects involved in attempting to improve patient outcomes. We hope that Cavali will contribute in some way towards this important goal, by raising or nurturing the interest for vasculitis in our current and future Canadian health care colleagues, and by providing them in a playful manner with some practical updates.

After having read the cases in this book, readers who wish to go even further, test their knowledge on vasculitides and/or receive a certificate to support a claim for CME credits, can complete two additional cases online at https://canvasc.ca/.

Introduction to the 2nd Edition

Christian Pagnoux

Cavali, Second edition, January 2019

The 1st edition of CAVALI was printed in March 2017. All the 400 books from this 1st edition were distributed (for free) within a few months and demand for more had been overwhelming since then. More importantly, new results from several important studies had become available. Hence, we thought it was (already) time to update the cases and print a new edition of the book.

We have not added any new cases, but edited several sections of the original ones, with the new available information, and incorporated the answers for the final two evaluation cases in the book, to facilitate direct self-assessment. Whereas the previously used online evaluation process was an exciting and playful option, only a few readers had time to complete the assessment online. The style of the book remains interactive in nature, as it includes real-life situations and case scenarios, with practical questions and straight-to-the-point answers.

This 2nd edition was again developed with the help of some of the previous fellows involved, who are now running their own independent practice, in different cities in Canada, especially Corisande Baldwin. They proudly continue to help manage patients with vasculitis and participate in the CanVasc initiatives. More fellows are now working with us on vasculitis, thus different other projects are in development.

The CAVALI 2nd edition book will again be distributed free of charge to physicians across Canada, through the CanVasc centres. The funding for this 2nd edition came from the remaining grant obtained in 2016 from the Canadian Initiative for Outcomes in Rheumatology cAre (CIORA), a few donations made to CanVasc over the past years by our patients or their relatives, to whom we are extremely thankful, and educational funding support from a couple of pharmaceutical companies (that had no direct role in the writing, reviewing, editing or printing of the book), Hoffmann-LaRoche and GSK.

Enjoy this new, revised, and updated edition of CAVALI!

Introduction to the 3rd Edition

Christian Pagnoux

Cavali, Third revised edition, December 2022

The success of the previous two CAVALI editions motivated us to work on a new version. The pace at which new results and data have been produced in vasculitis has continued to increase over the past 3 years, and it became necessary to update, once again, the content of this very unique teaching material.

We edited a few cases, added new information that we considered important, such as the new classification criteria, sections on genetically determined vasculitides or vasculopathies, and new recommendations from CanVasc (and other societies). Results from several therapeutic trials on various types of vasculitis have also been published since the last edition, which had to be incorporated in this revised version, even though not all of them have yet translated into any significant changes in our clinical practice. We also added two new cases on anti-GBM disease and retinal vasculitis.

This 3rd Edition was again developed with the help of several young colleagues, including Drs. Joanne Jiang and Frédéric Lefebvre, when they were completing their vasculitis fellowships in Toronto. They are now running their own independent practices, in other centres in Canada. Dr. Medha Soowamber has been involved since the 1st Edition in the development and subsequent update of several cases in the book. All previous co-authors, and past and present CanVasc members have played essential roles in the development, dissemination and "survival" of this book.

This time, for various reasons, the book is available directly as an electronic "pdf e-book", and more functionalities have been added, such as clickable links to cases. CanVasc really wanted to keep offering the CAVALI book free of charge to all health care professionals with an interest in vasculitis. An even more user-friendly version of the book (an "app") is under consideration, under the guidance of other CanVasc core members.

Although the book is provided free of charge and no authors are being paid for this work (nor has this ever been the case), in order to achieve such a professional result, the editing process was obviously not free and required us to work with professional editing companies. CanVasc was supported for this endeavor by the remaining funds from a grant obtained in 2016 from the Canadian Initiative for Outcomes in Rheumatology cAre (CIORA), by generous donations from a few patients and families, and new educational funding grants from three pharmaceutical companies (which, like before, had no role in the writing, reviewing, or editing of the book), and these were purposely different companies from the ones who supported the previous editions. We are extremely thankful to all of them for having helped CAVALI survive, grow and become an international reference in teaching on vasculitis.

Enjoy this new edition, and we hope that you will find it useful for your training and daily clinical practice. If it helps you treat your patients, in some way and for the best, all the time and efforts put into the creation and subsequent updates of this book would have been worthwhile!

Case 1
Giant cell arteritis

A 72-year-old woman with hypertension, dyslipidemia and a 50 pack-year smoking history presents with a two-week history of worsening left-sided temporal headache, scalp tenderness, especially in the left temporal area, general malaise and an 8-kg weight loss. C-reactive protein is elevated at 55 mg/l (normal <10 mg/l). The patient is diagnosed with presumed giant cell arteritis (GCA) and started on prednisone 60 mg/day. Ten days later, a temporal artery biopsy is done. The histopathology is negative (normal artery with minimal, chronic atherosclerotic changes). She is referred to you for further diagnostic evaluation and management.

1. *Describe the clinical manifestations of GCA. What are the possible neurological, ocular, and extracranial vascular complications of GCA?*
2. *Describe the existing diagnostic and classification criteria for GCA. What are the limitations of these criteria?*
3. *What is the sensitivity and specificity of temporal artery biopsy in patients with suspected GCA? How does treatment with glucocorticoids impact the sensitivity and specificity of temporal artery biopsy?*
4. *Which imaging modalities can be of use in the diagnosis of GCA?*

The patient followed a gradual prednisone tapering regimen. At 4 months, she is on 10 mg/day prednisone (tapered down from 15 mg/day two weeks ago). She complains of returning temporal headache and fatigue. The physical examination is normal. C-reactive protein is high again at 68 mg/l (versus 6 mg/l a month ago).

5. *How would you manage and treat this patient now?*

Learning objectives

1. To describe the prevalence, the typical demographics and clinical characteristics of GCA.
2. To describe the classic laboratory results, histopathology and imaging of GCA.
3. To describe the role and limitations of temporal artery biopsy and imaging modalities in the diagnosis of GCA.
4. To describe the evidence for the use of glucocorticoids, glucocorticoid-sparing agents, and biologics in the treatment of GCA.
5. To list the possible complications of GCA and its treatment.

Answers

1. Describe the clinical manifestations of GCA. What are the possible neurological, ocular, and extracranial vascular complications of GCA?

GCA is the most common form of idiopathic systemic vasculitis in adults ≥50 years of age, with incidence peaking at 70-80 years. It is more common in women (sex ratio, 2.5), at least in Northern European countries. GCA seems rarer in African, Asian, Hispanic and Arab populations. Incidence is estimated between 100 to 400 cases per million population over 50 years old.

GCA affects large vessels and can cause systemic manifestations and ischemic complications. Systemic manifestations are common at the time of diagnosis, with fatigue, general malaise, symptoms of polymyalgia rheumatica in up to 60% of the patients (conversely, up to 20-23% of patients with a diagnosis of polymyalgia rheumatica have [subclinical] GCA), fever (most often low grade), weight loss, or dry cough. In some instances, these unspecific systemic symptoms can precede by weeks or months the other and more suggestive signs of GCA. The latter relate to the vessels predominantly involved (mainly the external carotid artery and its branches, uni- or bilaterally, but other large vessels can be affected). The most frequent clinical symptoms include headache, often frontotemporal and of subacute onset, scalp tenderness, temporal artery induration and tenderness, and jaw claudication. More severe ischemic complications include vision loss in 10-20% of patients. Vision loss may be transient (amaurosis fugax) or permanent (especially when there is acute anterior ischemic optic neuritis). Visual loss in one eye may lead to involvement of the contralateral eye in up to 25-50% if initially unrecognized. Other ischemic complications include diplopia, stroke or transient ischemic attack (0.5-7% of patients, mostly in the vertebrobasilar areas), tongue or scalp infarct, and, more exceptionally, myocardial infarction. Extracranial large vessels can be involved in up to 30–80% of patients, depending on the detection technique used (<30% of the patients by US; up to 80% with PET-CT, but isolated uptakes found only on PET-CT are still of unclear clinical significance). These large-vessel vasculitic lesions can cause limb ischemia, digital ischemia with ulcers and/or gangrene, or aortitis in up to 10–30% of patients, with a risk of subsequent aortic aneurysm and/or dissection (Figure 1.1), and/or aortic valvular insufficiency. The dissection or aneursym can develop years after the diagnosis, when the disease is otherwise in clinical remission. Aortic and/or extracranial vessel involvement are associated with higher risks of relapses and mortality from cardiovascular causes.



Figure 1.1. Parasagittal thoraco-abdominal CT in an 80-year-old female with a diagnosis of giant cell arteritis, made 2 years earlier, showing a thoracic aorta dissection (arrow). Vessel imaging was normal at the time of diagnosis.

2. Describe the existing diagnostic and classification criteria for GCA. What are the limitations of these criteria?

There are currently no diagnostic criteria for GCA. Classification criteria are by design validated for research classification purposes only, and should therefore be used with caution in clinical settings.

The 1990 American College of Rheumatology (ACR) classification criteria were:

- Age at disease onset ≥50 years
- New onset or new type of localized pain in the head
- Temporal artery tenderness to palpation or decreased pulsation not related to atherosclerosis of the cervical arteries
- Elevated erythrocyte sedimentation rate (ESR) ≥50 mm/h (Westergren method)
- Biopsy with artery showing vasculitis with predominant mononuclear cell infiltrate or granulomatous inflammation, usually with multinucleated giant cells

The presence of least three of these five criteria is associated with a sensitivity of 93.5% and specificity of 91.2%.

Collaborative international efforts led to the new 2022 classification ACR/European Alliance of Associations for Rheumatology [EULAR] Classification Criteria for GCA (Table 1.1).

Table 1.1. Summary of the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for giant cell arteritis (Adapted from Ponte et al. Ann Rheum Dis 2022).

The classification criteria for giant cell arteritis can be considered only in patients in whom:		
1. a diagnosis of medium-vessel or large-sized vessel vasculitis has been made		
& 2. all alternate diagnoses have been excluded		
& 3. age at time of diagnosis is ≥50 years (absolute requirement)		
And with the following:		
Clinical criteria:		
	Morning stiffness in shoulders or neck	+2
	Sudden visual loss	+3
	Jaw or tongue claudication	+2
	New temporal headache	+2
	Scalp tenderness	+2
	Abnormal examination of temporal artery (pulse or tenderness)	+2
Laboratory, imaging and biopsy criteria:		
	Maximum erythrocyte sedimentation rate ≥50 mm/h or C-reactive protein ≥10 mg/L	+2
	Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
	Bilateral axillary involvement on imaging	+2
	Fluorodeoxyglucose-positron emission tomography (FDG-PET) activity throughout aorta	+2
A cumulative, sum score of ≥6 is needed for classification of giant cell arteritis. The sensitivity of these criteria was 87.0% (95%CI; 82–91%) and specificity 94.8% (95%CI; 91–97.4%).		

3. What is the sensitivity and specificity of temporal artery biopsy in patients with suspected GCA? How does treatment with glucocorticoids impact the sensitivity and specificity of temporal artery biopsy?

Every effort should be made to confirm a diagnosis of GCA. Original recommendations advised temporal artery biopsy in every case of suspected GCA. More recent guidelines recommend confirmatory diagnostic testing, whether it be by imaging (e.g. with US of the temporal arteries, or cranial artery MRI), or by histology. There are strong proponents for each method, and access to these techniques obviously impacts clinical choices.

The sensitivity of temporal artery biopsy is relatively low. It varies broadly according to published series, between 30–85% (average of 77% in a recent meta-analysis). This variability is possibly due to the focal and segmental distribution of the inflammation. Bilateral temporal artery biopsy can increase the sensitivity and chance to detect GCA features by up to 12%, but also carries a small risk of scalp necrosis. Therefore, a negative biopsy does NOT rule out GCA. Specificity is high, but not 100% (temporal arteritis can occur in other vasculitides, such as polyarteritis nodosa, microscopic polyangiitis, or granulomatosis with polyangiitis).

The most typical findings of GCA on biopsy are focal and segmental mononuclear inflammatory infiltrate in the adventitia and media with fragmentation of the internal elastic lamina. Multinucleated giant cells may or may not be present. Fibrinoid necrosis is usually not present in tissue samples, and should make one consider other systemic vasculitides.

Predictors of a positive temporal artery biopsy in several studies included jaw claudication (likelihood ratio [LR] = 4.2), diplopia (LR = 3.4), temporal artery beading (LR = 4.6), prominence (LR = 4.3) and tenderness (LR = 2.6). There has been heated debate about the optimal length of the biopsy. Consensus is that the minimal length should be 0.5-0.7 cm. Sensitivity does not improve above 1.5 cm.

Glucocorticoid (GC) treatment can reduce the rate of a positive biopsy, but to a limited extent and not immediately (approximately by one-half after 1 month of GC treatment). A couple of case series and several case reports, however, clearly showed that the presence of giant cells can persist, months or years after remission has been achieved, under ongoing GC treatment or after its discontinuation.

Thus, although the timing of temporal artery biopsy should not delay initiation of medical treatment, a biopsy should be performed as soon as possible, ideally within 1 to 2 weeks after GC introduction. Present guidelines suggest unilateral temporal artery biopsy should be adequate in the majority of patients, provided it is guided by the patient's symptoms and signs.

4. Which imaging modalities can be of use in the diagnosis of GCA?

Doppler and duplex ultrasonography of the temporal arteries are operator-dependent imaging modalities that may help in the diagnostic evaluation of patients with suspected GCA. A "halo sign" on ultrasound, characterized by dark hypoechoic circumferential thickening (the width of vessel-wall thickening should be measured to determine if this is above physiological), carries a sensitivity of 69-100%, when compared to temporal artery biopsy, and a specificity of 89-91%. Bilateral positive ultrasonography carries a higher specificity but sensitivity is only 43%. The "compression sign" (the inflammatory wall thickening of the temporal artery is not compressible upon application of pressure with the probe) is another key elementary US lesion of GCA. Some researchers believe that temporal artery biopsy can now be reserved for those patients with negative ultrasonography.

Scalp and temporal artery magnetic resonance imaging (MRI) requires specific sequences and further validation studies, but its negative predictive value could be higher than that of ultrasonography (if negative, GCA could be ruled out). Although a few fast-track GCA clinics with access to either US or MRI of the temporal arteries have been (or are being) implemented in several centres across Canada, these modalities are not yet widely and/or readily available (training is also lengthy, before gaining the necessary experience to perform reliable ultrasonographies of the temporal arteries). As with biopsy, imaging should be performed as early as possible, ideally within 1 week, as GC use rapidly lowers the sensitivity of both US and MRI of the temporal arteries. That being said, the 2008 EULAR recommendations state that "US, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA". The access and place of PET-CT for GCA is even more limited at present in Canada. PET may be more relevant when there is a need to distinguish between vasculitis, infection or malignancy.

Imaging of the aorta and its main branches should be considered systematically, as large vessels other than cervico-cephalic arteries, can be affected in GCA, at diagnosis and/or later. A chest X-ray and abdomen ultrasound can be considered for screening, but for patients with decreased and/or asymmetrical peripheral pulses, or large vessel bruits, a computerized tomography (CT)-or MR-angiography (CTA or MRA) should be ordered. There is no consensus on the frequency of repeated large vessel imaging; some groups suggested a control at least every 2 to 5 years. Patients with extracranial vessel disease tend to relapse more often, and those with aorta involvement can develop aneurysms and/or dissection.

5. How would you manage and treat this patient now?

After excluding differentials (especially an infection), the diagnosis of a clinical and biological relapse can likely be made. In practice, up to 60% of GCA patients treated with GC alone relapse, especially within the first 12 months post diagnosis. Control imaging of large vessels should be considered, and the prednisone dose should be increased again. A GC-sparing agent should also be considered.

Several societies have now published their recommendations for the treatment of GCA, including the ACR, the EULAR, the British Society of Rheumatology and the French Study Group for Large Vessel Vasculitis (GEFA). Patients with active, newly diagnosed GCA should be treated with high-dose GC of 0.7–1 mg/kg/day prednisone-equivalent (40–80 mg/day), for 2 to 4 weeks, followed by a gradual taper over a period of 6 months, targeting a dose of 10-15 mg/day by month 3 or 4. The optimal duration of GC thereafter is unknown and varies between centres from 6 to >24 months. Two small randomized controlled trials investigated the effect of initial IV methylprednisolone (MP) pulses, which are often considered in patients with GCA and visual manifestations. However, none of those was powered enough to show anything with regard to vision loss prevention, or stroke risk reduction. One of these studies (with MP 15 mg/kg/day for 1 to 3 days) suggested a lower rate of relapse at month 19, while the other (MP 240 mg at day 1) simply showed no obvious benefit. It must be kept in mind that one-third of deaths in GCA are due to infections, especially during the first year and in patients on a GC dose still greater than 10 mg/day at the end of the first year of treatment.

The systematic use of aspirin in GCA (as well as anticoagulants) is not (or no longer) recommended by every society. A couple of meta-analyses of the existing studies and only 6 retrospective

studies on this topic concluded that antiplatelet/anticoagulant therapy prior to GCA diagnosis was not associated with a reduction in severe ischemic complications, although this therapy demonstrated a marginal benefit, when used with GC, in patients with established disease. The GEFA stated in 2016 that "low-dose aspirin (75–300 mg/day) should be considered for every patient with newly diagnosed GCA upon benefit–risk assessment; for GCA with ophthalmic involvement, prescribing low-dose aspirin should be advised". In the recent 2021 ACR/Vasculitis Foundation Guidelines, adding aspirin is conditionally recommended "for patients with GCA who have critical or flow-limiting involvement of the vertebral or carotid arteries". Whereas in 2009, the EULAR "recommend[ed] the use of low-dose aspirin in all patients with GCA", the 2018 update stated that "antiplatelet or anticoagulant therapy should not be routinely used for treatment of [GCA] unless it is indicated for other reasons (e.g. coronary heart disease, cerebrovascular disease, etc)." Aspirin (and/or anticoagulants, as indicated) should thus be considered on an individual basis, especially in GCA patients suffering from vascular ischemic complications, ophthalmic involvement or stroke, as well as those at high risk of cardiovascular disease.

The use of adjunct methotrexate (MTX; 15-25 mg/week orally or subcutaneously) can be considered for its GC-sparing effect and in relapsing patients. It is rarely used as first-line treatment, especially since a meta-analysis of three small randomized controlled trials (RCT) showed that the benefit of MTX (15 mg/week) was indeed modest (higher dosages, up to 25 mg/week, have not been studied in RCT). Anti-tumour necrosis factor (TNF)-alpha agents have not been found effective in GCA in three different RCT, with adalimumab, etanercept or infliximab.

A small RCT (30 patients) first showed some benefit from intravenous (IV) tocilizumab (an anti-interleukin [IL]6 receptor monoclonal antibody; 8 mg/kg IV every 4 weeks for 1 year) in GCA. A larger study (GiACTA; 251 patients), evaluated subcutaneous tocilizumab in GCA, as first-line treatment or for relapsers, for 12 months, in combination with GC for a short duration (6 months). At 12 months, the sustained remission rate was 53% with tocilizumab compared to 14% in patients treated with GC alone for 6 months and 18% in those treated with GC alone for 12 months. Serious infections occurred in 6% of patients on tocilizumab (and a 6-month course of GC) versus 12% in those on GC alone for 12 months. Based on these results, in October 2016, the Food and Drug Administration (FDA) granted breakthrough therapy designation for tocilizumab in GCA. Health Canada also approved it in October 2017. Whether tocilizumab should be used in all patients with newly diagnosed GCA or only in those who are GC-dependent or who relapse remains a matter of debate. Cost-effectiveness studies are still needed to help in making that decision.

The 2021 ACF/Vasculitis Foundation recommendation was, for patients with newly diagnosed GCA, to conditionally (only) recommend the use of oral GC with tocilizumab over oral GC alone. The use of tocilizumab for relapsers or GC-dependent patients is more strongly supported (also by the EULAR recommendations), conditionally over that of MTX. One unresolved question is the optimal duration of tocilizumab, because only 42% of the patients remained in sustained remission off-GC following the discontinuation of tocilizumab after one year of treatment in the GiACTA study.

Abatacept (a cytotoxic T lymphocyte antigen-CTLA4-Ig fusion protein, which inhibits the activation of T cells; 10 mg/kg IV on days 1, 15, 29, then every 4 weeks) was also evaluated with some positive results in patients with relapsing and/or refractory GCA. A new and larger randomized study just started to investigate it further (ABAGART with subcutaneous abatacept 125mg/week vs. placebo; ClinicalTrials.gov Identifier: NCT04474847).

Other agents have been and/or are also being investigated in GCA, including mavrilumab (anti-GM-CSF-receptor, with promising results from a small phase II trial); ustekinumab (anti-IL12/23, but with mitigated results in a couple of studies); various JAK inhibitors (baracitinb, tofacitinib, upadacitinib); anakinra (anti-IL1); secukinumab (anti-IL17); and guselkumab (anti-IL23). Clearly, there are several pathogenic pathways involved in GCA, and there is to date no agent that seems to act upon all of them, thereby the persistent issue of relapses or GC dependency.

Hence, besides the GC dose intensification, the use of an adjunct immunosuppressant can be considered for the patient depicted in this case. The dose of GC to prescribe in cases of relapses can be adjusted based on the disease manifestations: a return to the previously effective dose of prednisone can be sufficient in patients with recurrent mild headache or joint stiffness; patients with worsening or new large-vessel disease, eye and other ischemic features should return to high-dose prednisone. Isolated, non-symptomatic biological anomalies (e.g. moderately elevated ESR or CRP) most often warrant close monitoring without an automatic increase in the prednisone dose. MTX (15-25 mg/week) can be used as a GC-sparing agent in GCA, but its efficacy is limited. Tocilizumab (subcutaneously) could represent a better alternative here. Leflunomide (20 mg/day) has also been used as GC-sparing agent in patients with relapsing GCA, with occasional favourable responses in case reports or small series.

References

Mukhtyar C et al. 2008. EULAR Recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68(3):318-23.

Osman M et al. The role of biological agents in the management of large vessel vasculitis: a systemic review and meta-analysis. PLoS One 2014;9(12):1-18.

Muratore F et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford) 2015;54(3):463-70.

Alsolaimani RS et al. Severe Intracranial Involvement in Giant Cell Arteritis: 5 Cases and Literature Review. J Rheumatol 2016;43(3):648-56.

Bienvenu B et al. Management of giant cell arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). Rev Med Interne 2016;37(3):154-65.

Rhéaume M et al. High-resolution Magnetic Resonance Imaging of scalp arteries for the diagnosis of giant cell arteritis: Results of a prospective cohort study. Arthritis Rheumatol 2017;69(1):161-8.

Stone JH et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med 2017;377:317-28.

Langford CA et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis & Rheumatol 2017;69(4):837–845.

Dejaco C et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77(5):636-43.

Mackie SL et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis: executive summary. Rheumatology (Oxford) 2020;59(3):487-94.

Hellmich B et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79(1):19-30.

Maz M et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol 2021;73(8):1349-65.

González-Gay MA. The role of PET/CT in the evaluation of patients with large-vessel vasculitis: useful for diagnosis but with potential limitations for follow-up. Rheumatology (Oxford) 2022 May [Epub].

Cid MC et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis 2022;81(5):653-61.

Pugh D et al. Large-vessel vasculitis. Nat Rev Dis Primers 2022;7(1):93.

Ponte C et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis; Nov 2022 [Online ahead of print].

Case 2
Takayasu arteritis

A 27-year-old South Asian woman presents with a 6-month history of fatigue, intermittent fever, a 5 kg weight loss, and left arm muscular pain during her daily activities. An initial work-up by her family physician has revealed decreased left radial pulse and blood pressure, elevated erythrocyte sedimentation rate (ESR; 67 mm at 1st hour; normal <19 mm) and C-reactive protein (CRP) level (73 mg/l; normal <10 mg/l), and a low hemoglobin level at 96 g/dl (normal 110-160 g/dl).

1. *Describe the clinical manifestations of Takayasu arteritis. What are the potential vascular complications?*
2. *Describe the diagnostic and classification criteria for Takayasu arteritis. What are the limitations of these criteria?*

You order a MR angiogram, which demonstrates circumferential wall thickening and narrowing of the left subclavian and brachial arteries (Figure 2.1).



Figure 2.1. MR angiogram of the aortic arch and supra-aortic arteries, showing narrowing of the left subclavian (arrow) and brachial arteries, with development of collateral vessels.

3. *How will you treat this patient? What is the role of surgical and endovascular treatments for vascular stenoses in Takayasu arteritis?*

Two years later, on treatment, this patient continues to be asymptomatic, with normal inflammatory markers. She confides in you that she wishes to conceive.

4. *What are the possible risks of pregnancy in patients with Takayasu arteritis?*

Learning objectives

1. To describe the prevalence, the typical demographics and clinical characteristics of Takayasu arteritis (TAK).
2. To describe the classic laboratory and imaging findings of TAK.
3. To describe the evidence for treatment of TAK.
4. To list the possible complications of TAK and their management.
5. To discuss the risks of pregnancy in patients with TAK.

Answers

1. Describe the clinical manifestations of Takayasu arteritis. What are the potential vascular complications?

Takayasu arteritis (TAK) is a primary large-vessel vasculitis that predominantly affects women under the age of 40 years, especially of Asian or Indian descent, and is often referred to as the pulseless disease. Its annual incidence varies from 0.4 per million in European countries up to 4 per million in Asia and Kuwait, and prevalence varies from 4 to 40 per million, the latter in Japan. Its prevalence is probably even higher in India.

Clinically, TAK includes systemic and vascular manifestations. Systemic symptoms are present in about half of patients, which involves fatigue, general malaise, night sweats, fever, and weight loss. A few patients (<10%) also have recurrent tender skin nodules (erythema nodosum), uveitis and/or episcleritis. Pyoderma gangrenosum, erythema induratum, as well as ulcerative lesions, have also been described. Vascular manifestations depend on which vessels of the aortic arch are affected. Subclavian artery involvement translates into progressive arm claudication, numbness or coolness, decreased or absent radial and/or axillary pulse, and asymmetrical blood pressure. The left subclavian artery is one of the most commonly affected arteries in series of TAK. Carotid artery involvement may cause carotidynia, dizziness, malaise or syncope. Strokes are rare, as the disease process is usually chronic and collaterals have usually developed when a cervico-cephalic artery becomes occluded. Aorta involvement, aortic insufficiency and coronary artery involvement may manifest as angina, abdominal aorta and mesenteric artery involvement as abdominal angina or mesenteric ischemia, and ilio-femoral involvement as lower limb claudication. Renal artery involvement can cause renovascular hypertension, with associated complications such as hypertensive retinopathy or encephalopathy. Pulmonary artery involvement can also occur in 50-86% of patients, with up to half of them having pulmonary hypertension. Auscultation of the affected arteries may reveal bruit(s).

Arterial wall thickening and stenosis are the most common lesions observed in TAK, with aneurysms occurring in just 25% of patients, predominantly affecting the aorta. Dissection, mainly of the ascending aorta, is less frequent (up to 11% of patient cohorts in a pediatric study). The most common vessels involved also vary geographically, with the aortic arch and its branches being more common in Japanese cohorts and the abdominal aorta and renal arteries being more common in Indian patients.

2. Describe the diagnostic and classification criteria for Takayasu arteritis. What are the limitations of these criteria?

The 1990 ACR criteria for the classification of TAK were developed for research purposes and to help distinguish patients with known vasculitides. According to these criteria, patients had to have three of six of the following criteria to be classified as having TAK:

- Age at disease onset ≤40 years
- Claudication of extremities
- Decreased brachial artery pulse
- Blood pressure difference >10 mmHg (between arms)
- Bruit over subclavian arteries or aorta
- Abnormalities on angiography

The sensitivity and specificity of these criteria were 90.5% and 97.8%, respectively.

The 1994, and then the revised 2012 Chapel Hill Consensus Conference nomenclature defined TAK as a large-vessel vasculitis, predominantly affecting the aorta and/or its major branches, often granulomatous, with onset usually in patients younger than 50 years.

The newly published 2022 ACR/EULAR criteria for TAK (Table 2.1) have a sensitivity of 93.8% and a specificity of 99.2%. Vasculitis classification criteria for children have also been published, including for TAK.

In 1988, the Ishikawa diagnostic criteria were developed after analysis of a cohort of Japanese patients, based on the age at onset of the disease (an obligatory criterion), clinical, laboratory and angiographic findings (with two major and nine minor criteria). These criteria had a sensitivity of 84%, but when applied to an Indian population, where aortic and renal artery involvement are more common, sensitivity and specificity dropped to 60.4% and 77.4%, respectively. Ishikawa diagnostic criteria were thus modified by Sharma et al. and, in 2008, by the Japanese Cardiovascular Society. These diagnostic criteria had greater sensitivity and specificity but are rarely used in clinical practice.

For establishing a diagnosis of TAK, physicians must rely on a combination of clinical signs and symptoms of ischemia, elevation of inflammatory markers, as well as vascular imaging, typically CT scan and for MRI-MRA.

3. How will you treat this patient? What is the role of surgical and endovascular treatments for vascular stenoses in Takayasu arteritis?

Before considering treatment, all differential diagnoses must be considered. They include (premature, accelerated) atherosclerosis, non-inflammatory large-vessel diseases, such as fibromuscular dysplasia, Ehlers-Danlos (type IV), Marfan syndrome or segmental arterial mediolysis. Infections (syphilis and tuberculosis being the two main infections to rule out) and other systemic inflammatory conditions (ankylosing spondylitis, rheumatoid arthritis, IgG4-related disease, sarcoidosis, inflammatory bowel disease) should also be ruled out, mainly when the disease is localized to the aorta.

The 2008 EULAR recommendations for the treatment of large-vessel vasculitis mainly focused on giant cell arteritis, with only a few low-grade evidence statements for TAK. In 2021, a French group published its recommendations for TAK, as did the ACR/Vasculitis Foundation. Most of these recommendations are based on expert opinions, conditional in nature, and/or based on series only. Only four randomized placebo-controlled trials have been completed and published on TAK to date. One trial investigated abatacept (10 mg/kg IV on days 1, 15, 29, then every 4 weeks) and failed to show significant superiority in terms of relapse prevention. The second, smaller trial investigated tocilizumab (anti-IL6-receptor monoclonal antibody; weekly 162 mg subcutaneously) and showed some limited benefits in preventing relapses, that warrant further investigation. In the latter study, 40% of patients with TAK still experienced progression in wall thickness within 96 weeks of treatment with tocilizumab. The remaining two trials were on curcumin (vs. placebo), and resveratrol (vs. placebo), two naturally occurring compounds. Both studies showed improvement in the Birmingham Vasculitis Activity Score (BVAS), which is not ideal to assess TAK activity, and is associated with several biases.

The patient in this case should be treated with glucocorticoids (GC), as she has active disease, with recent and worsening clinical symptoms, and systemic inflammatory syndrome. According to the 2008 EULAR guidelines for large-vessel vasculitides, she should be treated with prednisone, starting at a dose of 1 mg/kg/day (maximum of 60 mg/day) for 1 month, followed by a gradual taper, down to 10-15 mg/day by month 3 (plus all regular treatments indicated in combination with long-term use of GC, including vitamin D and calcium supplementation). Given the frequent adverse effects of GC therapy, EULAR recommendations advocate for the use of a GC-sparing immunosuppressant to aid in prednisone taper. The 2021 ACR/VF

recommendations suggest the same approach, although only with conditional recommendations. The most commonly used conventional agent is methotrexate (15–25 mg/week, orally or subcutaneously). Azathioprine (2 mg/kg/day) or leflunomide (20 mg/day) can be also be considered; tofacitinib or other JAK inhibitors have also been tried with some interesting results (but only in small cohort or case series). Cyclophosphamide (IV pulses of 7.5–15 mg/kg, monthly, or orally 2 mg/kg/day) has also been used for severe cases but exhibits a higher toxicity profile. Systematic reviews and meta-analyses also support the use of anti-TNF-alpha agents (mainly infliximab, 5-10 mg/kg IV on days 1, 15, then every 4 to 8 weeks; or etanercept, 25 to 50 mg subcutaneously, twice per week), mostly for severe cases and/or as a second-line choice, as per the 2021 ACR/VF recommendations. The latter recommend TNF-alpha inhibitors over tocilizumab, but acknowledge that tocilizumab can be considered in patients in whom anti-TNF-alpha agents are contraindicated or ineffective.

Ustekinumab, an anti- IL12/IL23-blocking monoclonal antibody, has also been used in a few Japanese patients with refractory TAK.

Low-dose aspirin should also be considered in patients with active TAK and critical cranial or vertebrobasilar involvement (but there is no data to support systematic prescription of aspirin [or anticoagulant] in every patient with TAK).

Because the geographic distribution map of TAK greatly overlaps that of high-prevalence areas of tuberculosis, all patients with a new diagnosis of TAK must be screened for (latent) tuberculosis, and treated as needed.

Surgical bypass and percutaneous angioplasty with stent placement must be considered in patients with critical stenosis and occlusions (e.g. with severe cerebrovascular or cardiovascular disease, uncontrolled hypertension secondary to renal artery involvement, and critical limb ischemia). Outcomes of those procedures in TAK are not as favourable as in atherosclerosis. Re-stenosis is frequent (14%-25% early, before 7 years post procedure; 34%-67% later, at 10 years), especially in patients undergoing these procedures while the disease is still active, with persistent inflammation (elevated CRP level) and/or not treated with GC or another immunosuppressant at the time of the procedure. In this respect, many physicians (and the 2021 ACR/VF guidelines) recommend the prescription of (high-dose) GC in patients with TAK who are undergoing a surgical intervention, in the periprocedure period, especially if the patient has active disease.

4. What are the possible risks of pregnancy in patients with Takayasu arteritis?

Many women with TAK who become pregnant deliver normal, healthy babies, but there is a risk for maternal and fetal complications related to both the disease and its treatment.

Patients with TAK wishing to conceive should ideally seek the support and guidance of their treating rheumatologist or general internist and an obstetrical medicine specialist before conceiving. The disease should be in remission for at least 6 months prior to conception. The risk of a flare during pregnancy is small but patients must be monitored with regard to their medications and hypertension. Reported rates of TAK exacerbation during pregnancy vary between 3 and 39%, with a recent literature review averaging that risk at 18%.

Obstetric complications have been reported in up to 40% of pregnancies and include hypertension (especially in women with renal artery and aortic involvement) with associated risks of pre-eclampsia/eclampsia, congestive heart failure, aortic insufficiency, stroke, intracerebral bleed (especially in the 2nd trimester), hypertensive nephropathy and retinopathy. Thirty to 50% of pregnant TAK patients will deliver by cesarean section, and most often, this will be elective.

Risks to the infant include intrauterine growth retardation secondary to hypertension as well as prematurity. Miscarriage and intrauterine demise secondary to hypertension and placental insufficiency are also risks that have been associated with abdominal aortic involvement. There are currently no data to support (nor contra-indicate) the systematic use of low-dose aspirin in young pregnant women with TAK and no prior obstetrical history.

Hence, vascular intervention (renal artery percutaneous transluminal angioplasty, stenting or surgical bypass) should be considered prior to conception in women with renovascular involvement. Several immunosuppressants are contraindicated during pregnancy and should be discontinued prior to conception according to their half-lives and the Food and Drug Administration (FDA)'s Pregnancy and Lactation Labeling Final Rules (PLLR). Society recommendations, informing physicians about immunosuppressive therapy use in pregnancy, have been published, such as the 2020 ACR guideline for the management of reproductive health in rheumatic and musculoskeletal disease.

On the other hand, in a patient in sustained remission on low-dose GC, it may be wiser to wait until after the pregnancy and delivery before trying to wean off the GC.

Table 2.1. Summary of the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for Takayasu arteritis (Adapted from Grayson et al. Ann Rheum Dis 2022).

The classification criteria for Takayasu arteritis can be considered only in patients in whom:		
1. a diagnosis of medium-vessel or large-vessel vasculitis has been made		
& 2. all alternate diagnoses have been excluded		
& 3. age at time of diagnosis is ≤60 years		
& 4. there is evidence of vasculitis on imaging		
And with the following:		
Clinical criteria:		
	Female sex	+1
	Angina or ischemic cardiac pain (attributable to vasculitis)	+2
	Arm or leg claudication	+2
	Arterial, vascular bruit	+2
	Reduced pulse in upper extremity	+2
	Reduced or absent pulse of the carotid artery or carotidynia	+2
	Systolic blood pressure difference in arms ≥20 mmHg	+1
Laboratory, imaging and biopsy criteria:		
	Angiographic and ultrasound findings of affected arterial territories	+1 for 1 arterial territory + 2 for 2 arterial territories + 3 for ≥3 arterial territories
	Symmetric involvement of paired arteries	+1
	Abdominal aorta involvement with renal or mesenteric involvement	+3
A cumulative, sum score of ≥5 is needed for classification of Takayasu arteritis. The sensitivity of these criteria was 93.8% (95% CI; 88.6–97.1%) and specificity 99.2% (95% CI 96.7–100%).		

References

Sharma BK et al. Diagnostic criteria for Takayasu arteritis. Int J Cardiol 1996;54 Suppl:S141-7.

Japanese Circulation Society. JCS Joint Working Group. Guideline for management of vasculitis syndrome (JCS 2008). Circ J 2011;75(2):474-503.

Clifford A and Hoffman GS. Recent advances in the medical management of Takayasu arteritis: an update on use of biologic therapies. Curr Opin Rheumatol 2014;26(1):7-15.

Osman M et al. The Role of Biological Agents in the Management of Large Vessel Vasculitis (LVV): A Systematic Review of the Literature. PLoS One 2014;9 (12): 1-18.

Comarmond C et al. Takayasu Arteritis and Pregnancy. Arthritis Rheumatol 2015;67(12):3262-9.

Aeschlimann FA et al. Arterial dissection in childhood Takayasu Arteritis: not as rare as thought. Pediatr Rheumatol Online J 2016;14(1):56(1-6).

Langford CA et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Takayasu Arteritis. Arthritis Rheumatol 2017;69(4):846-853.

Barra L et al. Variations in the clinical practice of physicians managing Takayasu arteritis: a nationwide survey. Open Access Rheumatol 2017;9:91-9.

Nakaoka et al. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis 2018;77:348–354.

de Graeff N et al. European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides - the SHARE initiative. Rheumatology (Oxford) 2019;58(4):656-71.

Ross C, D'Souza R, Pagnoux C. Pregnancy Outcomes in Systemic Vasculitides. Curr Rheumatol Rep 2020;22(10):63.

Nakaoka Y et al. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. Rheumatology (Oxford) 2020;59(9):2427-34.

Mustapha N et al. Efficacy of leflunomide in the treatment of vasculitis. Clin Exp Rheumatol 2021;39 Suppl 129(2):114-8.

Padiyar S, et al. Update on pregnancy in Takayasu arteritis-A narrative review. Int J Rheum Dis 2021 Jun;24(6):758-65.

Saadoun D et al. French recommendations for the management of Takayasu's arteritis. Orphanet J Rare Dis 2021;16(Suppl 3):311.

Maz M et al. Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol 2021;73(8):1349-65.

Misra DP et al. Disease-modifying anti-rheumatic drugs for the management of Takayasu arteritis-a systematic review and meta-analysis. Clin Rheumatol 2021 Nov;40(11):4391-416.

Jiang Z et al. Variations in Takayasu arteritis characteristics in a cohort of patients with different racial backgrounds. Semin Arthritis Rheum 2022;53:151971.

Ross C, Lefebvre F, Pagnoux C. Cessation of immunosuppressive therapies in patients with Takayasu arteritis with sustained inactive disease. Semin Arthritis Rheum 2022 ;52:151934.

Grayson PC et al. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. Ann Rheum Dis; Nov 2022 [Online ahead of print].

Case 3

Aortitis and imaging of large-vessel vasculitis

A 67-year-old woman is referred to your clinic 2 months after having undergone surgery for an abdominal aorta aneurysm, which had been found incidentally on an abdominal ultrasound for non-specific abdominal pain for the past 6 months. The histopathology of the aorta was in favour of aortitis, with the presence of polymorphonuclear vessel wall infiltrate and areas of fibrinoid necrosis.

1. *What is aortitis and list the different conditions that can cause or mimic aortitis.*
2. *List the different non-radiological investigations you would order in this patient.*

The patient had no symptoms other than abdominal pain, which had resolved since the surgery. She is now doing well. At the time of her surgery and the day before you see her, she had some laboratory tests performed. C-reactive protein had been normal (3 mg/l before surgery and 2.7 mg/l the day prior to the visit). Complete blood cell count, creatinine level, urinalysis, liver tests, serum protein electrophoresis, antinuclear antibodies (ANA), rheumatoid factor, antineutrophil cytoplasm antibodies (ANCA), syphilis serology are all normal or negative. The chest X-ray is normal.

3. *What radiological investigations would you order in this patient, now and/or for subsequent follow-up?*

Patient had a CT angiogram of the chest and abdomen that did not show additional areas of aortic involvement or branch vessel abnormalities.

4. *What treatments (if any) will you suggest for this patient?*

Learning objectives

1. To list the conditions that can cause or mimic aortitis.
2. To discuss the roles, pros and cons of the different imaging techniques for the diagnosis and follow-up of patients with large-vessel vasculitides.
3. To discuss the treatment approach of aortitis in general, and clinically isolated aortitis (CIA) in particular.

Answers

1. What is aortitis and list the different conditions that can cause or mimic aortitis.

The 2015 Consensus Statement on Surgical Pathology of the Aorta from the Society for Cardiovascular Pathology and the Association for European Cardiovascular Pathology identified 3 distinct major categories of inflammatory aortic disease: atherosclerosis, atherosclerosis with excessive inflammation (e.g. inflammatory atherosclerotic aneurysm [IAA]), and aortitis or periaortitis. Aortitis refers to any aortic vessel wall inflammation involving the media and/or intima. When the inflammatory process is restricted to the adventitia, particularly when there is extension to the periaortic space, the term periaortitis is recommended.

In practice, there are two major etiological categories of aortitis (Table 3.1): infectious (most often secondary to septicemia and/or infective endocarditis), and non-infectious (inflammatory, most commonly in the thoracic aorta). When the patient is found to have no signs of systemic disease, the term Clinically Isolated Aortitis (CIA) is employed. CIA most frequently affects the ascending aorta, and is either an incidental finding on imaging or, as with the patient in this case, on pathological examination of the aortic specimen, obtained after surgery for aneurysm or dissection. The pattern of the inflammatory infiltrate may also help in the diagnosis: granulomatous infiltrates are suggestive of GCA, some ANCA-associated vasculitides, TAK, sarcoidosis, rheumatoid arthritis, or mycobacterial infections. A lymphoplasmacytic pattern would suggest IgG4-related disease, lupus or syphilis.

Aortitis, regardless of etiology, can cause inflammatory aortic aneurysm, leading to vessel wall rupture, dissection, or stenosis. The main clinical presentation of aortitis is gradual onset of abdominal, dorsal and/or thoracic pain. Aortic aneurysms can also cause dysphagia, dyspnea, voice hoarseness, cough, and superior vena cava compression syndrome. However, aortitis can also be asymptomatic or, in contrast, present more dramatically as an acutely ruptured aneurysm or with subacute ischemic manifestations. Aortitis with aorta wall thickening can be difficult to differentiate from periaortitis, and both can coexist, and overlap with retroperitoneal fibrosis. The diagnostic work-up and etiology of periaortitis and retroperitoneal fibrosis are quite superimposable.

Periaortitis mostly involves the lower abdominal aorta and the common iliac arteries. Other vascular territories (e.g. the thoracic aorta or medium-size arteries) are involved in up to one-third of patients. Periaortitis can be idiopathic (two-thirds of the cases), be due to an immune-mediated condition, such as IgG4-related disease or, less often, autoimmune thyroid diseases, ANCA-associated vasculitis, lupus, or rheumatoid arthritis (the latter conditions can cause aortitis and/or periaortitis). Periaortitis can also result from other various conditions, including malignancies (lymphoma, carcinoid sarcoma), non-Langerhans cell histiocytosis (Erdheim-Chester disease), infections (such as tuberculosis, histoplasmosis, actinomycosis), drugs (ergot derivatives, methysergide, methyldopa, hydralazine), or radiotherapy.

Besides atherosclerosis, the differential of aortitis also includes non-inflammatory aortic diseases, such as abdominal aortic coarctation syndrome (in children), neurofibromatosis, Marfan syndrome, Ehlers-Danlos or Loeys-Dietz syndromes.

Table 3.1. Main causes of aortitis.

	Comments/main characteristics
Vasculitis with possible aortitis	
Giant cell arteritis or Takayasu arteritis (large-vessel vasculitides)	The most common vasculitides causing aortitis
Cogan syndrome	See Case 19
Behçet syndrome	See Case 18
Granulomatosis with polyangiitis and other small-vessel or medium-sized vessel vasculitides	Rare
IgG4-related disease	Can cause aortitis, aneurysms, but also periaortitis and retroperitoneal fibrosis. Multiple other extravascular manifestations are possible. Diagnosis is histology-based as IgG4 measurement in serum is not sensitive and not specific (dense lymphoplasmacytic infiltrations with predominance of IgG4-positive plasma cells (IgG4+cell/IgG+ cell ratio >40%); storiform fibrosis; obliterative phlebitis; eosinophil infiltrate).
Polymyalgia rheumatica	Overlaps with giant cell arteritis, with extracranial vessel involvement
Sarcoidosis	Rare
Rheumatoid arthritis	Rare
Systemic lupus, Sjögren syndrome	Rare
Inflammatory bowel diseases (Crohn's disease or ulcerative colitis)	Isolated or as part of a more diffuse, associated large-vessel vasculitis
Spondyloarthropathies	Often HLA B27-positive
Malignancy	Mostly lymphoma, intravascular or not
Infections	Can be primary or secondary (contamination from another source/focus)
Bacterial	*Staphylococcus, Enterococcus* and *Streptococcus*: most common bacteria *Salmonella* (mostly of the abdominal aorta) *Listeria, Haemophilus, Bacteroides fragilis, Clostridium septicum* Syphilis *(Treponema pallidum)* *Mycobacterium tuberculosis* *Capnocytophaga canimorsus*
Fungal	Candida, Aspergillus
Viral	Hepatitis B virus, Hepatitis C virus Epstein-Barr virus, cytomegalovirus, varicella-zoster virus and herpes simplex virus, human immunodeficiency virus (case reports, often unclear if really the causative agents)
Idiopathic aortitis	Necessitates having ruled out all differentials listed above.
Clinically isolated aortitis	Subtype of idiopathic aortitis where appropriate imaging of thoracic and abdominal aortic branch vessels fails to reveal abnormalities. Most of the time, will remain isolated. Risk of relapse or of new vessel lesions up to 45%; risk of progression to a systemic or diffuse large-vessel vasculitis considered low (<15%), but limited data available.

2. List the different non-radiological investigations you would order in this patient.

There are no standard investigations to order in patients with aortitis. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) should be ordered to assess inflammation, and indirectly assess the activity of the disease. ESR is not very specific as it can be elevated in patients with anemia or monoclonal gammopathy, and increases with age. CRP is more specific of inflammation, but does not distinguish between infections versus non-infectious conditions. CRP and ESR can be normal in patients with histologically active aortitis (normal in up to 10% of patients with giant cell arteritis). Complete blood count (with differential cell count), creatinine level, urinalysis, liver enzymes with aspartate/alanine aminotransferase and alkaline phosphatase, coagulation tests, and serum protein electrophoresis should be ordered at baseline and in anticipation of the possible use of systemic immunosuppressives.

Depending on the patient's history, symptoms and physical examination, rheumatoid factor (and anti-cyclic citrullinated peptide [CCP]), antinuclear antibodies (and anti-double stranded DNA) and/or anti-extractable nuclear antigen [ENA], ANCA, complement fractions and/or IgG4 level can also be ordered. Tuberculosis should be ruled out with a chest X-ray, a tuberculin skin test and/or an interferon gamma release assay. Syphilis and other infections must also be screened for, with the appropriate serologies.

Other investigations are guided by the clinical findings, and results of the first investigations. If spondyloarthropathies are suspected, human leukocyte antigen (HLA-B27) typing can be useful. If inflammatory bowel diseases are suspected, colonoscopy can be considered.

3. What radiological investigations would you order in this patient, now and/or for subsequent follow-up?

Vascular imaging is aimed at assessing the extent of the disease, looking for other vessel involvement and, ideally estimating (and then monitoring) the disease activity. However, no currently available imaging modality can provide all this information at once and in a perfectly reliable way.

Conventional, digital subtraction angiography is somewhat invasive and requires contrast. While it is useful in visualizing the vessel lumen and has a good resolution, it does not allow for visualization of the vessel wall itself, which can be thickened in aortitis and other large-vessel vasculitides.

CT angiography is less invasive, but still requires the use of ionizing radiation and injection of contrast medium. It allows for visualizing the vessel lumen and the vessel wall thickening (Figure 3.1). It can also help identify atherosclerotic, calcified plaques.

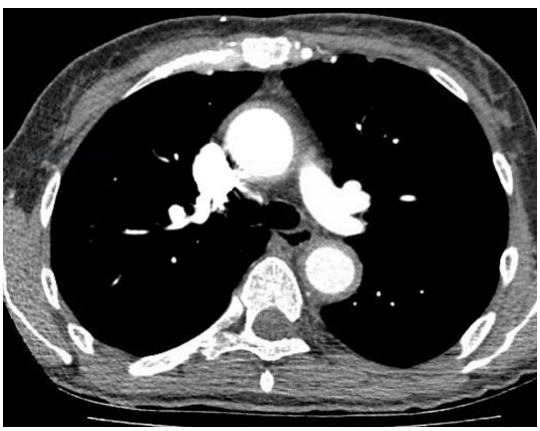


Figure 3.1. CT of the chest and aorta, with contrast iodine dye; supra-aortic horizontal view. Circumferential aortic wall thickening in a 60-year-old female patient with isolated aortitis.

MR angiography is similarly less invasive than conventional angiography, and can visualize the vessel lumen, vessel wall thickening (Figure 3.2) and vessel wall edema and enhancement, which

have not, however, clearly been correlated with disease activity.

18-fluorodeoxyglucose positron emission tomography (PET) makes use of the increased metabolic activity associated with vessel wall inflammation and thus can be useful for diagnosing early inflammatory vessel disease and obtaining a good mapping of the vessel involved at baseline. However, PET is not widely available and has not been clearly standardized. Its value for monitoring disease activity remains an area of debate. Vessel uptake can indeed persist despite the total absence of clinical or biological disease manifestation and does not have a clear predictive value (a comparable problem to vessel wall enhancement with MR angiography). Vascular remodeling and scarring may yield vessel wall enhancement on MR or increased uptake on PET scan, and can be misinterpreted as disease progression.

Further studies are therefore needed to better determine the value of vessel wall abnormalities with these latter imaging techniques, as well as with other recent ones, such as high-resolution ultrasound.

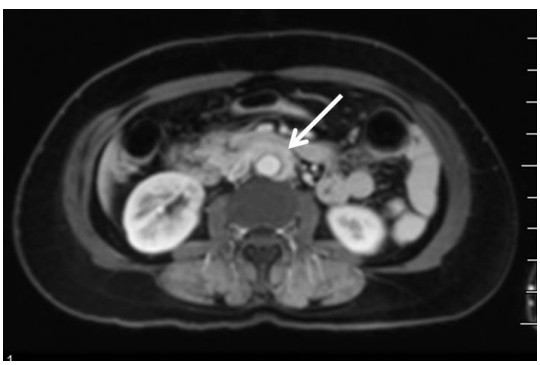


Figure 3.2. MRI of the abdomen and aorta, with gadolinium contrast; horizontal view – T1 sequence, post gadolinium. Abdominal aorta wall thickening in a 55-year-old female patient with isolated aortitis. Note the peripheral wall enhancement and the presence of some periaortitis.

Disease activity is therefore best monitored by following clinical symptoms in combination with inflammatory markers and periodic imaging to look for new or worsening stenoses or extension of the vessel wall thickening. This grossly corresponds to the definition of "active disease" in a study on Takayasu arteritis from the National Institutes of Health (NIH; Kerr et al.), which includes the presence of constitutional symptoms, new bruits, acute-phase response or new angiographic features. There is no perfect tool to score disease activity in large-vessel vasculitides (the Birmingham vasculitis activity score [BVAS] was not developed specifically for large-vessel vasculitides; the Indian Takayasu Arteritis Activity Score [ITAS2010] does not score imaging). A challenging and common situation in large-vessel vasculitides is when only one of these three parameters is abnormal.

In this patient, additional vessel imaging is needed in order to re-assess the aorta wall post surgery and better assess the branches of the aorta, including the cervico-cephalic, abdominal and ilio-femoral arteries. A CT or MR angiography would provide this information. A PET scan, if available, could also be considered, in addition or instead of the former. One should, however, avoid changing technique during the follow-up, as comparing images from different modalities can be misleading.

4. What treatments (if any) will you suggest for this patient?

Treatment of aortitis depends on its cause. When it is associated with a systemic vasculitis or another systemic condition, the treatment should be aimed at the underlying condition. For example, if giant cell arteritis is suspected as the underlying cause, the associated aortitis should be treated with a course of glucocorticoids (GC) with or without another immunosuppressive agent.

Treatment of idiopathic and clinically isolated aortitis is much less established. As in the case presented here, there does not appear to be any active residual disease, considering that 1) the affected area of the aorta has been surgically removed, 2) the remaining vascular tree is normal on imaging studies, and 3) inflammatory markers are not elevated. Therefore, it could be reasonable to not give any specific treatments at this time and monitor the patient with periodic clinical assessments, biochemical tests and imaging studies. Indeed, series of pathologically defined CIA report conflicting results. Following surgical aortic aneurysm resection, the risk of new vascular events, such as distal aortic aneurysm and/or dissection, varies from a reassuring 0% (without any treatment) to almost 50%, after a median follow-up of 3 to 8 years. If, on the other hand, imaging studies show additional vascular territories affected by the inflammatory process and/or if there is ongoing biological inflammation, it could be appropriate to give the patient a course of GC and assess the response. Cases with aggressive or refractory disease manifested as progressive vascular involvement may warrant additional immunosuppressive agents such as methotrexate, cyclophosphamide, or tocilizumab.

References

Kerr GS et al. Takayasu arteritis. Ann Intern Med 1994;120:919–29.

Rojo-Leyva F et al. Study of 52 patients with idiopathic aortitis from a cohort of 1,204 surgical cases. Arthritis Rheum. 2000;43(4):901-7.

Mukhtyar C et al. EULAR Recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2008:86;318-23.

Liang KP et al. Noninfectious ascending aortitis: a case series of 64 patients. J Rheumatol 2009; 36(10):2290-7.

Svensson LG et al. Inflammatory disease of the aorta: patterns and classification of giant cell aortitis, Takayasu arteritis, and nonsyndromic aortitis. J Thorac Cardiovasc Surg 2015;149(2 Suppl):S170-5.

Murzin et al. A case series of surgically diagnosed idiopathic aortitis in a Canadian centre: a retrospective study. CMAJ Open 2017;5(2):E483-7.

Dejaco C et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77(5):636-43.

Clifford AH et al. Outcomes among 196 patients with non-infectious proximal aortitis. Arthritis Rheumatol 2019;71(12):2112-20.

Goldhar HA et al. Characteristics and outcomes in a prospective cohort of patients with histologically diagnosed aortitis. Rheumatol Adv Pract 2019;3(1):rky051.

Ferfar Y et al. Long-Term Outcome and Prognosis Factors of Isolated Aortitis. Circulation 2020;142(1):92-4.

Pugh D et al. Aortitis: recent advances, current concepts and future possibilities. Heart 2021;107(20):1620-29.

Erdogan M. Aortitis: an update. Curr Opin Rheumatol. 2021;33(1):34-40.

Case 4

Polyarteritis nodosa and genetically determined forms of vasculitis

A 45-year-old man with a 3-week history of fever, anorexia, 5-kg (11 lbs) weight loss, night sweats, and diffuse severe abdominal cramping pain with some intermittent presence of bright red blood in the stools, presents to the emergency department with new right foot drop. He felt some right foot numbness on the previous day, then woke up with associated tingling and was unable to lift his foot and had some new numbness in the left hand. He has no specific past medical history. On examination, besides the peripheral nerve involvement in the right foot and left hand, there is some diffuse abdominal tenderness, with additional left flank pain on palpation. Blood pressure, symmetrical on both arms, is 155/90 mmHg.

Blood work reveals anemia (hemoglobin 95 g/dl; normal 120-180 g/dl) and an elevated C-reactive protein (CRP) at 164 mg/l (normal <10 mg/l). Creatinine is elevated at 160 µmol/l (normal 60-90 µmol/l). Urinalysis reveals 1.5 g/l of protein (1.8 g/day), without hematuria or casts.

1. *Describe the most common clinical features of polyarteritis nodosa.*
2. *What other investigations would you order to confirm the diagnosis and rule out differential diagnoses?*

The diagnosis of polyarteritis nodosa (PAN) is confirmed on the basis of the patient's symptoms and the investigations you ordered.

3. *What is this patient's five-factor score?*
4. *What induction therapy would you recommend?*
5. *What is the usual prognosis and risk of relapse of polyarteritis nodosa?*
6. *What is DADA2 (deficiency of adenosine deaminase-2)?*

Learning objectives

1. To describe the prevalence, typical demographics and clinical characteristics of polyarteritis nodosa (PAN).
2. To describe the diagnostic investigations and the treatment of patients with PAN.
3. To understand the role of hepatitis B virus (HBV) infection in patients with PAN-type vasculitis, and how to manage this HBV-associated vasculitis.
4. To describe the main outcomes of patients with PAN.
5. To recognize deficiency of adenosine deaminase-2 (DADA2) as a genetically determined form of PAN, and know about other genetically determined vasculitides or vasculopathies.

Answers

1. Describe the most common clinical features of polyarteritis nodosa.

Polyarteritis nodosa (PAN) was among the first systemic vasculitides described, in the late 1860s. It is a systemic, necrotizing medium-sized vessel vasculitis. PAN primarily affects people between the ages of 40-60 years, with a mild male, but no ethnic, predilection. In the 1990-2000s, its annual incidence was around 1-8 cases/million in Europe and its prevalence was about 20-30 cases/million. The main etiology of PAN in those past decades was (primo-)infection with hepatitis B virus (HBV). With the development of anti-HBV vaccine and vaccination campaigns since the early 1990s, and reinforced blood transfusion safety policies, the incidence of HBV primo-infection and, subsequently, HBV-related PAN have dramatically decreased. Prior to vaccination against HBV, one-third to half of PAN cases were attributed to HBV. Today, that rate is only 5%. According to the revised 2012 Chapel Hill consensus conference (Table 4.1), HBV-associated vasculitis is now classified distinctly from (idiopathic, primary) PAN. Hepatitis C virus (HCV) has also, more rarely, been associated with medium-sized (PAN-type) vasculitis (HCV is more associated with cryoglobulinemic vasculitis – see Case 16).

The clinical features of PAN relate to which organs are affected. Systemic symptoms are common and include fever, chills, night sweats, myalgias, arthralgias, anorexia and weight loss. The most frequently involved organ systems are the peripheral nervous system (50-75% of patients), manifested as sensorimotor mononeuritis multiplex, as in this case, the skin (30-60%) with palpable purpura, often necrotic, livedo reticularis, or subcutaneous nodules. Gastrointestinal and renal involvement are also common (15-40% and 10-60%, respectively); the latter being manifested as renal infarcts which can cause hypertension and produce micro- or macroscopic hematuria with mild-to-moderate proteinuria in addition to hypertension (glomerulonephritis does not occur in PAN). Central nervous system (CNS) involvement is rare (3-25%) and can cause strokes. Recurrent strokes in a young (often pediatric) patient with a PAN-like presentation should prompt genetic testing for DADA2. Patients with HBV-associated PAN have more frequent peripheral neuropathy, abdominal pain, orchitis, cardiomyopathy (5-20% of patients with PAN), and hypertension compared with patients with non–HBV-related PAN.

Single-organ PAN is a rare form of PAN that has been described to affect essentially any internal organ (apart from the lungs), including the gallbladder, appendix, testicles and breasts, among others. These patients can often be treated with surgical excision alone, though monitoring for systemic involvement is still advised. When single-organ PAN presents as an isolated medium-sized cutaneous disease, it can be called cutaneous arteritis.

The 1990 ACR criteria included: 1) weight loss of ≥4kg; 2) livedo reticularis; 3) testicular pain or tenderness; 4) myalgias, weakness or leg tenderness; 5) mononeuropathy or polyneuropathy; 6) diastolic blood pressure >90 mmHg; 7) elevated blood urea nitrogen >40 mg/dl or creatinine >1.5 mg/dl; 8) HBV; 9) arteriographic abnormality (aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other non-inflammatory causes); 10) biopsy of small- or medium-sized vessel containing polymorphonuclear neutrophils. A patient was classified as having PAN if at least three of the 10 criteria were present, with a sensitivity and specificity of 82.2% and 86.6%, respectively. These criteria were intended for research classification only. They were limited in a variety of ways, specifically in their inability to

distinguish PAN from microscopic polyangiitis (which was described later in 1994 by the Chapel Hill consensus conference, after the discovery of antineutrophil cytoplasm autoantibodies [ANCA] in the late 1980s). Collaborative international efforts are still ongoing to develop new classification criteria for PAN (ACR/EULAR DCVAS).

Table 4.1. Place and definition of PAN in the nomenclature of systemic vasculitides by the 2012 Chapel Hill consensus conference group (note that PAN no longer referred to or included HBV-associated vasculitis, and that a dermatological addendum was published in February, 2018 [integrated in this Table]).

Large-vessel vasculitides*: Giant cell arteritis; Takayasu arteritis
Medium-sized-vessel vasculitides:
Polyarteritis nodosa
Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasm antibodies (ANCAs).
Kawasaki disease
Small-vessel vasculitides:
ANCA-associated vasculitides†
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Microscopic polyangiitis
Immune-complex small-vessel vasculitides
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulinemic vasculitis
Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
Anti-glomerular basement membrane disease (with anti-GBM antibodies)
Variable vessel vasculitides: Behçet disease; Cogan syndrome
Single-organ vasculitides: cutaneous IgM/IgG immune complex vasculitis; nodular cutaneous vasculitis; erythema elevatum diutinum; recurrent macular vasculitis in hypergammaglobulinemia; normocomplementemic urticarial vasculitis; primary central nervous system vasculitis; isolated aortitis; others
Vasculitides associated with systemic disease: lupus vasculitis; rheumatoid vasculitis; sarcoid vasculitis; others
Vasculitides associated with probable etiology: HCV–associated cryoglobulinemic vasculitis; HBV–associated vasculitis; syphilis-associated aortitis; drug-associated immune complex vasculitis; drug-associated ANCA-associated vasculitis; cancer-associated vasculitis; others (which would now include genetically determined vasculitis or vasculopathy such as DADA2)

** Large vessels are the aorta and its major branches and the analogous veins. Medium vessels are the main visceral arteries and veins and their initial branches. Small vessels are intraparenchymal arteries, arterioles, capillaries, venules, and veins. It is important to remember that different sizes of vessels can be involved in every type of vasculitis. For example, whereas medium-sized vessels are predominantly affected in PAN, it is very common to also observe some small vessel involvement.*

† Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e. capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g. MPO-ANCA, PR3-ANCA, ANCA negative.

2. What other investigations would you order to confirm the diagnosis and rule out differential diagnoses?

The differential diagnosis for PAN is broad and can apply to almost any other systemic vasculitis. It includes:

- **Infections**: especially infectious endocarditis; serologies for HBV and HCV are mandatory as the treatment of HBV- or HCV-associated vasculitides differs (and "HBV-related PAN" should no longer be used as PAN now refers only to PAN without an identified cause)
- Multifocal **embolic** and/or **thrombotic** conditions: atrial myxoma, antiphospholipid syndrome, thrombotic microangiopathy, hypercoagulability disorders
- **Atherosclerosis**
- Malignant **hypertension**
- **Celiac axis stenosis**, secondary to atherosclerosis or compression by the median arcuate ligament with subsequent development of mesenteric aneurysms due to increased flow
- **Calciphylaxis** (vascular calcification with thrombosis and skin necrosis, mostly described in patients with chronic kidney disease)
- **Toxic**: ergot use and ergotism
- **Vasculopathy** (non-inflammatory): fibromuscular dysplasia, Ehlers-Danlos, Marfan syndrome, Loeys-Dietz syndrome, Grange syndrome, Turner syndrome, segmental arterial mediolysis
- **Malignancies**: especially lymphoma (which can be intravascular), myelodysplasia or solid cancers (with embolic lesions or paraneoplastic vasculitis)
- **Metabolic**: Fabry's disease, diabetes mellitus (the main cause in general of mononeuritis multiplex)
- **Thromboangiitis obliterans** (Buerger's disease): a smoking-induced inflammatory vasculopathy characterized by thrombus formation in small and medium blood vessels, usually affecting the distal lower extremities.
- Other **systemic inflammatory conditions**, including other small- or medium-sized vasculitides (e.g. cryoglobulinemic vasculitis or ANCA-associated vasculitides), systemic lupus or inflammatory myositis

The investigations to order should thus aim at excluding those possible differentials, and provide, if possible and feasible, some clear evidence of medium-sized vasculitis, with a biopsy of an affected organ and/or vessel imaging.

There is no standard, consensus laboratory work-up for PAN, but it must include complete blood count (with differential cell count) to look for anemia and elevated neutrophil count, creatinine level, urinalysis, C-reactive protein, liver enzymes with aspartate/alanine aminotransferase, blood glucose level, coagulation tests, serum protein electrophoresis, blood cultures, HBV and HCV serologies. Other serologies should be considered, including for human immunodeficiency virus (HIV) as well as antinuclear antibodies (ANA), ANCA, complement fraction, cryoglobulin, HbA1c, lipid profile, and blood smears.

Besides conventional radiographic studies (chest X-ray, abdomen ultrasound and/or CT) to assess end-organ lesions and/or rule out differentials (e.g. echocardiography to rule out endocarditis), vessel imaging should be considered. Whereas conventional renal and celio-mesenteric angiography represented the gold standard for the past decades, high-resolution CT and MR angiographies can now reveal vessel lesions of medium-sized vessels as well. Typical findings in PAN include segmental arterial lesions that usually occur in branching points, with multiple saccular or fusiform micro-aneurysms of about 1–5 mm in diameter, coexisting with stenotic lesions (beading appearance; Figure 4.1). The most commonly affected arteries are the renal, mesenteric and hepatic artery branches.

Biopsy of an affected organ can demonstrate necrotizing vascular inflammation of medium- and, often, small-sized arteries, mainly with neutrophils in early active lesions. The diagnostic yield is dependent on the tissue biopsied. Muscle and nerve tissue sensitivity is about 80% in patients with neuromuscular manifestations. Gastrointestinal (GI) biopsies have low sensitivity as they are often too superficial (sensitivity is <10% for gastric and around 30% for colon biopsy) and carry a risk of perforation (especially if trying to have deep mucosal samples). Due to the risk of aneurysm rupture, biopsies of highly vascular tissues such as liver and kidneys are not recommended and may be extremely hazardous. In addition, as renal involvement in PAN is related to infarcts and not glomerulonephritis, there is no reason or interest in PAN in biopsying the kidneys for diagnostic confirmation.

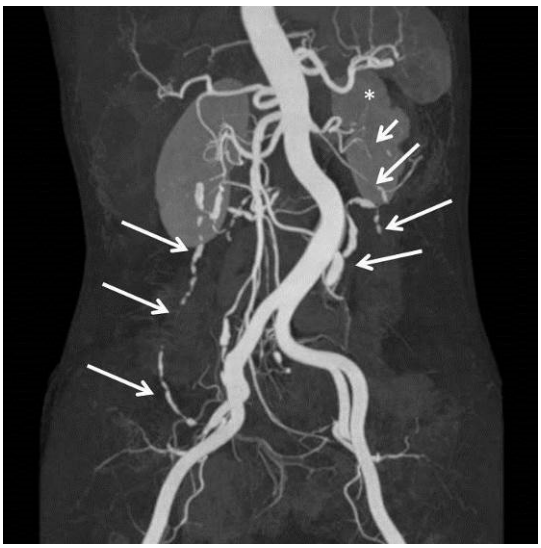


Figure 4.1. CT angiography of the abdomen, coronal view. Multifocal aneurysms of the visceral branches of the mesenteric vessels (arrows) in a 45-year-old woman with probable PAN. The left renal artery is also beaded and ectatic, and the left kidney (asterix) shows irregular cortical contour, suggestive of previous infarcts (there is also a benign cyst).

3. What is this patient's five-factor score?

The original 1996 Five-Factor Score (FFS) is a survival prognostic score that was developed based on the analysis of a French cohort of patients with PAN, eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss syndrome) or microscopic polyangiitis (MPA). The five identified poor prognostic markers included:

1. Cardiomyopathy due to vasculitis
2. CNS involvement due to vasculitis
3. Severe GI tract symptoms due to vasculitis (including gut infarction or GI bleeding)
4. Serum creatinine level >140 µmol/l (1.58 mg/dl)
5. Proteinuria >1 g/day

Patients with zero, one or ≥2 of these parameters had 5-year mortality rates of 12%, 26% and 46%, respectively. In addition, survival of patients with one or more of these parameters was better when they had been treated more aggressively with a combination of glucocorticoids (GC) and cyclophosphamide (CYC) than with GC alone. Survival of patients with FFS=0 was good with GC therapy alone.

A repeat analysis of the same French cohort, but with more patients and including granulomatosis with polyangiitis (GPA; Wegener's), was conducted in 2011. The parameters associated with higher mortality in this revised FFS were:

1. Age at diagnosis >65 years
2. Cardiac symptoms due to vasculitis
3. GI involvement related to vasculitis
4. Serum creatinine peak level at diagnosis ≥150 µmol/l
5. Absence of ear, nose and throat (ENT) symptoms for GPA and EGPA patients only

Patients with zero, one or ≥2 of these parameters had 5-year mortality rates of 9%, 21% and 40%, respectively. The revised FFS is useful when

discussing prognosis with patients but has not been studied or validated for therapeutic guidance and therefore, should not be used to guide treatment decisions (only the original FFS can be used for therapeutic guidance).

In this case, the patient's (original) FFS is 3 on the basis of a creatinine of 160 µmol/l, proteinuria 1.8 g/day and GI involvement (pain and hematochezia). Revised FFS is 2 (creatinine peak of 160 µmol/l and GI involvement).

4. What induction therapy would you recommend?

As stated above, patients with FFS=0 can be initially treated with GC alone. By doing so, however, up to 40% may require the addition of another immunosuppressant because of refractory disease or relapse. The systematic first-line addition of azathioprine (AZA) did not appear to lower this latter rate. The immunosuppressant to add is decided based on the clinical manifestations (most often: CYC if FFS≥1, AZA or methotrexate [MTX] if FFS=0). Severe, progressing mononeuritis multiplex remains a debated and challenging situation, as it can require an immunosuppressant, in combination with GC, even in patients with FFS=0. However, no study has yet been conducted to demonstrate that such combination improves neurological recovery, compared with GC alone, in PAN (or other systemic vasculitides).

Given the original FFS of 3 in this patient case, a combination of GC and CYC must be considered, if the patient is HBV- and HCV-negative. Induction therapy includes pulse GC for more severe forms, with IV methylprednisolone 7.5-15 mg/kg per pulse, daily for 1-3 days, followed by prednisone at a dose of 1 mg/kg/day. CYC can be given orally at 2 mg/kg/day (maximum daily dose 200 mg daily) or with IV pulses at 15 mg/kg (dose not to exceed 1200 mg) every 2 weeks for the first three pulses, then every 3 weeks for the next three to six subsequent pulses (dose to decrease by 25-50% in patients >65 years old and to adjust to renal function). Once remission has been achieved (defined as sustained absence of active systemic features, normalization of inflammatory markers), usually after 3 to a maximum of 6 months of CYC, the patients can be transitioned to maintenance therapy (with AZA for example at 2 mg/kg/day, MTX at 20-25 mg/week, or leflunomide at 20 mg/day). The duration of treatment should be a minimum of 18 months, but RCT are lacking to determine when it can be optimally stopped.

In case of refractory disease, the diagnosis should be reviewed again, and genetically determined forms of vasculitis should be considered. TNF-α inhibitors and tocilizumab have been used successfully in small case series of refractory PAN (but some of these patients might have had DADA2 (deficiency of adenosine deaminase-2) or another genetic condition), while rituximab does not seem to offer substantial benefit.

Treatment for HBV-associated vasculitis involves the initial use of high-dose GC (as detailed above) in combination with antiviral therapy (nowadays, mainly entecavir [0.5 mg/day] and/or tenofovir disoproxil fumarate [300 mg/day]) and plasma exchange (until seroconversion HBe-Ag to HBe-Ab occurs). CYC is avoided and the duration of GC therapy should be limited (≤3 months), unless the disease worsens despite the former regimen. As HBV-associated vasculitis has become extremely rare, the management of affected patients should ideally be discussed with physicians from a referral centre for vasculitis.

5. What is the usual prognosis and risk of relapse of polyarteritis nodosa?

Untreated, PAN carries a poor prognosis, with a 5-year survival rate of <13%. The prognosis is worse in patients with FFS>0 and/or major organ involvement. With treatment, prognosis has improved, with a 5-year survival rate of 60–80%,

varying according to the FFS, as detailed above. Patients with HBV-associated PAN previously had a poorer prognosis. Their global 5-year survival rate was previously quoted at 35%, but with newer antiviral therapy, would likely be better if re-assessed today.

Unlike ANCA-associated vasculitides, PAN is most often a monophasic disease, with a lower relapse rate. In a large French cohort, the rates of relapse after a mean follow-up of 68 months were 28% in patients with PAN and 11% in those with HBV-associated vasculitis. The relapse rate of "cutaneous, isolated PAN" (cutaneous arteritis) is higher (around 50%).

Complications related to the disease and/or its treatment are frequent in survivors, mainly nerve damage resulting in persistent weakness or numbness. In order to limit the possible side effects of GC, patients should be initiated on calcium (600-1200 mg/day), vitamin D (1000-2000 IU daily) and, when indicated according to osteoporosis guidelines, a bisphosphonate for the duration of GC use. Patients on IV CYC should receive bladder protection with mesna and all patients on IV or oral CYC should receive systematic prophylactic preventative therapy for *Pneumocystis jiroveci* pneumonia (PJP) with trimethoprim/sulfamethoxazole (160/800 mg 1 tablet DS 3 times per week, or 80/400 mg daily), while on CYC and for 3 months more after CYC cessation. Patients in whom trimethoprim/sulfamethoxazole compounds are contraindicated (for example, due to sulfa allergies) should be given alternate prophylaxis with either dapsone, atovaquone or aerosolized pentamidine.

6. What is DADA2 (deficiency of adenosine deaminase-2)?

Deficiency of adenosine deaminase-2 (DADA2) is an autosomal recessive inflammatory vasculopathy caused by mutations in the ADA2 (formerly CERC1) gene that is typically diagnosed in childhood and clinically resembles idiopathic PAN. The first case series were reported in 2014. The disease is characterized by a variable combination of systemic inflammation, early-onset strokes, livedoid rash, bone marrow dysfunction and/or recurrent infections due to immunodeficiency (hypogammaglobulinemia). First-line treatment for DADA2 is with TNF-α inhibitors. In the case of severe bone marrow dysfunction or immunodeficiency, hematopoietic stem cell transplant may be considered. Gene therapy and transfer strategies are under investigation, but are still only at the animal and cell level.

Other genetically determined vasculopathies have been identified since then, including SAVI and the more recently discovered VEXAS syndrome (see Table 4.2).

Table 4.2. Summary of the main, currently known genetically determined conditions with possible vasculitis

	Genetic abnormality	Manifestations	Treatment
DADA2 (Deficiency of adenosine deaminase-2)	Autosomal recessive loss-of-function mutation in ADA2 (formerly CERC1)	Systemic inflammation, livedoid rash, early-onset strokes, cytopenias, bone marrow failure, recurrent infections, hypogammaglobulinemia. **Usually in children**, but can occur and be diagnosed later (up to the 60s)	TNF-α inhibitors Hematopoietic stem cell transplant (HSCT) for severe bone marrow dysfunction or immunodeficiency
SAVI (STING-associated vasculopathy with onset in infancy)	Autosomal dominant, gain-of-function mutation in stimulator of interferon gene STING1	**Neonatal-onset** systemic inflammation with small-vessel vasculopathy, failure to thrive, chronic fevers, interstitial lung disease, severe cutaneous lesions affecting acral regions (fingers, toes, nose, cheeks and ears) leading to skin ulcers and necrosis, polyarthritis	Potential benefit with JAK inhibitors **Poor response** to glucocorticoids and other conventional immunosuppressive agents
VEXAS (Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) **syndrome**	Somatic mutations in ubiquitin-like modifier activating enzyme 1 gene (UBA1)	**Adult-onset** inflammation, fevers, cytopenias, painful skin rashes, myelodysplasia, neutrophilic cutaneous and pulmonary inflammation, chondritis, vasculitis. Described mainly in older males, most patients meet criteria for an inflammatory syndrome (e.g. relapsing polychondritis, Sweet's syndrome, PAN or GCA)	**Poor response** to glucocorticoids and conventional immunosuppressive agents

References

Guillevin L et al. Prognostic Factors in Polyarteritis Nodosa and Churg-Strauss Syndrome: A Prospective Study in 342 Patients. Medicine 1996;75(1): 17-28.

Pagnoux C et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. Arthritis Rheum 2010;62(2):616.

Guillevin L et al. The Five-Factor Score Revisited – Assessment of Prognoses of Systemic Necrotizing Vascuitides Based on the French Vasculitis Study Group Cohort. Medicine 2011;90(1):19-27.

Jennette JC et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65(1):1-11.

Zhou Q et al. Early-onset Stroke and Vasculopathy Associated with Mutations in ADA2. NEJM 2014;370(10):911-20.

Puéchal et al. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial. Arthritis Rheumatol. 2017 Nov;69(11):2175-86.

Sunderkötte et al. Nomenclature of Cutaneous Vasculitis: Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheumatol 2018;70(2):171-84.

Human A & Pagnoux C. Diagnosis and management of ADA2 deficient polyarteritis nodosa. International Journal of Rheumatic Diseases 2018;22(S1):69-77.

Beck DB et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. NEJM 2020;383:2628-38.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa. Arthritis Rheumatol 2021;73(8):1384-93.

Case 5
Kawasaki disease

An 8-month-old boy with no past or familial medical history (parents are originally from South Asia) presents to the hospital with a 5-day history of fever (up to 39.3^{0}C) associated, for the past 3 days, with a diffuse erythematous maculopapular rash, most marked in the groin area, non-purulent conjunctivitis, red cracked lips with a strawberry tongue (Figure 5.1), and sore throat. On examination, multiple left cervical and submandibular enlarged lymph nodes are also noted (Figure 5.2). Chest auscultation and neurological examinations are normal.

1. *What is the most likely diagnosis? What are the main presenting clinical features of this disease and its differentials?*
2. *List the possible complications of Kawasaki disease.*
3. *What investigations would you order for the work-up of this patient?*
4. *How would you treat this patient?*
5. *What is the role of glucocorticoids in the treatment of Kawasaki disease?*
6. *What is multisystem inflammatory syndrome in children (MIS-C)? How is it distinguished from Kawasaki disease?*

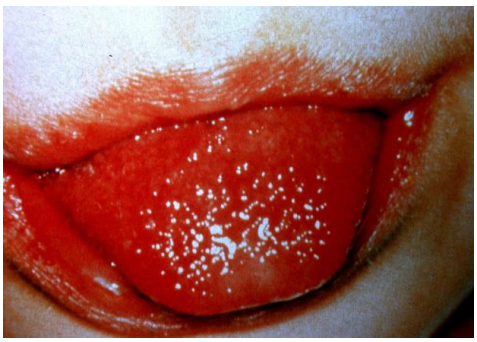


Figure 5.1. Strawberry tongue.



Figure 5.2. Left cervical lymphadenitis.

Learning objectives

1. To describe the prevalence, typical demographics, clinical characteristics and possible complications of Kawasaki disease (KD).
2. To develop a time-efficient diagnostic management plan for patients with suspected KD.
3. To list first-line and second-line therapies used in the treatment of KD.
4. To recognize Multisystem Inflammatory Syndrome in Children (MIS-C) due to COVID-19 as a mimicker of KD.

Answers

1. What is the most likely diagnosis? What are the main presenting clinical features of this disease and its differentials?

Kawasaki disease (KD) must clearly be considered in this case.

KD is an acute, medium-sized vessel vasculitis that predominantly affects children below the age of 5 years, especially of Asian descent, and with a male predilection. Its annual incidence is between 5 to 90 per 100,000 children 0-5 years old in the USA and Canada, greater in areas with high Asian populations, and up to 260-2000 per 100,000 children 0-5 years old in Japan. It can more rarely affect neonates, older children or adults, most often with an incomplete KD form in the latter. There are epidemics and seasonal variations in the incidence of KD, which is higher in winter in Canada, likely because environmental factors (e.g. changing wind patterns, possibly carrying a triggering agent, possible microbial material in the troposphere or heavy metal particles such as mercury or cadmium) and/or infections are involved in its pathogenesis, in addition to genetic predispositions.

Clinically, KD most characteristically presents initially with fever and irritability, then mucosal manifestations (e.g. conjunctival edema, cracked lips [cheilitis], strawberry tongue), skin rash, most often erythematous maculopapular, and can have perianal and perineal desquamation (within the first 5 days of fever), swelling of dorsum of the hands and feet, with redness of the palms and soles, and cervical lymphadenopathies, often unilateral and greater than 1.5 cm in diameter. Periungual desquamation of hands and feet is also classical in KD but occurs later, during the subacute phase of the disease when fever has subsided.

Diagnostic criteria for KD, according to the American Heart Association (AHA), include a mandatory item of fever persisting for at least 5 days although the presence of other classical features may be sufficient to consider the diagnosis earlier (fever is not mandatory in the Japanese Ministry of Health definition of the disease), and the presence of at least four of the following five principal features:

- Changes in extremities: acute: erythema and edema of hands and feet, coalescent; desquamation of fingers and toes in week 2 and 3
- Polymorphous exanthema
- Bilateral, painless bulbar conjunctival injection without exudates
- Changes in lips and oral cavity: erythema and cracking of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosae
- Cervical lymphadenopathy (≥1.5 cm in diameter), usually unilateral and anterior

Patients with fever and fewer than four principal features can also be diagnosed with KD – incomplete KD.

Other diagnoses should be excluded, but without delaying the treatment of KD if suspicion of the latter is high. The main ones are infections, especially viral (e.g. measles or dengue), but also group A streptococcus bacterial scarlet fever, toxic shock syndrome and staphylococcal scalded skin syndrome, bearing in mind that coexisting infectious agents do not exclude the diagnosis of KD. Other possible mimickers include Stevens-Johnson syndrome, systemic onset juvenile idiopathic arthritis (Still's disease), or Sweet's syndrome. Other vasculitides, especially PAN, are rare in children and do not present with all those typical skin and mucosal lesions of KD.

2. List the possible complications of Kawasaki disease.

The most dreaded manifestation of KD is the development of coronary artery aneurysms, which can occur in up to 25% of cases if KD is not promptly recognized and appropriately treated, and still in 5–7% (up to 18% in a few series) of the children treated with intravenous immunoglobulins (IVIg). Those coronary artery aneurysms can be giant (Figure 5.3) with a potential for intravascular thrombus formation, the most serious acute complication of KD.

In children, transthoracic echocardiography is usually able to assess the absolute dimensions of the coronary arteries and body surface area–adjusted Z scores (i.e. standard deviations above or below age- or size-adjusted measurements), along with the other usual parameters (e.g. ejection fraction).



Figure 5.3. Giant coronary aneurysm (coronary angiography in a patient with KD).

If not initially fatal, undiagnosed KD with coronary involvement can also lead to accelerated myocardial ischemia and infarcts in early adulthood. Even small- to moderate-sized aneurysms that apparently regress or resolve on follow-up echocardiography in childhood can lead to stenosis and thrombosis decades later (there is no consensus on the follow-up of adults with a history of KD, and this risk must be kept in mind).

Other common complications during the acute phase of disease are related to the multisystem inflammation and include inflammatory arthritis, gallbladder hydrops, hepatitis, KD shock/myocarditis and macrophage activation syndrome.

Rarely, KD can cause lesions in other arteries and cause peripheral artery aneurysms, ischemia and ischemic gangrene of the extremities, strokes or ischemic bowel perforations.

3. What investigations would you order for the work-up of this patient?

There is to date no specific laboratory test to confirm KD but the AHA has recommended a list of supplementary laboratory features that support a diagnosis of KD, especially in those with incomplete features. Laboratory investigations should include C-reactive protein (or ESR) to look for inflammation, complete blood count (with differential cell count), liver enzymes with aspartate/alanine aminotransferases, serum albumin, and urinalysis. Supplementary laboratory criteria include the following: hypoalbuminemia, anemia for age, elevated transaminases, elevated platelet count after day 7 of illness, elevated WBC and sterile pyuria. Those with fever but only 3 or fewer compatible clinical criteria, and with at least 3 of these supplementary laboratory criteria, or a positive echocardiogram in the presence of elevated CRP/ESR, can be considered to have incomplete KD.

Early electrocardiogram and echocardiography should be systematically done at the time of the initial presentation during the acute phase of illness with a follow-up echocardiogram in

all children 4-6 weeks later. Earlier and more frequent echo follow-up may be required in the presence of coronary artery lesions.

4. How would you treat this patient?

There are no specific Canadian guidelines for KD, but in 2021, the American College of Rheumatology/Vasculitis Foundation published their guidelines for its management. The patient requires admission and prompt treatment for KD, which includes an infusion of IVIg (2 g/kg over 10-12 hours), and aspirin. There is still debate around whether or not there is a need for high-dose aspirin initially, which also varies by region and studies, from 30–50 mg/kg/day in Japan to 80-100 mg/kg/day in North America. After the initial high-dose aspirin treatment (or directly if no high-dose), a lower daily antiplatelet dose of 3-5 mg/kg should be given for at least 6 to 8 weeks until all laboratory signs of inflammation have subsided and the echocardiogram is normalized. IVIg should optimally be given during the acute phase of illness, which in most studies has been defined as within the first 10 days after onset of fever. IVIg can reduce inflammation and clinical symptoms but also prevent the development of coronary artery abnormalities (decreases the incidence of coronary artery abnormalities from 18%-25% to 4%-5%). There is an urgency to make the diagnosis of KD and initiate treatment. The best predictor of poor coronary outcome is the duration of fever.

IVIg acts via several mutually nonexclusive mechanisms, including the inhibition of activation of several immune cells, such as dendritic cells (DCs), macrophages, monocytes or neutrophils, the modulation of B-cell responses, the suppression of inflammatory cytokines, such as IL-1, IL-6, IL-10, IL-17A and interferon-gamma, or the inhibition of TNF-alpha-induced nuclear factor kappa (NF-kB) activation in monocytes and macrophages, and also anti-microbial and anti-cytokine antibodies.

Up to 30% of patients have persistent or recurrent fever after the initial IVIg infusion, thus have resistant or refractory KD. They have a higher risk of developing coronary aneurysms (12% versus <2% in those who responded to the initial IVIg infusion in one study). There are no perfect predictors or risk scores (e.g. the Kobayashi risk score or the more recent Kawanet score, which includes hepatomegaly, ALT level>30 IU/L, lymphocyte count <2400/mm^3 and time to treatment <5 days) to help with the accurate and early identification of those patients in every ethnic population. Patients with refractory KD may receive a second infusion of IVIg (same dose) and additional treatments should be considered, including glucocorticoids (GC), cyclosporin A, TNF antagonists and IL-1 blockers – see below.

The rate of late recurrence of KD is low, estimated around 1–2% or 3 episodes/1,000 patient-years, at a median of 1.5 years after the initial episode (range, 2 weeks-5 years).

5. What is the role of glucocorticoids in the treatment of Kawasaki disease?

Patients with resistant or refractory KD are challenging and are usually given systemic GC and additional IVIg. If there is no response to this treatment, then an anti-TNF-alpha agent should be considered. However, most studies of GC therapy with additional IVIg treatment for refractory KD and a meta-analysis on TNF-alpha blockers as first-line therapy showed that both options were associated with significantly faster resolution of fever, but similar rates of treatment resistance and coronary artery aneurysms.

The 2021 American College of Rheumatology/ Vasculitis Foundation Guideline for the Management of Kawasaki Disease also states that for “acute KD and persistent fevers after repeated treatment with IVIg, either non-GC immunosuppressive therapy or GC may be used.”

The latter guidelines also suggest that "for patients with acute KD who are at high risk of IVIg resistance or developing coronary artery aneurysms, use of IVIg with adjunctive GC as initial therapy is conditionally recommended over treatment with IVIg alone." A recent French National document (https://www.has-sante.fr/jcms/p_3363015/fr/maladie-de-kawasaki) on KD similarly recommends treatment with IVIg and GC patients with the most severe forms, defined as age <1 year, presence of shock and/or macrophagic activation syndrome, and/or early development of coronary artery dilations or aneursyms.

The role of methotrexate, cyclophosphamide, cyclosporine A, IL-1 receptor antagonists, IL-6 inhibitors, and plasma exchange remains uncertain.

6. What is multisystem inflammatory syndrome in children (MIS-C)? How is it distinguished from Kawasaki disease?

In early 2020, after COVID-19 was declared a global pandemic, a new hyperinflammatory shock syndrome, termed multisystem inflammatory syndrome in children (MIS-C), was identified in a small number of children several weeks after COVID-19 exposure. Presentation is similar to incomplete KD, with additional core features of unrelenting fever, gastrointestinal symptoms, and shock. Other symptoms are typical of KD, including rash, conjunctivitis and mucosal involvement. Cardiac involvement (including myocardial dysfunction and coronary aneurysms) has also been described. Onset of MIS-C is usually 2-6 weeks after acute COVID-19 infection or exposure, though longer lag times have been reported.

Whether MIS-C is distinct from KD or on the same disease spectrum remains a subject of debate, but MIS-C appears on the more severe end of the inflammation spectrum, with more severe cardiac (hypotension/shock) and MAS features compared with pre-pandemic KD. Despite many children with MIS-C also meeting criteria for complete or incomplete KD, both syndromes are heterogeneous and have both shared and differentiating features including:

- MIS-C more commonly affects older children and in more racialized communities that are also more often affected by COVID.
- Gastrointestinal symptoms (especially abdominal pain) is more common and severe in MIS-C than in KD.
- Cardiac involvement typically presents as myocardial dysfunction in MIS-C, whereas in KD, coronary aneurysms are the main cardiac feature, though patients with MIS-C can also develop coronary aneurysms.
- At presentation, children with MIS-C tend to have lower platelet counts, lymphopenia, and higher CRP levels than those with KD, reflecting MAS/evolving MAS.

Similar to KD, management for MIS-C involves hospital admission and close cardiac monitoring. Treatment consists of an infusion of IVIg (2 g/kg), glucocorticoids with prednisone-equivalent dose of 1-2 mg/kg/day (pulse therapy may be needed if shock and/or if MAS is present), and low-dose aspirin (until normalization of platelet count and normal coronary artery imaging at 4 weeks after diagnosis). Anakinra (>4 mg/kg/day SC or IV) may be considered for refractory disease or when there are features of macrophage activation syndrome.

References

Newburger JW et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation 2004;110(17):2747-71.

Lin YT et al. Repeated systematic surveillance of Kawasaki disease in Ontario from 1995 to 2006. Pediatr Int 2010;52(5):699-706.

Luca NJ, Yeung RS. Epidemiology and management of Kawasaki disease. Drugs 2012;72(8):1029-38.

Shulman ST, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. Nat Rev Rheumatol 2015;11:475–82.

Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. J Am Coll Cardiol 2016;67(14):1738-49.

Rodó X et al. Revisiting the role of environmental and climate factors on the epidemiology of Kawasaki disease. Ann N Y Acad Sci 2016;1382(1):84-98.

Riphagen S et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395(10237):1607-8.

Yeung RS, Ferguson PJ. Is multisystem inflammatory syndrome in children on the Kawasaki syndrome spectrum? J Clin Invest 2020;130(11):5681-5684.

Piram M et al. Defining the risk of first intravenous immunoglobulin unresponsiveness in non-Asian patients with Kawasaki disease. Sci Rep 2020;10:3125.

McArdle AJ et al. Treatment of Multisystem Inflammatory Syndrome in Children. N Engl J Med 2021;385(1):11-22.

Gorelik M et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Kawasaki Disease. Arthritis Rheumatol 2022;74(4):586-596.

Henderson LA et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. Arthritis Rheumatol 2022;74(4):e1-e20 [Epub].

Case 6

Granulomatosis with polyangiitis – diagnosis and induction treatment of severe disease

A 22-year-old woman presents to the emergency department with hemoptysis and respiratory distress. She has a 4-month history of rhinitis and sinusitis, for which she took several ineffective courses of antibiotics, and a 3-week history of progressive fever with cough. She has no significant past medical or social history and no known allergies. On examination, she looks pale, with blood pressure of 90/75 mmHg, a rapid regular heart rate at 120 beats per minute, buccal temperature of 38.2^{0}C, and is tachypneic with a respiratory rate of 28 per minute. Her weight is 65 kg and height is 161 cm. Auscultation of the chest reveals bilateral crackles and decreased air entry. Her oxygen saturation on room air is 86% (then 94% with 6 l/min oxygen on Venturi mask). Electrocardiogram (ECG) shows rapid sinus rhythm. Portable chest X-ray (Figure 6.1) reveals bilateral, diffuse alveolar consolidation with possible nodules and moderate bilateral pleural effusion.

1. *What other investigations would you order in this patient?*

The patient also has acute kidney injury, with a serum creatinine level of 467 µmol/l (normal 60-90 µmol/l) and 3+ microscopic hematuria and 3+ proteinuria on urine dipstick (leukocytes and nitrites are negative). Her C-reactive protein is 211 mg/l (normal <10 mg/l), serum albumin is 34 g/l (normal 40-53 g/l), liver enzymes are normal, troponin is normal, and D dimer is 4.89 mg/l (normal 0–0.5 mg/l). Her ANCA screening test by ELISA is positive for PR3-ANCA at 732 chemiluminescent units (CU; normal <20 CU), and negative for MPO-ANCA (at <2 CU, with normal <20 CU).

2. *List the different ANCA-associated vasculitides; explain what ANCA stands for and how it is detected and measured.*
3. *List the causes of a positive ANCA test other than the primary ANCA-associated vasculitides.*
4. *What are the new 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for GPA?*
5. *What induction therapy would you initiate in this patient?*



Figure 6.1. Portable antero-posterior chest X-ray of the lungs.

Learning objectives

1. To describe the different tests used to detect antineutrophil cytoplasm antibodies (ANCA) and their interpretation in the appropriate clinical settings.
2. To establish a treatment plan for the induction of remission of systemic granulomatosis with polyangiitis (GPA).
3. To list the main clinical trials that helped devise the current induction treatment strategies for GPA.

Answers

1. What other investigations would you order in this patient?

This patient may have vasculitis, particularly granulomatosis with polyangiitis (GPA). The investigations will aim at confirming this diagnosis and ruling out differential diagnoses and/or associated conditions, especially infections. The patient will also be screened for potential target-organ involvement, and to obtain baseline values for the most important parameters that can impact treatment choices. As listed in the CanVasc recommendations for the management of ANCA-associated vasculitides, the suggested investigations for this patient should include complete blood cell count (to look for normochromic/normocytic anemia, thrombocytosis and leukocytosis), CRP, liver enzymes, serum creatinine, urinalysis (granular casts, proteinuria, hematuria), and ANCA.

In order to rule out other inflammatory conditions, antinuclear antibodies (ANA), anti-glomerular basement membrane antibodies (anti-GBM), C3, C4, rheumatoid factor should be ordered. To rule out or diagnose associated infections, sputum sample for gram and culture, as well as blood and urine cultures should also be ordered, as necessary. HBV, HCV and HIV serologies should also be checked at baseline.

In addition to the chest X-ray, a CT of the chest (Figure 6.2) should be considered. High-resolution chest CT (without contrast, as it is not needed and is contraindicated if serum creatinine is high) will provide the most detailed information in terms of characterizing pulmonary infiltrates and nodules. CT of the sinuses can also be considered as well as a renal ultrasound (before a possible kidney biopsy).

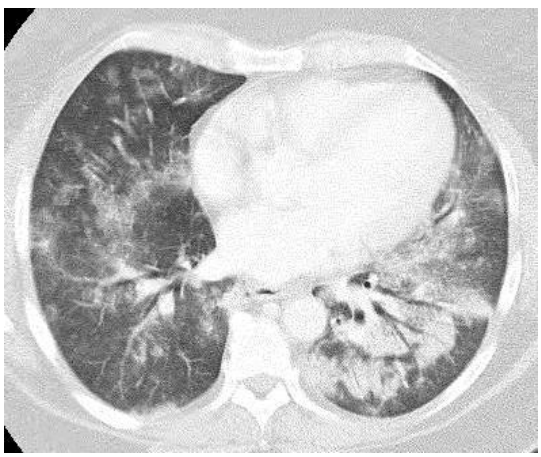


Figure 6.2. Axial chest CT of the case's patient (same as Figure 6.1), revealing diffuse, patchy, ground-glass opacities and consolidated areas in both lungs.

A biopsy of an affected organ can ideally confirm the diagnosis of ANCA-associated vasculitis, but this can sometimes be risky and must not delay the initiation of treatment in a patient with typical, severe GPA, as in this case. A positive ANCA test can be sufficient in practice to support the diagnosis in such case. If infection has been ruled out, a positive ANCA in the right setting can provide enough supportive evidence to initiate specific therapy for vasculitis. The sensitivity of standard ear, nose and throat (ENT) biopsies is <25% in GPA, while endoscopic bronchial biopsy is associated with a sensitivity of <40% and surgical lung biopsy with a sensitivity of approximately 80%. Sensitivity of renal biopsy in patients with renal involvement is >90% (renal biopsy can also provide some information on the reversibility or not of the renal lesions, thereby the renal prognosis, and chances of renal recovery).

2. List the different ANCA-associated vasculitides; explain what ANCA stands for and how it is detected and measured.

According to Chapel Hill consensus conference nomenclature (see Table 4.1), there are three main ANCA-associated vasculitides: GPA (formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg–Strauss syndrome). These three diseases have some similarities but also several important differences (Table 6.1). Renal-limited ANCA-associated disease (or vasculitis) is often listed as another and fourth ANCA-associated condition, as sometimes it is impossible (or would remain debatable) to definitively conclude whether a patient with biopsy-proven, renal-limited disease, with pauci-immune glomerulonephritis on histology and ANCA-positive, has GPA or MPA.

ANCA stands for antineutrophil cytoplasm (or cytoplasmic in several textbooks or articles, although these antibodies are directed towards a cytoplasmic protein but do not themselves enter the cytoplasm) antibodies (or auto-antibodies). ANCA can be detected by indirect immunofluorescence (IF), which uses ethanol-fixed neutrophils to detect ANCA in the patient's sera, or by enzyme-linked immunosorbent assay (ELISA). IF is modestly more sensitive than ELISA, but ELISA is more specific and is now the sole recommended technique to be used in practice for ANCA detection (and most labs in Canada do no longer offer ANCA testing by IF). High-quality immunoassays, such as new-generation ELISA, are now considered the recommended screening diagnostic tests (rather than IF). Multiplex microbead assays are now often used, as they can simultaneously screen for both myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA (and sometimes anti-GBM as well). MPO is a peroxidase enzyme and PR3 is a serine protease; both of which are expressed in neutrophils and play a role in oxidative burst and/or degradation of extracellular proteins at sites of inflammation.

ANCA are detectable in 90% of patients with systemic GPA and 70–80% of those with limited GPA, mainly with a cytoplasmic immunofluorescence pattern in IF (cANCA), and PR3 specificity on ELISA. Some GPA patients are ANCA-negative, and a few have atypical ANCA or MPO-ANCA (most Asian patients with a clinical diagnosis of GPA are in fact MPO- rather than PR3-ANCA-positive for example). Up to 90% of MPA patients are MPO-ANCA-positive (others are ANCA-negative or, exceptionally PR3-ANCA-positive). Only 30–40% of EGPA patients are ANCA-positive, mostly with a pANCA and MPO-ANCA.

As stated in the revised Chapel Hill consensus conference nomenclature, one should systematically specify both the clinical diagnosis and ANCA reactivity (for example, PR3-ANCA GPA or ANCA-negative MPA).

There have been several publications and repeated attempts to suggest that ANCA-associated vasculitides would be better classified (and diagnosed) based only on the ANCA status (positive or negative) and type (PR3- or MPO-ANCA), thereby completely dropping the terms GPA and MPA. Whereas evidence exists to support this alternative, including strong genetic, clinical and therapeutic data, the use of GPA and MPA adds valuable information and clinical meaning.

Table 6.1. Main characteristics (and differences) of ANCA-associated vasculitides.

	Microscopic polyangiitis	**Eosinophilic granulomatosis with polyangiitis**	**Granulomatosis with poly-angiitis**
Clinical manifestations			
Constitutional symptoms	55-80%	30-50%	70-100%
Skin	Purpura (35-60%)	Purpura, pseudo-urticarial rash, nodules (50-70%)	Purpura (10-50%)
ENT manifestations	None? ENT manifestations are often considered as a marker of GPA. A few patients in MPA series (2-30%) had ENT symptoms, including sinusitis, but not destructive or granulomatous	Frequent (20-80%): allergic rhinitis, sinus polyposis (not destructive)	Frequent (50-95%): crusting rhinitis, destructive sinusitis, saddle-nose deformity, nasal septum perforation, otitis media, decreased/ loss of smell or taste, gum hypertrophy/pain
Lung involvement	Frequent (60-80%): alveolar hemorrhage, interstitial lung disease with fibrotic lung changes	Frequent (50%): transient patchy infiltrates, eosinophilic pleural effusion, rarely nodules	Frequent (60-80%): lung solid and/or cavitary nodules, alveolar hemorrhage, bronchial and/or subglottic stenosis
Asthma	No	Yes (90–100%)	No
Kidney involvement	Very frequent: glomerulonephritis (pauci-immune). 80%	Not frequent: glomerulonephritis (pauci-immune), 20%	Frequent: glomerulonephritis (pauci-immune): 60-80%
Peripheral neuropathy (mononeuritis multiplex)	Possible (35%)	Very frequent (65-75%)	Possible (25%)
Other "classical" manifestations	Venous thrombosis 7-8%	Cardiac manifestations (10-50%; cardiomyopathy); venous thrombosis 7-8%	Eye manifestations (scleritis, orbital tumour); pachymeningitis; venous thrombosis 7-8%
Biology			
Standard	Non-specific inflammatory syndrome	Eosinophilia, often >3,000/ mm^3 Non-specific inflammatory syndrome	Non-specific inflammatory syndrome
ANCA	Yes (60-80%): mainly MPO-ANCA, perinuclear (pANCA)	Yes (30-40%): mainly MPO-ANCA, perinuclear-(pANCA)	Yes (90% if systemic disease): mainly PR3-ANCA, cytoplasmic (cANCA)
Histology			
	Necrotizing vasculitis of small-sized vessels	Granuloma, including eosinophils (frequent); necrotizing vasculitis of small-sized vessels	Granuloma (frequent but not always); necrotizing vasculitis of small-sized vessels

Table 6.2. Main conditions or causes of positive ANCA screening tests, other than primary ANCA-associated vasculitides (GPA, MPA or EGPA).

IIF pattern	ELISA specificity	Condition/disease/cause
cANCA	PR3	Infective endocarditis (up to 10% of patients, with any type of microorganisms, including *Staphylococcus aureus*, *Streptococcus viridans* or *bovis*, *Bartonella* spp, and *Tropheryma whipplei*) Tuberculosis (rare and controversial) Amebiasis
	Bacterial permeability increasing (BPI) protein	Cystic fibrosis TAP deficiency (bare lymphocyte syndrome) Infections
pANCA	MPO	Rheumatoid arthritis (Felty's; low titre) Medications (mostly propylthiouracil, hydralazine) Infections (including HIV and HCV with or without cryoglobulinemia) Autoimmune liver disease Ulcerative colitis (more rarely Crohn's disease) Cholesterol emboli syndrome (more rarely with PR3-ANCA)
pANCA or atypical (xANCA)	Cathepsin G	Ulcerative colitis Autoimmune liver disease
	Lactoferrin	Ulcerative colitis Rheumatoid arthritis
	Elastase (and/or PR3)	Cocaine-levamisole vasculopathy*
	Other (azurocidin, lysozyme, etc.), negative or unknown	Infections (including HIV and HCV) Rheumatoid arthritis Systemic lupus Ulcerative colitis Autoimmune liver diseases Medications

** Levamisole-tainted cocaine, which represented 75% of the cocaine circulating in North America in the early 2000s, can induce clinical features very similar to GPA. The most common features are nasal septum perforation, saddle-nose deformity and retiform purpura-hemorrhagic and necrotic skin lesions (extremely suggestive when they affect the tip of the nose and lobes of the ears, which are not usually affected in GPA). On skin histology, there are histological changes of the vessels with necrosis and thrombosis, but usually less inflammation than in primary vasculitides. Some patients may develop more severe small-vessel disease with lung hemorrhage and pauci-immune glomerulonephritis. Biologically, these patients can have any type of ANCA pattern in IIF and ELISA, including double-positive MPO- and PR3-ANCA, or paradoxical pANCA in IIF but PR3-ANCA in ELISA. The real target of the ANCA is most often elastase, which is not routinely tested. Neutropenia and positive antiphospholipid antibodies are also common.*

TAP, transporter associated with antigen processing.

3. List the causes of a positive ANCA test other than the primary ANCA-associated vasculitides.

Few conditions other than primary ANCA-associated vasculitides can be associated with a positive ANCA screening test, by IF, ELISA or both, either transiently or more persistently. Most of these conditions are listed in Table 6.2. The most important ones to remember in clinical practice are infectious endocarditis, HIV and HCV infections, with or without cryoglobulinemia, autoimmune liver disease, inflammatory bowel disease, and drug-induced vasculopathy (and vasculitis), especially due to cocaine-levamisole use or propylthiouracil.

Anti-GBM disease can also be associated with ANCA positivity, mostly due to a cross-reaction when anti-GBM titre is high, or as a possible consequence of the renal damage and endothelial cell exposure to immune cells. Reciprocally, patients with high titres of ANCA can transiently have some anti-GBM positivity. The presentation and outcomes of those rare but really double-positive patients may differ from those with only one antibody, with a frequently worse overall renal prognosis (see Case 17).

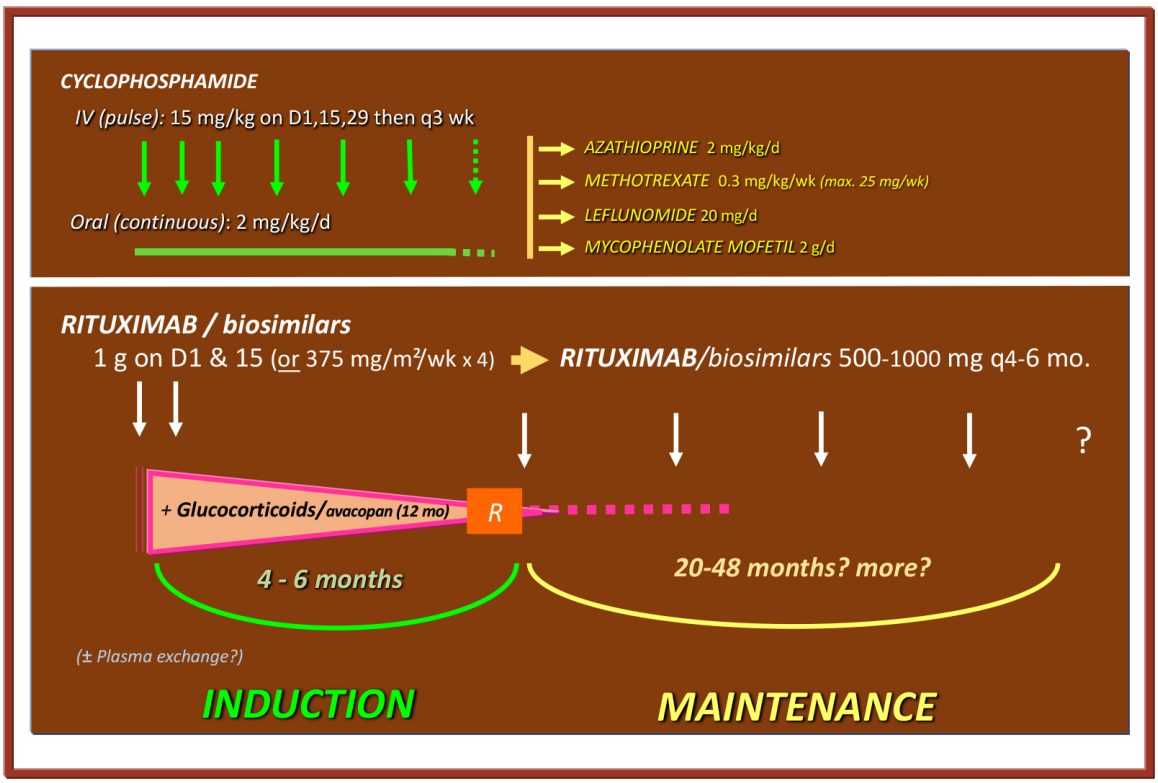


Figure 6.3. Principles of treatment of severe, systemic GPA.

Table 6.3. Summary of the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis and microscopic polyangiitis (Adapted from Robson et al. and Suppiah et al. Ann Rheum Dis 2022).

The classification criteria for granulomatosis with polyangiitis can be considered only in patients in whom:		
1. a diagnosis of small- or medium-sized vessel vasculitis has been made		
& 2. all alternate diagnoses have been excluded		
And have the following:		
Clinical criteria:		
	Nasal involvement: bloody discharge, ulcers crusting, congestion, blockage or nasal septum defect/perforation	+3
	Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, saddle nose deformity)	+2
	Conductive or sensorineural hearing loss	+1
Laboratory, imaging and biopsy criteria:		
	Cytoplasmic antineutrophil cytoplasm antibody (cANCA) or antiproteinase 3 ANCA (PR3-ANCA) positivity	+5
	Pulmonary nodules, mass or cavitation on chest imaging	+2
	Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
	Inflammation, consolidation or effusion of the nasal/ paranasal sinuses, or mastoiditis on imaging	+1
	Pauci-immune glomerulonephritis on biopsy	+1
	Perinuclear ANCA (pANCA) or antimyeloperoxidase ANCA (MPO-ANCA) positivity	*-1 (subtract)*
	Blood eosinophil count ≥1x10^9/litre	*-4 (subtract)*
A cumulative, sum score of ≥5 is needed for classification of granulomatosis with polyangiitis. The sensitivity of these criteria was 93% (95% CI; 87-96%) and specificity 94% (95% CI; 89-97%).		

The classification criteria for microscopic polyangiitis can be considered only in patients in whom:		
1. a diagnosis of small- or medium-sized vessel vasculitis has been made		
& 2. all alternate diagnoses have been excluded		
And have the following:		
Clinical criteria:		
	Sino-nasal symptoms or signs (nasal involvement: bloody discharge, ulcers crusting, congestion, blockage or septal defect/perforation)	*-3 (subtract)*
Laboratory, imaging and biopsy criteria:		
	Perinuclear antineutrophil cytoplasm antibody (pANCA) or antimyeloperoxidase ANCA (MPO-ANCA) positivity	+6
	Pauci-immune glomerulonephritis on biopsy	+3
	Lung fibrosis or interstitial lung disease on chest imaging	+3
	Cytoplasmic ANCA (cANCA) or antiproteinase 3 ANCA (PR3-ANCA) positivity	*-1 (subtract)*
	Blood eosinophil count ≥1x10^9/litre	*-4 (subtract)*
A score of ≥5 is needed for classification of microscopic polyangiitis. The sensitivity of these criteria was 91% (95% CI; 85-95%) and specificity 94% (95% CI; 92-96%).		

4. What are the new 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for GPA?

The previous 1990 ACR criteria for the different vasculitides had become outdated, especially given the many advances in available lab tests, including ANCA detection, imaging and other new definitions. The DCVAS study was designed in 2010 with the goal of developing updated classification criteria (and originally, also another set of diagnostic criteria) for systemic vasculitides. These new 2022 ACR/EULAR Classification Criteria for GPA are listed in table 6.3. Whereas the recognition and addition as part of these criteria of PR3-ANCA as a strong characteristic of GPA is an advance, the negative value of having an MPO-ANCA is already being challenged by many groups, especially from Asian countries, in which most patients with a clinical diagnosis of GPA are MPO-ANCA positive.

5. What induction therapy would you initiate in this patient?

This patient has severe PR3-ANCA GPA, with severe renal disease and diffuse alveolar hemorrhage (pulmonary-renal syndrome). As such, she requires urgent treatment initiation, in parallel with investigations to rule out infections, such as those listed above, and to check for other conditions, including anti-GBM disease. Without treatment, median survival of patients with severe GPA is 5 months after the onset of first symptoms.

Several pivotal studies helped determine the current optimal induction therapy for ANCA-associated vasculitides (Table 6.4). Treatment of severe GPA (or MPA) includes an induction regimen and once remission has been achieved, a prolonged maintenance treatment (Figure 6.3). At present, the rate of remission at 6 months in GPA is 80–90%. The mortality rate remains high, around 10%, due to either the underlying vasculitis or early infections. The 2020 updated CanVasc, 2021 American College of Rheumatology/Vasculitis Foundation, revised 2016 European EULAR/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommendations for the management of ANCA-associated vasculitides can assist physicians in their therapeutic decision-making (updated EULAR recommendations should be published in late 2022).

This patient requires a combination of high-dose glucocorticoids (GC) and/or avacopan, plus either oral or IV cyclophosphamide (CYC) or rituximab (RTX). Given this patient's young age and potential fertility concerns with the use of CYC, RTX might be preferred since it has similar efficacy (in newly diagnosed patients) and short-term safety profile (in terms of infection), based on the RAVE and RITUXVAS studies, but does not carry the risk of infertility or late bladder cancer. However, the risk of sterility with CYC in a young CYC-naïve patient remains limited at the recommended doses and durations for GPA.

GC treatment in such a severe case most often consists of initial methylprednisolone IV pulses (7.5–15 mg/kg/day; up to 1000 mg/day) for 1 to 3 days, followed by prednisone 1 mg/kg/day (maximum 80 mg) for 2 weeks, then gradually tapered by approximately 10% of the dose every 2 weeks until reaching 5 mg/day around the 4-5th month of treatment. The need for and possible benefits of the initial methylprednisolone IV pulses are unclear. Only retrospective studies (and somehow the MEPEX trial; see Table 6.4) looked at this, and only showed that these IV pulses were associated with more infections and diabetes. The optimal tapering regimen and duration of GC treatment remain also subjects of debate and require more studies. In the LoVAS trial (see Table 6.4), the reduced-dose prednisolone group (starting at 0.5 mg/kg/day for induction of remission) was noninferior to the high-dose option (starting at

1 mg/kg/day) with regard to induction of remission at 6 months. Most recent studies also showed that a relatively fast tapering of the GC dose can be done, as in the PEXIVAS trial (see Table 6.4), especially in light of new standards of therapy with RTX. GC are stopped at month 6 in several centres, while they are continued at a low dose (5 mg/day) for several months or years in others. The TAPIR trial is currently underway in North America to study the effects of stopping GC treatment between months 6 and 12 after induction therapy in patients with GPA vs. continuing low-dose prednisone (5 mg/day) for 6 months more (NCT01933724; expected completion in mid-2023). The MAINEPSAN trial (in France) has a grossly similar design, but only for patients receiving RTX for maintenance (NCT03290456; recruiting).

In late 2021, the results of the ADVOCATE trial led to the approval by the FDA, and then in April 2022 by Health Canada, of avacopan, a complement C5a receptor antagonist, as an option to further reduce the use of GC, thereby the rate of many of the inherent and numerous side effects of GC. In this trial, oral avacopan at a fixed dose of 30 mg x 2/day (for all patients, regardless of their weight, and for 12 months) was compared with a 5-month prednisone treatment with a now-relatively-standard tapering schedule. All patients also received either RTX for induction (then no other maintenance agent) or CYC (followed by azathioprine [AZA] for maintenance). Patients in the avacopan arm were still allowed to receive some (unblinded) prednisone initially, as per physician decision, for up to a maximum of 4 weeks. Avacopan was noninferior to prednisone for remission at week 26 (72% vs. 70%), and was superior to prednisone taper for sustained remission at week 52 (65% vs. 55%). Patients in the prednisone group received over 2.5 times the mean cumulative prednisone dose compared with the avacopan group (3655 mg vs. 1349 mg). Infections and several types of adverse events occurred at numerically lower rates in the avacopan group. Avacopan could thus be used instead of GC for induction of remission, or with a much lower GC dose. In practice, it is likely that most physicians will still prescribe (for some time at least) some GC to their patients, initially and/or for those with the more severe disease forms. The optimal duration of avacopan treatment also remains to be determined (for 1 year, as in the ADVOCATE study, or for a longer, or, alternatively, a shorter duration, because of the high cost of this new agent).

RTX can be given at a dose of 375 mg/m^2 IV every week for 4 consecutive weeks, or 1 g at days 1 and 15, which is more practical and was shown in a meta-analysis of a few cohorts and randomized studies to be as effective as the 4-week dosing option. CYC can be given orally or IV if it is preferred, or until RTX can be given (RTX is not readily available in every centre and/or an approval for cost coverage might be needed before accessing the drug). The oral CYC dose is 2 mg/kg/day (maximum 200 mg/day), to be taken in the morning with a large glass of water, for 3 months to a maximum of 6 months. The IV CYC regimen is based on pulses of 15 mg/kg (maximum 1200 mg) every 2 weeks for the first 3 doses, then every 3 weeks for the next 3 to 6 doses. The dose of oral or IV CYC must be decreased by 25–50% in patients with impaired renal function and/or in those over 60 years of age, and of course in cases of dose-related side effects, such as neutropenia. Patients receiving IV CYC should receive bladder protection with good concomitant hydration and mesna at each pulse (1/3 of the CYC pulse dose, in mg, given IV with the infusion, and again, IV or orally, 4 and 8 hours later).

Due to the risk of *Pneumocystis jiroveci* pneumonia with (GC and) both RTX or CYC, patients should be given prophylactic therapy with trimethoprim/sulfamethoxazole (either double strength [DS], 160/800 mg 1 tablet 3 times per week, or a single-strength 80/400 mg tablet daily [or 3 times per week only, for patients

with impaired renal function or on dialysis]). Patients in whom trimethoprim/sulfamethoxazole compounds are contraindicated (for example due to sulfa allergies) should be given alternate prophylaxis with dapsone, atovaquone or aerosolized pentamidine.

Whether or not plasma exchange (PLEX) should also be used in the treatment of severe GPA or MPA with renal involvement and/or severe alveolar hemorrhage has been debated for years. The MEPEX trial compared additional PLEX versus initial methylprednisolone IV pulses in patients with severe renal ANCA-associated vasculitides (AAV) and showed that renal recovery was better in the PLEX arm at month 12, but the difference did not last beyond this time.

The PEXIVAS trial was designed to better evaluate the role of PLEX in patients with ANCA-associated vasculitis with severe renal and/or lung disease. The study found that the addition of PLEX did not lead to a reduction in death and/or ESRD. Hence, the updated 2020 Canvasc recommendations stated that "urgent plasma exchange is not recommended as part of initial induction therapy for most adult patients with severe GPA or MPA". The recommendation text emphasized however that PLEX might still be considered, but with limited expectations, in patients with creatinine >350 µmol/l, refractory pulmonary hemorrhage, and/or specific renal histological characteristics, as the study may have been underpowered to detect differences in several subgroups. Another point to consider before using PLEX is the patient's infection risk, as a 2020 Cochrane meta-analysis (which included PEXIVAS data) showed that PLEX was associated with an increased risk of serious infections (RR 1.26, 95% CI 1.03 to 1.54), further confirmed in another recent meta-analysis from the PEXIVAS investigators. The same meta-analysis suggested that PLEX had no benefit in terms of survival in patients with alveolar hemorrhage, but may have some (limited) benefits in patients with advanced renal disease (but with this increased risk of infections).

There are to date no alternatives to CYC or RTX in severe GPA (or MPA). MTX and MMF were shown to be noninferior to CYC for induction of remission at 6 months in newly diagnosed GPA or MPA without severe renal or life-threatening disease (i.e. not like this patient case).

However, patients in the MTX or MMF groups had subsequent higher relapse rates, especially the PR3-ANCA-positive patients. Abatacept is currently being studied in the ABROGATE trial, but only for patients with non-severe (relapsing) GPA (NCT02108860; results expected in 2024).

Other agents may have a role in the remission-induction therapeutic armamentarium for GPA. IVIg have been used in addition to (or, in non-severe cases, instead of) CYC, and may have some efficacy, although most often transient (and there is potential interest in use in pregnant women and/or patients with associated severe, active infections). Alemtuzumab or deoxyspergualin have also been used for induction in patients with refractory and/or relapsing GPA, but they are not practical to use and carry some non-negligible risks of severe side effects. A few case reports also suggested possible efficacy of tocilizumab in patients with refractory MPA (but only a few cases with GPA).

Table 6.4. Summary of the main completed and published RCT of ANCA-associated vasculitides on induction treatment

Study name/ acronym	Sample size	Inclusion criteria	Studied interventions	Primary endpoints	Main results/conclusions
CYCAZAREM (Jayne et al. EUVAS, 2003)	144	Newly diagnosed GPA, MPA or renal-limited disease, with at least one major organ involved (but creatinine level <500 µmol/l)	All induced with oral CYC and GC until remission (3-6 months) then randomized for maintenance with oral AZA (2 mg/kg) or continuation of oral CYC (1.5 mg/kg) until month 12 (then AZA for all until month 18)	Relapse (major or minor) and adverse events at month 18	No difference in relapse and adverse event rates at 18 months: CYC-based induction can be stopped after remission is achieved - At longer term (8.5 yr), 52% relapsed in the AZA group vs. 36% in the CYC group (subHR 1.63, 95% CI 0.99–2.71; P=0.06). Same rates of side effects or deaths
NORAM (De Groot et al. EUVAS, 2005)	100	Newly diagnosed GPA or MPA, with creatinine level <150 µmol/l and no major organ involvement	MTX (15 mg/week initially increased to 25 mg/week) vs. daily oral CYC + (in both arms) oral GC All treatments stopped at month 12	Remission at month 6	For limited GPA, remission rate was not inferior with MTX vs. oral CYC, but remission was delayed in patients with more extensive or pulmonary disease, and relapse rate at 18 months was higher in the MTX group. Adverse events were less frequent with MTX, except for liver dysfunction
MEPEX (Jayne et al. EUVAS, 2007)	137	Newly diagnosed GPA or MPA with renal disease and creatinine >500 µmol/l	PLEX vs. methylprednisolone pulses (IV 1 g/day for 3 days) + (in both arms) oral GC and oral CYC for 6 months, then AZA	Renal recovery at 3 months (dialysis independence)	24% reduction in risk of progression to ESRD with PLEX at 12 months (no global survival benefit) - At longer term (4 yr): HR for PLEX vs. IV methylprednisolone for death or ESRD of 0.81 (95% CI 0.53–1.23) with a subHR for ESRD of 0.64 (95% CI 0.40–1.05)
CYCLOPS (De Groot et al. EUVAS, 2009)	149	Newly diagnosed GPA or MPA with renal disease (creatinine 150-500 µmol/l)	Pulse (IV mainly) CYC (15 mg/kg) vs. oral CYC (2 mg/kg/day) until remission + (in both arms) GC and 3-month consolidation of CYC after remission, then AZA until month 18	Time to remission	Pulse IV CYC induces remission as well as daily oral CYC, at a reduced cumulative CYC dose (8.6 vs. 18 g) and caused less leucopenia - At longer term (4.3-yr follow-up), no difference in survival but the relapse rate was lower in the daily oral group (HR 0.50, 95% CI 0.26–0.93)
RAVE (Stone et al. USA, 2010)	197	New or relapsing ANCA+ severe GPA or MPA (but creatinine <354 µmol/l and no life-threatening manifestation)	RTX (375 mg/m^2 weekly x 4) vs. oral CYC then AZA (only in the CYC-induced arm) + (in both arms) GC (aiming to stop at month 6)	Complete remission off GC at 6 months	RTX is not inferior to CYC-AZA sequence at month 6 (and 18), and superior to CYC-AZA for relapsing OR PR3-ANCA+ patients at month 6 but only not inferior at month 18 (RTX is superior at 6 and 18 months for PR3-ANCA+ AND relapsing patients). Similar infection rates in both arms.
RITUXVAS (Jones et al. EUVAS, 2010)	44 (3:1 ratio)	Newly diagnosed ANCA+ GPA, MPA or kidney-limited disease with renal disease	RTX (375 mg/m^2 weekly x 4) + two IV pulses of CYC (15 mg/kg at day 1 and 15) vs. IV CYC pulses only (15 mg/kg) for 3-6 months, then AZA + (in both arms) GC	Sustained remission and severe adverse events at 12 months	RTX was not superior to CYC-AZA sequence at 12 months. Sustained remission rates were high in both groups. Similar rates of early severe adverse events in both groups

Study name/ acronym	Sample size	Inclusion criteria	Studied interventions	Primary endpoints	Main results/conclusions
CORTAGE (Pagnoux et al. FVSG, 2015)	108	Systemic necrotizing vasculitides (including 36 GPA and 44 MPA), patients' age >65 years	GC for 9 months and six 500-mg fixed-dose IV CYC pulses, every 2–3 weeks vs. 26 months of GC and IV CYC 500 mg/m^2, then AZA or MTX in both groups	>1 serious adverse event within 3 years of follow-up	Fewer adverse events with the lower, fixed-dose CYC regimen (500 mg per pulse): 60% vs. 78% (P=0.04). No significant difference in failure rates (11% with fixed dose vs. 14%), mortality (17% vs. 24%) or relapses (44% with fixed dose vs. 29%; P=0.15)
MYCYC (Jones et al. 2019)	140	Newly diagnosed GPA or MPA, without any life-threatening disease, rapidly declining renal function or GFR <15 ml/ min/m^2	Induction with GC and either IV CYC (15 mg/kg every 2-3 weeks, adjusted to age and renal function) or oral MMF (2 g/day), then maintenance with AZA (2 mg/kg/day) after achieving remission (between 3 and 6 months)	Remission at month 6 (with GC tapered as per protocol)	At 6 months, noninferiority with remission in 67% in the MMF group vs. 61% in the IV CYC group (risk difference 5.7%, 90% CI -7.5 to 19%). Similar rate of serious infections (26% MMF vs. 17% CYC) - At month 18, more subsequent relapses had occurred in the MMF (33%) vs. CYC (19%) group, especially in PR3-ANCA patients
PEXIVAS (Walsh et al. 2020)	704	New or relapsing ANCA+ GPA or MPA with renal (eGFR <50 ml/min/1.73m^2) and/or pulmonary (including alveolar hemorrhage) involvement	1. Adjunctive PLEX (7 sessions over 14 days) vs. no PLEX 2. Reduced-dose vs. standard-dose GC regimen All patients received standard induction therapy (CYC or RTX)	All-cause death or ESRD (composite)	Up to 7 years of follow-up: no reduction in death or ESRD with PLEX (28.4% PLEX vs. 31% control, HR 0.86; 95% CI 0.65-1.13) reduced-dose GC was noninferior to standard-dose regimen (absolute risk difference, 2.3 percentage points; 90% CI, −3.4 to 8.0), and less serious infections at 1 year in reduced-dose group (IRR 0.69; 95% CI 0.52-0.93)
RITAZAREM pre-randomization (Smith et al. 2020)	188	Relapsing ANCA+ GPA or MPA (not on current RTX maintenance)	Induction for all with RTX (375 mg/m^2 x4) then, if in remission, randomized at month 4 to either AZA or RTX for maintenance (see Table 9.2)	Remission by 4 months	90% achieved remission at month 4 (17 patients did not, including 4 who died in the induction phase)
ADVOCATE (Jayne et al. 2021)	330	New or relapsing ANCA+ GPA or MPA, severe/ diffuse (= requiring CYC or RTX) but with eGFR ≥15 ml/min/1.73m^2 and no massive alveolar hemorrhage requiring mechanical ventilation	Avacopan 30 mg x2/day (for 52 weeks) vs. prednisone tapering (over 20 weeks) All patients received standard induction therapy (CYC followed by AZA, or RTX [without maintenance RTX or AZA])	Remission at week 26 (BVAS = 0) and sustained remission at week 52	At week 26, avacopan was noninferior to prednisone tapering for remission (72.3% vs. 70.1%) At week 52, avacopan was superior to prednisone tapering for sustained remission (65.7% vs. 54.9%; P=0.007). Avacopan group received less than half the mean total prednisone dose (1349 mg vs. 3655 mg)
LoVAS (Furuta et al. 2021)	140	New ANCA+ vasculitis (with eGFR ≥15 ml/ min/1.73m^2 and no alveolar hemorrhage requiring oxygen support)	Reduced-dose prednisolone (0.5 mg/ kg/day, tapered and stopped over 5 months) vs. "standard" high-dose prednisolone (1 mg/kg/day, tapered to 10mg/day by 5 months) All patients received induction RTX (4x 375 mg/m^2/wk)	Remission at 6 months	Reduced-dose prednisolone regimen was noninferior to high-dose regimen (remission in 71% vs. 69.2%) Less serious infections in the reduced-dose group (7.2% vs. 20.0%; P=0.04)

HR, hazard ratio; 95% CI, 95% confidence interval; ESRD, end-stage renal disease; subHR, subdistribution hazard ratio

References

Jayne D et al. A Randomized Trial of Maintenance Therapy for Vasculitis Associated with Antineutrophil Cytoplasmic Autoantibodies. New Engl J Med 2003;349(1):36-44.

De Groot K et al. Randomized Trial of Cyclophosphamide Versus Methotrexate for Induction of Remission in Early Systemic Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Rheum 2005;52(8):2461-9.

Jennette JC et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65(1):1-11.

Guillevin L et al. Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. New Engl J Med 2014;371(19):1771-80.

Pagnoux C et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. Arthritis Rheumatol. 2015;67(4):1117-27.

Yates M et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75(9):1583-94.

Bossuyt et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol 2017;13(11):683-92.

Jones RB et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis 2019 Jan. ;78:399-405.

Walters GD et al. Interventions for renal vasculitis in adults. Cochrane Database Syst Rev 2020;1:CD003232.

Walsh et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med 2020;382:622-31.

Smith et al. Rituximab as therapy to induce remission after relapse in ANCA-associated vasculitis. Ann Rheum Dis 2020;79(9):1243-9.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheum 2021;48:555-66.

Jayne DRW et al. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 2021;384(7):599-609.

Furuta S et al. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. JAMA 2021;325(21):2178-87.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83.

Suppiah et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Microscopic Polyangiitis. Arthritis Rheumatol 2022;74(3):400-6.

R, Robson et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Granulomatosis With Polyangiitis. Arthritis Rheumatol 2022;74(3):393-9.

Ross C, Makhzoum JP, Pagnoux C. Updates in ANCA-associated vasculitis. Eur J Rheumatol 2022;9(3):153-66.

Walsh M et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ Rapid Recommendations Group. BMJ 2022 Feb;376:e064604.

Case 7
Limited granulomatosis with polyangiitis

Mrs. J is a 30-year-old woman with no significant past medical or familial history, married with one 3-year-old son. She works in an office, does not smoke or drink and denies any recreational drug use. She has been suffering from recurrent sinusitis for the past 3 years, for which she received repeated courses of antibiotics, with or without short courses of prednisone. She had negative allergic skin tests.

She was recently seen by an ENT colleague of yours, who found a nasal septum perforation, crusting rhinitis with irregular mucosal erosions in the nasal cavities. Nasopharyngoscopy revealed no subglottic stenosis. CT of the sinuses showed filling of the left maxillary sinus and nasal perforation (Figure 7.1). A sinus biopsy showed non-specific inflammation, consisting mostly of neutrophils. ANCA screening test was negative. Chest X-ray was normal, as well as serum creatinine (65 µmol/l) and urinalysis. C-reactive protein was 29 mg/l (normal <10 mg/l).

1. *What is the definition of limited granulomatosis with polyangiitis?*
2. *What are the possible treatment options for this patient with a limited form of granulomatosis with polyangiitis?*
3. *What is the Birmingham vasculitis activity score? What is this patient's BVAS? What is her BVAS/WG score?*

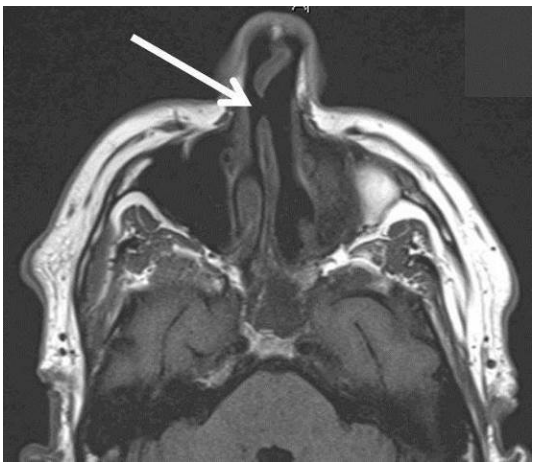


Figure 7.1. Horizontal sinus CT. Nasal septum perforation (arrow) and left sinus filling (sinusitis).

Learning objectives

1. To understand the difference between severe (diffuse, generalized, systemic) and limited (localized, non-severe) forms of GPA.
2. To establish a treatment plan for limited, non-renal GPA.
3. To be able to use the Birmingham vasculitis activity score (BVAS) and BVAS/Wegener's granulomatosis (BVAS/WG) to assess disease activity in patients with GPA.

Answers

1. What is the definition of limited granulomatosis with polyangiitis?

Two main forms of granulomatosis with polyangiitis (GPA) have been described, but whose names and definitions vary according to the study or author. One is the severe form, also referred to as generalized, diffuse or systemic. The other is the limited form, also referred to as localized or non-severe. The limited form in WGET (Wegener's Granulomatosis Etanercept Trial), was defined as GPA without any disease features posing an immediate threat to a critical individual organ or to the patient's life. Specifically, there could be no red blood cell casts in the urine, and if hematuria was present (without casts), the serum creatinine had to be stable, not higher than 25% of the baseline level, and ≤1.4 mg/dl (124 µmol/l). For patients with lung involvement, it had to be circumscribed, with room air PO_2 >70 mmHg and/or O_2 saturation >92%, and in the case of pulmonary hemorrhage, there had to be no evidence of progression. Finally, patients could not have critical organ manifestations (e.g. gastrointestinal [GI] tract, eyes, central nervous system [CNS]) that, without immediate treatment, would threaten the function of that organ and/or their life. All patients not meeting the criteria of limited GPA described above were, by definition, classified as severe (the term used in WGET). The EULAR/ European Vasculitis Society (EUVAS) used slightly different definitions, although there is clearly some overlap (Table 7.1).

2. What are the possible treatment options for this patient with a limited form of granulomatosis with polyangiitis?

The NOn-Renal Wegener's granulomatosis treated Alternatively with Methotrexate (NORAM) trial (Table 6.4) demonstrated that (oral) methotrexate (MTX; 25 mg/week for 12 months) was not inferior to oral, daily cyclophosphamide (CYC; 2 mg/kg/day and reduced to 1.5 mg/kg after remission), both combined with glucocorticoids (GC), for the treatment of early systemic, non-renal GPA or microscopic polyangiitis (MPA). Adverse events were less frequent with MTX, except for liver dysfunction, which was more frequent with MTX. However, remission was delayed in patients with more extensive or pulmonary disease, and the relapse rate at 18 months was higher in the MTX group (who received no more treatment after month 12). Thus, when MTX is effective, it should be given for longer than 12 months (optimal duration is unknown). Whether azathioprine, leflunomide or mycophenolate mofetil (MMF) can achieve the same results as MTX remains to be studied. The MYCYC study compared CYC and MMF for the induction of remission (followed by azathioprine for maintenance) in patients

with GPA or MPA without any life-threatening manifestation but with at least one major or three minor BVAS 2003 items. The final study results showed similar remission rates, but higher, early relapse rates with MMF-based induction therapy (see Table 6.4).

The place of rituximab or other biologics, which are often considered to be less toxic than CYC (at least regarding fertility issues and risk of late cancers), is unclear at this time (however, a trend over the past decade has been to use rituximab more often, in combination with GC, in limited GPA). Abatacept has been used with promising results in an open-label study in patients with relapsing limited GPA. A larger randomized control trial is ongoing (ABROGATE, ClinicalTrials.gov Identifier: NCT02108860) to further assess its possible therapeutic role for relapsing limited GPA. However the results of this trial may not apply to the patient in this case as she is newly diagnosed.

The patient in this case could thus be treated with a combination of GC (prednisone, starting at 30–60 mg/day, depending on the severity of her symptoms, followed by gradual dose tapering) and MTX, aiming for 25 mg/week (with folic acid supplementation, for example, 5 mg/day except on the day she takes the MTX). Avacopan, instead of (or in addition to, at a lower dose) GC could be considered, but the patient is ANCA negative (trials on avacopan included ANCA+ patients only). She should have routine labs every 2–4 weeks and be seen in follow-up at 3 months to assess her response to this treatment. Rituximab could be considered instead of MTX, especially if the latter is not effective after 3-6 months of MTX at the proper dosage.

Nasal rinses with saline solution can help symptomatically. Local, intranasal application of antibiotic creams (e.g. fucidin cream, or mupirocin) can also be considered as adjuvant treatments. Some early studies suggested that the latter could further reduce relapse rates of ENT manifestations in GPA, including in patients not carrying *Staphylococcus aureus* in their nostrils. All of those local treatments, if attempted, must only be used as adjuvant to systemic treatments.

Table 7.1. Definitions of GPA forms.

Study group	Clinical subgroup	Systemic vasculitis outside ENT tract and lung	Threatened vital organ function	Other definitions	Serum creatinine (µmol/l)
EUVAS/ EULAR	Localized	No	No	No constitutional symptoms	<120
	Early systemic	Yes	No	Constitutional symptoms present ANCA positive or negative	<120
	Generalized	Yes	Yes	ANCA positive	<500
	Severe	Yes	Organ failure	ANCA positive	>500
	Refractory	Yes	Yes	Refractory to standard therapy	Any
WGET	Limited	Allowed	No	Not severe	≤124 but no red cell casts present
	Severe	Yes	Yes	Organ- or life-threatening disease implies need for remission induction with CYC	Any

Evidence for trimethoprim/sulfamethoxazole as an alternative induction agent for limited GPA is very limited (mainly case reports or small studies; hence, trimethoprim/sulfamethoxazole, alone or with GC only, cannot be considered as a standard option for induction of remission in limited GPA, and never in generalized, systemic GPA). In patients in remission and who become intolerant to MTX (or other immunosuppressive agents), one may consider trimethoprim/sulfamethoxazole to limit the risk of relapse. In a randomized placebo-controlled trial, 82% of patients with GPA in remission randomized to trimethoprim/sulfamethoxazole 160 mg/800 mg twice a day, and who could tolerate it for 24 months, remained in remission as compared with 60% of those in the placebo arm. High-dose trimethoprim/sulfamethoxazole can be difficult to tolerate however (20% of patients in the trial had to stop it due to side effects), is hazardous to use with methotrexate, and should be avoided in patients with advanced kidney dysfunction.

3. What is the Birmingham vasculitis activity score? What is this patient's BVAS? What is her BVAS/WG score?

Activity scores have been developed to standardize the assessment of disease activity in clinical trials of patients with systemic vasculitis. There are a few different ones, including the Disease Extent Index (DEI) and the Vasculitis Activity Index, and some that are specific to a particular vasculitis, such as the Indian Takayasu Arteritis Activity Score (ITAS2010). The Birmingham vasculitis activity score (BVAS) is the most commonly used tool for ANCA-associated and all other types of vasculitides. The first version was developed in 1994, with the lastest revision in 2007 (version 3). A version more specific to GPA (the BVAS/WG) was developed in 2001.

The BVAS V3 includes 9 sections for the different organs or systems possibly affected, a 10th section for any other unlisted significant disease manifestation, and a final box to indicate whether there is "persistent disease only" or if selected items include new or worse manifestations (the scoring varies for each of those two situations). Each item has a specific score, and the final score varies between 0 (no active or persistent disease) to a maximum of 63. There is also a modified, pediatric version of the BVAS, called the PVAS.

The BVAS/WG excluded items less relevant to GPA (e.g. bruits or loss of pulses) and emphasized some others, such as subglottic stenosis. It still includes 9 sections for different organs or systems, with some major and minor items and a 10th section to list other, rarer vasculitis manifestations. The final score usually varies between 0 and 13.

Using the scoring sheets (Figures 7.2 and 7.3), the calculated BVAS V3 and BVAS/WG in the patient in this case are 6 and 2, respectively (rhinitis and sinusitis, with active disease, for the BVAS V3 as this is her very first vasculitis assessment; only minor items in the BVAS/WG). The sheets can be accessed on the CanVasc website (https://canvasc.ca/tools-for-physicians/). Clinical cases for online BVAS training (and certification) have been developed by the original BVAS working group (https://bvasvdi.org).

Figure 7.2. Birmingham vasculitis activity score version 3 (adapted from Flossmann O et al. Ann Rheum Dis 2007, with permission).

*Only tick and score items attribuable to active vasculitis. If ALL abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the PERSISTENT box at the bottom right corner and use the second, usually lower, value to score (indicated **score value is for active new or worse/ persistent disease**). Major items are in bold and preceded by a ◆ sign.*

1. GENERAL	**|__| (maximum 3 / 2)**	**6. CARDIOVASCULAR**	**|__| (maximum 6 / 3)**
Myalgia	◘ 1 / 1	Loss of pulses	◘ 4 / 1
Arthralgia or arthritis	◘ 1 / 1	Valvular heart disease	◘ 4 / 2
Fever ≥38°C	◘ 2 / 2	Pericarditis	◘ 3 / 1
Weight loss ≥2 kg	◘ 2 / 2	◆ **Ischemic cardiac pain (angina)**	◘ 4 / 2
		◆ **Cardiomyopathy**	◘ 6 / 3
2. CUTANEOUS	**|__| (maximum 6 / 3)**	◆ **Congestive heart failure**	◘ **6 / 3**
Infarct	◘ 2 / 1		
Purpura	◘ 2 / 1	**7. ABDOMINAL**	**|__| (maximum 9 / 4)**
Ulcer	◘ 4 / 1	Peritonitis	◘ 9 / 3
◆ **Gangrene**	◘ 6 / 2	Bloody diarrhea	◘ 9 / 3
Other skin vasculitis	◘ 2 / 1	◆ **Ischemic abdominal pain**	◘ 6 / 2
3. MUCOUS MEMBRANES/EYES	**|__| (maximum 6 / 3)**	**8. RENAL**	**|__| (maximum 12 / 6)**
Mouth ulcer	◘ 2 / 1	Hypertension	◘ 4 / 1
Genital ulcer	◘ 1 / 1	Proteinuria >1 +	◘ 4 / 2
Adnexal inflammation	◘ 4 / 2	◆ **Hematuria >10 RBCs/hpf**	◘ 6 / 3
Significant proptosis	◘ 4 / 2	Creatinine 125–249 µmol/l (1.41-2.82 mg/dl)	◘ 4 / -
Scleritis/episcleritis	◘ 2 / 1	Creatinine 250–499 µmol/l (2.83-5.64 mg/dl)	◘ 6 / -
Conjonctivitis/blepharitis/keratitis	◘ 1 / 1	◆ **Creatinine ≥500 µmol/l (≥5.66 mg/dl)**	◘ 8 / -
Blurred vision	◘ 3 / 2	◆ **Rise in serum creatinine >30% or fall in creatinine clearance >25%**	◘ 6 / -
Sudden visual loss	◘ 6 / -		
Uveitis	◘ 6 / 2		
◆ **Retinal changes (vasculitis/thrombosis/ exudate/hemorrhage)**	◘ 6 / 2	**9. NERVOUS SYSTEM**	**|__| (maximum 9 / 6)**
		Headache	◘ 1 / 1
		Meningitis	◘ 3 / 1
4. ENT	**|__| (maximum 6 / 3)**	Organic confusion	◘ 3 / 1
Bloody nasal discharge/crusts/ulcers/granulomas	◘ 4 / 2	Seizures (not hypertensive)	◘ 9 / 3
Sinusitis, paranasal sinus involvement	◘ 2 / 1	◆ **Cerebrovascular accident (stroke)**	◘ 9 / 3
Subglottic stenosis	◘ 6 / 3	◆ **Spinal cord lesion**	◘ 9 / 3
Conductive hearing loss	◘ 3 / 1	◆ **Cranial nerve palsy**	◘ 6 / 3
◆ **Sensorineural hearing loss**	◘ 6 / 2	Sensory peripheral neuropathy	◘ 6 / 3
		◆ **Mononeuritis multiplex**	◘ 6 / 3
5. CHEST	**|__| (maximum 6 / 3)**		
Wheeze	◘ 2 / 1	**10. OTHER**	◘ - / -
Nodules or cavities	◘ 3 / -		
Pleural effusion/pleurisy	◘ 4 / 2		
Infiltrate	◘ 4 / 2	**PERSISTENT DISEASE ONLY**	
Endobronchial involvement	◘ 4 / 2	Tick here if ALL the abnormalities are due to persistent disease (and use the second column's value, usually lower, to calculate the BVAS)	☐
◆ **Massive hemoptysis/alveolar hemorrhage**	◘ 6 / 4		
◆ **Respiratory failure**	◘ 6 / 4		

Figure 7.3. Birmingham Vasculitis Activity Score/Wegener's granulomatosis (GPA-specific activity index; adapted from Stone JH et al. Arthritis Rheum 2001, with permission).

Tick the item only if abnormality is attributable to the presence of active GPA (chronic damage should be scored separately using a disease damage scoring system/index). Tick the new/worse box if the abnormality is newly present or worse within the previous 28 days. Tick the persistent box if abnormality is persistent disease activity since the last assessment and not worse within the previous 28 days. Major items are in bold and preceded by a ◆ sign. The presence of ≥1 major item defines severe disease and/or severe flare.

In calculating the final BVAS/WG score, the number of major items (either new/worse or persistent) is multiplied by 3 and added to the total number of minor items.

BVAS/WG = (number of major items x 3) + (number of minor items)

	New/worse	Persistent	None		New/worse	Persistent	None
1. GENERAL				**6. GASTROINTESTINAL**			
Arthralgia/arthritis				◆ **Mesenteric ischemia**			
Fever ≥38^{0}C							
				7. PULMONARY			
2. CUTANEOUS				Pleurisy			
Purpura				Nodules or cavities			
Skin ulcer				Other infiltrate secondary to GPA			
◆ **Gangrene**							
				Endobronchial involvement			
3. MUCOUS MEMBRANES/ EYES				◆ **Alveolar hemorrhage**			
				◆ **Respiratory failure**			
Mouth ulcers							
Conjunctivitis/episcleritis				**8. RENAL**			
Retro-orbital mass/ proptosis				Hematuria (no RBC casts) (≥1+ or 10 RBC/hpf)			
Uveitis				◆ **RBC casts** *(if both hematuria and RBC casts, score* ***only*** *RBC casts – the* ***major*** *item)*			
◆ **Scleritis**							
◆ **Retinal exudates/ hemorrhage**							
				◆ **Rise in creatinine >30% or fall in creatinine clearance >25%**			
4. EAR, NOSE & THROAT							
Bloody nasal discharge/ nasal crusting/ulcer							
				9. NERVOUS SYSTEM			
Sinus involvement				◆ **Meningitis**			
Swollen salivary gland				◆ **Cord lesions**			
Subglottic inflammation				◆ **Stroke**			
Conductive deafness				◆ **Cranial nerve palsy**			
◆ **Sensorineural deafness**				◆ **Sensory peripheral neuropathy**			
5. CARDIOVASCULAR				◆ **Motor mononeuritis multiplex**			
Pericarditis							
				10. OTHER			

Number of **Major** new/worse = x 3	Number of **Major** persistent = x 3	**BVAS/WG score =**	
Number of minor new/worse =	Number of minor persistent =		

Physician's global assessment (PGA) of disease activity (not including longstanding damage) within previous 28 days:

0 Remission — 10 Maximum Activity

References

DeRemee et al. Wegener's granulomatosis: observations on treatment with antimicrobial agents. Mayo Clin Proc 1985;60(1):27-32.

Luqmani RA et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87(11):671-8.

Stegeman CA et al. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med 1996;335(1):16-20.

Stone JH et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum 2001;44(4):912-20.

Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352(4):351-61.

Flossmann O et al. Development of comprehensive disease assessment in systemic vasculitis. Ann Rheum Dis 2007;66(3):283-92.

Hellmich B et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis 2007;66(5):605-17.

Jones RB et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis 2019 Jan.;78:399-405.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheum 2021;48:555-66.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83.

Puéchal X et al. Comparative study of granulomatosis with polyangiitis subsets according to ANCA status: data from the French Vasculitis Study Group Registry. RMD Open 2022;8(1):e002160.

Case 8

Granulomatosis with polyangiitis with subglottic stenosis

Miss Y is a 21-year-old Asian woman who was diagnosed 3 years ago with MPO-ANCA positive limited granulomatosis with polyangiitis. She had chronic rhinitis and sinusitis for 6 months, and gradually lost the sense of smell before she developed saddle node deformity (Figure 8.1) and subglottic stenosis (Figure 8.2). She received 8 months of glucocorticoid therapy (prednisone) and methotrexate, which she is still on (25 mg/week, with folic acid 5 mg every day except the day of the methotrexate injection). She improved clinically, but for the past month, her voice hoarseness has worsened and she reports breathing difficulties on exercise. Her rhinitis has remained stable, with occasional crusts, and she has no other clinical symptoms.

1. *How are MPO-ANCA-positive patients different from PR3-ANCA-positive patients in GPA?*
2. *What are the main differential diagnoses to consider in patients with chronic, erosive rhinitis and/or subglottic stenosis?*
3. *What are the treatment options for subglottic stenosis in patients with granulomatosis with polyangiitis?*
4. *What is the BVAS/WG score of this patient? Is there a more specific score that could be used to score ENT manifestations?*
5. *Can the saddle nose deformity regress? Does it reflect a more severe disease?*



Figure 8.1. Saddle nose deformity.



Figure 8.2. Coronal tracheal CT. Subglottic stenosis (arrow), around 2 cm below the vocal cord, with thickening of the tracheal mucosa.

Learning objectives

1. To recognize the phenotypic differences between MPO-ANCA-positive and PR3-ANCA-positive GPA.
2. To describe the epidemiology, characteristics and differential diagnoses of subglottic stenosis in granulomatosis with polyangiitis (GPA).
3. To discuss treatment options for subglottic stenosis in GPA.
4. To discuss reconstructive and plastic surgery for ear nose and throat (ENT) manifestations in GPA.

Answers

1. How are MPO-ANCA-positive patients different from PR3-ANCA-positive patients in GPA?

Positive MPO-ANCA is uncommon in non-Asian populations of GPA patients, occurring in up to 16.5% of GPA patients only. In cohorts of ANCA-associated vasculitis from Japan or Korea, more patients are MPO-ANCA positive (up to 80% of them in some series, the opposite of what is reported in cohorts from non-Asian countries), and more patients with a diagnosis of GPA are MPO-ANCA-positive. There is growing evidence that MPO-GPA is phenotypically different from PR3-GPA in non-Asian populations. In comparison, (non-Asian) MPO-positive GPA patients are more likely to:

- be female
- have a younger age at diagnosis
- have some more frequent ENT involvement (subglottic stenosis in particular)
- have limited disease without severe organ involvement (and therefore less need for aggressive immunosuppressive therapy)
- have fewer relapses

2. What are the main differential diagnoses to consider in patients with chronic, erosive rhinitis and/or subglottic stenosis?

Chronic, recurrent and erosive rhinitis/sinusitis, eventually leading to nasal deformity, can be due to conditions other than limited GPA. The diagnosis of the latter is challenging, as patients with limited GPA are often ANCA negative and the sensitivity of ENT biopsies is low (<25%; up to 50% with deep biopsy taken under general anesthesia or IV sedation). Hence, differential diagnoses must be excluded with the appropriate investigations but, sometimes, only disease progression over time will help confirm the diagnosis. The main differentials (although most do not include subglottic stenosis) to consider include:

- Chronic infectious rhinitis/sinusitis (different germs possible, including tuberculosis and fungal; allergic rhinitis should not cause erosions)
- Malignancies, including midline lymphoma and natural killer (NK)-T cell lymphoma
- Epstein-Barr virus (EBV)-related lymphomatoid granulomatosis
- (Levamisole-tainted) cocaine vasculopathy
- Relapsing polychondritis

- Antiphospholipid syndrome
- Systemic lupus
- Bare lymphocyte syndrome type I (transporter for antigen presentation [TAP]-deficiency)
- STING-associated vasculopathy (SAVI, mostly in children; STING, stimulator of interferon genes)
- Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) with ear/nose chondritis

Other rare conditions to consider include (congenital) syphilis, sarcoidosis, IgG4-related disease, leprosy, and rhinophyma. The latter three most commonly cause hypertrophic, dystrophic changes of the nose.

The differential diagnoses for subglottic stenosis include:

- Tracheal and tracheobronchial infections
- Tracheomalacia (congenital; idiopathic; or secondary to past intubation, tracheotomy, tracheal trauma or chronic obstructive pulmonary disease)
- Tracheal malignancies (including Kaposi sarcoma)
- Extrinsic tracheal compression (by an abscess, cysts, tumour, congenital vascular malformation, vascular ring or aorta aneurysm)
- Tracheal amyloidosis
- Relapsing polychondritis
- Sarcoidosis

3. What are the treatment options for subglottic stenosis in patients with granulomatosis with polyangiitis?

Subglottic stenosis in GPA must be managed in collaboration with experienced otorhinolaryngologists. It is reported in 3–25% of GPA patients, more frequently in women (female:male ratio 6:1) of younger age than average GPA patients (about 35 rather than 50 years). It is also a frequent manifestation in children with GPA. It can be isolated, occurring at diagnosis or later during the course of the disease. It can worsen or relapse, independently of the other more systemic manifestations. The tracheal lumen narrowing can be severe, thereby life-threatening. An additional challenge is to differentiate active inflammation due to the vasculitis from scarring and damage, with or without suprainfection or detached crusts or scabs.

Subglottic stenosis can be studied on CT scan (Figure 8.2) and must be evaluated by flexible nasolaryngoscopy. The lesion is typically segmental and located 1–2 cm below the vocal cords. Biopsy sensitivity is 50%, but endoscopy and biopsy are risky as they can trigger a local inflammatory reaction, worsen the stenosis, and/or lead to detached necrotic debris, then their inhalation, during or soon after the procedure. Spirometry may reveal blunting of the inspiratory curve. Laryngotracheal MRI utilizing edema-sensitive sequences and diffusion-weighted imaging was shown to be effective in detecting active subglottic inflammation, however this is not routinely used in clinical practice. Dynamic expiratory chest CT has also demonstrated promising results in detecting not only fixed tracheal stenoses, but also underappreciated dynamic airway changes, such as tracheobronchomalacia during respiration.

Hence, this patient needs a referral to an ENT specialist to better assess whether this isolated worsening of her subglottic stenosis is more due to suprainfection or a debris detachment, or more due to active vasculitis-inflammation. During the endoscopic examination, secretions can be cleared and other procedures can be performed, including CO_2 laser ablation, dilatation with bougies or balloon dilators followed by intralesional glucocorticoid (GC) injection. Excessive cicatricial scarring has been reported in patients receiving CO_2 laser treatment. Most GPA patients will require repeat procedures,

an average of three times at a mean interval of 11.5 months. In a study (Terrier et al. 2015), after the first endoscopic procedure, the cumulative incidence of recurrent stenosis requiring repeat procedure was 49% and 80% at 1 and 5 years, respectively. Factors associated with recurrence included the presence of associated bronchial stenosis. The utility of local applications of mitomycin-C, concomitant to dilations, is not well determined. Stenting is rarely performed due to technical challenges and the high rate of complications, including stent migration, infection and excessive granulation tissue formation leading to worsening obstruction. In cases of impending respiratory failure, temporary tracheostomy may be needed. Reconstructive laryngotracheal surgery is reserved for very severe cases and restricted to specialized centres.

Systemic treatments are often reported to exert minimal effect on subglottic stenosis. They cannot revert scarring and fibrotic subglottic stenosis. However, they can be transiently effective and should be given to patients with acute inflammatory exacerbations of their subglottic stenosis. A prednisone dose ≥30 mg/day at the time of endoscopic dilatation is associated with a lower cumulative incidence of treatment failure. Cyclophosphamide or rituximab can also be considered in severe cases, especially in patients with clear evidence of local, active vasculitic and/or inflammatory process.

4. What is the BVAS/WG score of this patient? Is there a more specific score that could be used to score ENT manifestations?

The BVAS/WG of this patient (Figure 7.3) is 1, due to the worsening of subglottic stenosis, which is a minor item. The minor, crusting rhinitis has remained stable in past years and should therefore be scored as damage (rather than persistent active manifestation).

A specific disease activity score (DAS) to assess ENT manifestations in GPA has been developed, called ENT/GPA DAS, but it requires an examination by an ENT specialist with nasofibroscopy. The score includes six items: reported bloody rhinorrhea; granulation; ulcers and/or friable mucosa in the upper airway on endoscopic evaluation; objective stridor; sudden sensorineural hearing loss; and inflamed tympanic membrane/middle ear without infection. It has better sensitivity and specificity than the ENT items of BVAS, but has not been validated yet and its reproducibility is unknown.

The Sino-Nasal Outcome Test (SNOT)-22 is a simple patient questionnaire, based on 22 questions and developed for the assessment of various sino-nasal diseases in adults. It is not specific to GPA but can be used for the follow-up of patients with GPA and ENT manifestations (Figure 8.3).

5. Can the saddle nose deformity regress? Does it reflect a more severe disease?

Saddle nose deformity is due to the destruction of nasal cartilage and is irreversible. It occurs in up to 20% of patients with GPA and it remains unknown why it affects some patients and not others. Analyses of case series did not reveal any specific association with other systemic manifestations. It usually develops rapidly, at diagnosis or later on, even sometimes during an effective induction treatment of a systemic GPA.

Patients can always consider nasal reconstructive surgery once the disease has been in sustained remission for a few years, with cartilage autotransplants from their ears or ribs. Nasal septum perforation repair is complicated because of the chronic relapsing nature of the disease and the frequently large size of the defect. A silicone septal button can be considered for small-sized defects.

Figure 8.3. Sino-Nasal Outcome Test-22 Questionnaire (adapted from Hopkins et al. 2009 - Copyright Washington University, with permission).

Below you will find a list of symptoms and social/emotional consequences of your nasal disorder. We would like to know more about these problems and would appreciate you answering the following questions to the best of your ability. There are no right or wrong answers, and only you can provide us with this information. Please rate your problems, as they have been over the past 2 weeks.

Considering how severe the problem is when you experience it and how frequently it happens, please rate each item below on how 'bad' it is by circling the number that corresponds with how you feel using this scale ➔	**No problem**	**Very mild problem**	**Mild or slight problem**	**Moderate problem**	**Severe problem**	**Problem as bad as it can be**	
1. Need to blow nose	0	1	2	3	4	5	
2. Sneezing	0	1	2	3	4	5	
3. Runny nose	0	1	2	3	4	5	
4. Cough	0	1	2	3	4	5	
5. Post-nasal discharge (dripping at the back of your nose)	0	1	2	3	4	5	
6. Thick nasal discharge	0	1	2	3	4	5	
7. Ear fullness	0	1	2	3	4	5	
8. Dizziness	0	1	2	3	4	5	
9. Ear pain	0	1	2	3	4	5	
10. Facial pain/pressure	0	1	2	3	4	5	
11. Difficulty falling asleep	0	1	2	3	4	5	
12. Waking up at night	0	1	2	3	4	5	
13. Lack of a good night's sleep	0	1	2	3	4	5	
14. Waking up tired	0	1	2	3	4	5	
15. Fatigue	0	1	2	3	4	5	
16. Reduced productivity	0	1	2	3	4	5	
17. Reduced concentration	0	1	2	3	4	5	
18. Frustrated/restless/ irritable	0	1	2	3	4	5	
19. Sad	0	1	2	3	4	5	
20. Embarrassed	0	1	2	3	4	5	
21. Sense of taste/smell	0	1	2	3	4	5	
22. Blockage/congestion of nose	0	1	2	3	4	5	
TOTAL							**TOTAL**

References

Langford CA et al. Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Arthritis Rheum 1996;39(10):1754-60.

Hopkins C et al. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol 2009;34(5):447-54.

Pagnoux C & Wolter NE. Vasculitis of the upper airways. Swiss Med Wkly 2012;142:w13541.

Klink T et al. Magnetic resonance imaging in patients with granulomatosis with polyangiitis (Wegener's) and subglottic stenosis. MAGMA 2013;26(3):281-90.

Del Pero MM et al. A disease activity score for ENT involvement in granulomatosis with polyangiitis (Wegener's). Laryngoscope 2013;123(3):622-8.

Terrier B et al. Granulomatosis with polyangiitis: endoscopic management of tracheobronchial stenosis: results from a multicentre experience. Rheumatology (Oxford) 2015;54(10):1852-7.

Schirmer JH et al. Myeloperoxidase-ANCA associated Granulomatosis with polyangiitis is a clinically distinct subset within ANCA-associated vasculitis. Arthritis Rheumatol 2016;68(12):2953-63.

Quinn KA et al. Subglottic stenosis and endobronchial disease in granulomatosis with polyangiitis. Rheumatology (Oxford) 2019;58(12):2203-11.

Unadkat SN et al. Nasal reconstructive surgery for vasculitis affecting the nose: our two-centre international experience. Eur Arch Otorhinolaryngol. 2020;277(11):3059-66.

Iudici M et al. Granulomatosis with polyangiitis: Study of 795 patients from the French Vasculitis Study Group registry. Semin Arthritis Rheum 2021;51(2):339-46.

Monti S et al. Anti-neutrophil cytoplasmic antibody specificity determines a different clinical subset in granulomatosis with polyangiitis. Clin Exp Rheumatol 2021;39(2):107-13.

Case 9

Microscopic polyangiitis – maintenance treatment

A 75-year-old woman presents to the emergency department with hemoptysis and dyspnea following a 4-month history of progressive weight loss and constitutional symptoms. On physical examination, she is febrile, tachycardic, and dyspneic with an O_2 saturation of 79% on room air. Auscultation of the lungs reveals crackles bilaterally. Chest X-ray reveals bilateral pulmonary infiltrates. A chest CT (without contrast) shows bilateral ground-glass opacities.

1. *List the main diseases or conditions that can cause diffuse alveolar hemorrhage.*

Labs reveal low hemoglobin at 85 g/l (normal 110-160 g/l), platelet count at 450 G/l (normal 150-450 G/l), and leukocytes at 17 G/l (normal 4-10 G/l) with predominant neutrophils. Creatinine is elevated at 250 µmol/l (normal 60-100 µmol/l) and urinalysis reveals 2+ blood, 2+ protein, with dysmorphic red blood cells and granular casts. C-reactive protein is 90 mg/l (normal <10 mg/l). ANCA is positive with a specificity for MPO-ANCA on ELISA. Aspartate transaminase (AST) and alanine transaminase (ALT) are both mildly elevated (2x the upper limit of normal). Sputum gram stain is negative. Staining for acid-fast bacillus (AFB) is also negative. Blood cultures are negative.

2. *What are the induction treatment options for this patient?*

Four months later, after having received glucocorticoids (high dose followed by a gradual tapering regimen) and oral daily cyclophosphamide, the patient is considered to be in remission. Her creatinine has decreased to 110 µmol/l and urinalysis shows no blood, but some persistent proteinuria at 0.5 g/l, which is stable. Her repeat chest CT shows complete resolution of the previous opacities. MPO-ANCA is negative.

3. *Do you agree that this patient is in remission and if so, can she be switched to maintenance treatment?*
4. *If you decide to move on to maintenance treatment, what would be the therapeutic options?*
5. *If the patient had been treated with rituximab for induction (1 g at days 1 and 15) instead of cyclophosphamide, what would be the options for maintenance?*

Learning objectives

1. To list the different conditions associated with alveolar hemorrhage and/or pulmonary renal syndrome.
2. To describe the epidemiology and main characteristics of microscopic polyangiitis (MPA).
3. To define remission in ANCA-associated vasculitis and be able to distinguish persistently active disease from damage.
4. To describe the different treatment options for induction and maintenance of MPA (and GPA).

Answers

1. List the main diseases or conditions that can cause diffuse alveolar hemorrhage.

The main differential diagnoses for diffuse alveolar hemorrhage are listed in Table 9.1. In practice, infections are the most important diagnoses to rule out. Cardiac failure and lung edema can also cause or increase alveolar bleeding.

2. What are the induction treatment options for this patient?

This patient has microscopic polyangiitis (MPA), which is an ANCA-associated vasculitis. She is presenting with severe systemic involvement, and specifically, with pulmonary-renal syndrome. Her original five-factor score is at least 1 (creatinine >140 µmol/l); she would get 2 points if proteinuria >1 g/24 hours is present (see Case 4, question/answer 3). MPA can be distinguished from granulomatosis with polyangiitis (GPA; see Table 6.1) by the absence of granulomatous manifestations (i.e. no granuloma on biopsy, erosive ENT manifestations, lung nodules, or orbital granulomatous tumour), and the more frequent association with pANCA MPO-ANCA (rather than cANCA PR3-ANCA). However, it is sometimes difficult to differentiate MPA from GPA; therefore, it is best to systematically specify the ANCA reactivity, as suggested by the 2012 Chapel Hill Consensus Conference. Therefore, this patient's diagnosis should be MPO-ANCA-positive MPA, with severe, life-threatening manifestations.

The treatment of severe MPA is currently superimposable to that of severe GPA as they are often grouped together in clinical trials (Figure 6.3 and Table 6.4). The induction treatment is based on the combination of high-dose glucocorticoids (GC) and/or avacopan, plus either oral/IV cyclophosphamide (CYC) or rituximab (RTX). The recent ACR/VF guidelines favour RTX over CYC for induction, but evidence behind this remains weak, especially for MPA, and this is mostly based on expert consensus because of the well-known risks associated with high levels of cumulative exposure to CYC (infertility, late cancers). In the absence of a clear contraindication to CYC, this would not be a mistake in this patient to choose CYC for induction instead of RTX.

GC treatment is urgent and usually consists of initial methylprednisolone IV pulses (7.5-15 mg/kg/day; maximum 1000 mg/day) for 1 to 3 days, followed by prednisone 1 mg/kg/day (maximum 80 mg) for 2 weeks, with a gradual taper by approximately 10% of the dose every 2 weeks until reaching 5 mg/day, around the 5th month of treatment. The optimal tapering regimen and duration of GC treatment have been the subject of much debate and require more research. The results of the PEXIVAS trial showed that a faster tapering regimen is feasible, effective, and is associated with less infections. Some experts stop GC at month 5 or 6, while others continue it at a low dose (5 mg/day) for several months to years.

As detailed in Case 6, the results of the ADVOCATE trial led to the approval by the FDA, and then in April 2022 by Health Canada, of avacopan, a complement C5a receptor antagonist, as an option to further reduce the use of GC. In this trial, oral avacopan was given at the dose of 30 mg x 2/day (for 12 months) instead of prednisone, with either RTX for induction (then no other maintenance agent) or CYC (followed by azathioprine [AZA] for maintenance). Avacopan was significantly superior to prednisone for sustained remission at week 52 (65% vs. 55%). Infections and several types of adverse events occurred at numerically lower rates in the avacopan group. In practice, it is likely that most physicians will still prescribe GC to their patients (for some time at least), initially and/or for those with the more severe disease forms. The optimal duration of avacopan treatment also remains to be determined.

Table 9.1. Main causes of diffuse alveolar hemorrhage.

Disease or disease group		Comments
Lung parenchymal disease/inflammation		
Small-vessel vasculitis	ANCA-associated vasculitides Anti-glomerular basal membrane (GBM) disease Immune-complex mediated vasculitides Isolated (idiopathic) lung capillaritis/vasculitis Rarely IgA vasculitis, cryoglobulinemic vasculitis	Mainly GPA and MPA (rarely EGPA) Often referred to as Goodpasture's syndrome/disease
Other systemic diseases	Systemic lupus erythematosus Antiphospholipid antibody syndrome Rheumatoid arthritis Systemic scleroderma Polymyositis/dermatomyositis Sarcoidosis	Order anticardiolipin, anti-beta2-glycoprotein 1 antibodies and lupus anticoagulant Through lung disease and/or associated vasculitis (RA or SSc) and/or veno-occlusive disease (SSc)
Drug-related lung toxicity	Propylthiouracil, diphenylhydantoin, amiodarone, mitomycin, D-penicillamine, methotrexate, gold, haloperidol, nitrofurantoin, all-trans-retinoic acid, bleomycin, carbimazole, hydralazine, sirolimus, CTLA-4 and PD-L1/PD-1 checkpoint inhibitors	Most cause interstitial lung infiltrates rather than diffuse alveolar hemorrhage
Toxic and irritant inhalation	Trimellitic anhydride, isocyanates, crack cocaine, amphetamines, pesticides, detergents	
Miscellaneous	Lung-graft rejection, radiation therapy, pulmonary infarction, hematopoietic stem cell transplant	
Infections	Human immunodeficiency virus, infective endocarditis, cytomegalovirus, herpes simplex virus, malaria, dengue, influenza (e.g. H1N1), hantavirus, invasive aspergillosis, legionellosis, mycoplasmosis, leptospirosis, other bacterial pneumoniae and any infection causing acute respiratory distress syndrome	
Not primarily due to lung parenchymal disease/inflammation		
Lung vessel and/or aneurysm rupture	Multiple causes: traumas, vascular malformation or fibrodysplasia, vasculitis-related aneurysms (Takayasu arteritis, Behçet's disease), lung abscess/cavity or bronchial lesions eroding nearby vessels, etc.	
Hemostasis disorders	Thrombotic thrombocytopenic purpura and idiopathic thrombocytopenic purpura, anticoagulants, antiplatelet agents, thrombolytics; disseminated intravascular coagulation	Usually associated with another underlying lung condition when causing diffuse alveolar hemorrhage
Mitral stenosis and mitral regurgitation, pulmonary edema		
Pulmonary veno-occlusive disease (e.g. in patients with SSc)		
Idiopathic pulmonary hemosiderosis		
Pulmonary embolism, cholesterol emboli syndrome		
Malignant conditions	Lung cancer, pulmonary angiosarcoma, Kaposi sarcoma, metastatic renal cell carcinoma, multiple myeloma, acute promyelocytic leukemia	
Other conditions	High-altitude pulmonary edema, barotrauma Lymphangioleiomyomatosis Pulmonary capillary hemangiomatosis Lymphangiography Tuberous sclerosis	

In this patient, CYC can be used in combination with GC as she has no major contraindications to CYC and there is no other obvious reason to favour RTX (e.g. no fertility concern). In addition, even though the RAVE study suggested that patients with PR3-ANCA vasculitis may respond better to RTX than CYC, there was no such superiority of RTX in patients with MPO-ANCA. The dose of CYC must be adjusted based on renal function and age. The French CORTAGE study showed that patients aged >65 years can achieve similar remission rates using a total of six IV pulses of CYC with a reduced and fixed dose of 500 mg, rather than the full 7.5-15 mg/kg per pulse. The pulses were still given every 2 weeks for the first three doses, then every 3 weeks for the next three to six doses.

If oral CYC is used, the daily dose is 1 to a maximum of 1.5 mg/kg/day (rather than the standard 2 mg/kg/day, corresponding to a 25–50% decrease; maximum 200 mg/day). Because of this patient's age and renal function, for oral CYC, a dose of 1 mg/kg/day and, for IV CYC, a dose of 10 mg/kg per pulse or a fixed dose of 500 mg per pulse should be chosen. Bladder protection with mesna for IV CYC is not mandatory with this limited dose of CYC (<600 mg per pulse), but adequate concomitant hydration remains crucial with either oral or IV CYC treatment. As mentioned already, using RTX (e.g. 1 g at days 1 and 15) instead of CYC was another option, which would have been favoured if following the recent 2021 ACR/VF guidelines.

Prophylactic therapy against *Pneumocystis jiroveci* pneumonia (trimethoprim/sulfamethoxazole, 80/400 mg 3 times per week [i.e. a lower dose than usual, because of the patient's impaired renal function, but this can be re-adjusted if function recovers]; dapsone 100 mg per day, atovaquone 1500 mg per day or aerosolized pentamidine 300 mg monthly in case of allergy to the former) must be given, while on CYC and for another 3 months after cessation. Prevention of osteoporosis should also be initiated, following the most recent guidelines on GC-induced osteoporosis.

The results of the PEXIVAS study showed that PLEX did not prolong the time to death and/or end-stage renal disease in patients with ANCA-associated vasculitis and severe renal and/or pulmonary involvement. It might still be considered in patients with severe alveolar hemorrhage who do not respond to the conventional induction treatments, but with limited expectations. As stated in the CanVasc recommendations for the management of ANCA-associated vasculitides, PLEX "may still be considered for patients who clinically deteriorate because of active vasculitis despite ongoing remission induction therapy, and/or with intermediate to severe renal disease (based on post-hoc analyses of cohorts and PEXIVAS data suggesting some limited renal improvement with PLEX, but with an associated higher risk of infections).

3. Do you agree that this patient is in remission and if so, can she be switched to maintenance treatment?

Remission can be defined as the absence of disease activity. In clinical trials, this usually corresponds to a BVAS of 0 (see Figure 7.2). In several trials, remission was defined as a BVAS of 0 for two consecutive visits at least 28 days apart. In some other trials, the definition of remission also included a prednisone dose threshold, such as having BVAS of 0 and being on a prednisone dose <5 mg/day (or being off prednisone totally).

Hence, if there has been no sign of active disease in the past month, one can consider this patient to be in clinical remission. Her lung lesions have completely resolved. However, the challenge is to differentiate damage from persistent disease activity and active renal disease, as there is still some proteinuria and the creatinine level may not have returned to the level prior to disease onset. Persistent, minor microscopic hematuria is not uncommon at the time of remission. In the absence of red blood cell (RBC) casts or dysmorphic RBCs, this often represents damage.

If unclear, a renal biopsy may be required. In practice, if renal parameters have improved since initiating treatment and all other systemic manifestations have resolved or improved, the patient is considered to be in remission and is switched to maintenance therapy.

The persistence of ANCA does not influence the decision to continue induction treatment or to switch to maintenance therapy, as not all patients who achieve clinical remission become ANCA-negative with treatment. Even though patients with persistent ANCA at the time of remission may have a higher risk of subsequent relapse if treated with azathioprine (AZA) or methotrexate (MTX) for maintenance, there has been to date no proven benefit in continuing or intensifying their induction treatment. Of note, checking ANCA status at the time of remission is common practice, but not a recommendation by CanVasc or any other international vasculitis study groups.

4. If you decide to move on to maintenance treatment, what would be the therapeutic options?

Currently, the maintenance treatment for MPA, following induction with GC and CYC, is similar to that of systemic GPA (Table 9.2 summarizes the main published trials on maintenance therapy in GPA/MPA). AZA, MTX, leflunomide (LEF), mycophenolate mofetil (MMF) were the conventional agents to consider before RTX became the gold standard for maintenance, as per both the CanVasc and 2021 ACR/VF recommendations. Maintenance treatment with RTX is more effective in preventing relapses in ANCA-associated vasculitides, based on the MAINRITSAN results, although this trial only included a few MPO-ANCA MPA patients. RTX was approved in October 2018 by the US FDA for maintenance ("follow-up treatment", after remission has been achieved), of remission in patients with GPA or MPA (it has not been approved by Health Canada, as the pharmaceutical company marketing RTX in Canada did not apply for it; however, RTX has been gradually covered since early 2019 in every province, and with biosimilars of RTX available since 2021, access to RTX for maintenance has become simpler).

When using CYC for induction, maintenance treatment can be initiated as soon as the patient has achieved remission (based on the CYCAZAREM study results), usually after 6 to a maximum of 9 pulses of IV CYC, or after 3 to a maximum of 6 months of oral CYC. The first RTX maintenance infusion is usually given 2 to 4 weeks after the last IV dose of CYC, or within 1 to 15 days after the last oral CYC dose.

RTX maintenance regimen (post CYC-based induction treatment) in the MAINRITSAN trial was two consecutive infusions of 500 mg two weeks apart at month 4, followed by repeat 500 mg infusions every 6 months for three more times. Post-hoc analyses of this trial and the subsequent MAINRITSAN 2 showed that the initial day 15 infusion could be omitted (hence, a simpler regimen of 500-mg RTX infusions at remission (day 1) then every 6 months for a total of 2 years). The RITAZAREM study (ClinicalTrials.gov Identifier: NCT01697267) used RTX 1000 mg infusions at month 4, then every 4 months for four more doses in patients with relapsing GPA or MPA, who have received RTX for induction. This study confirmed the superiority of RTX over AZA in preventing relapse (hazard ratio of 0.41; 95% confidence interval of 0.27-0.61).

Previous studies that used a maintenance regimen for 1 to 3 years with conventional drugs (i.e. AZA or MTX) showed that the relapse rate is around 34% in MPA after a median follow-up of 72 months (vs. 35–64% at 7 years in GPA). In the MAINRITSAN trial, the global rate of major relapses at 28 months was 5% with RTX, all occurring in patients with GPA, vs. 29% with AZA (P = 0.002). None of the 8 patients with MPA had a relapse on RTX maintenance (vs. 3/15 on AZA; P = 0.53). The longer follow-up of the MAINRITSAN trial showed a major relapse-free survival rate at 60 months of

71.9% with RTX and a minor and major relapse-free survival rate of 57.9%.

The optimal duration of maintenance therapy with GC and/or other agents is unknown, and may vary individually according to the patient and disease characteristics. A meta-analysis has suggested that long-term use (beyond 12 months) of low-dose GC (5 mg/day of prednisone) was associated with a lower relapse rate (when conventional AZA or MTX were used in combination). The results of the European REMAIN trial, which compared 2 vs. 4 years of maintenance with AZA (or MTX) and prednisone 5 mg/day, showed that the continuation of this maintenance treatment for 4 years was associated with fewer relapses, especially for patients with persistent ANCA-positivity at remission (see Table 9.2). However, a cohort study from Chapel Hill revealed that long-term prednisone treatment did not reduce the risk of relapse but increased the risk of infections. TAPIR is an ongoing trial in GPA comparing the continuation of low-dose GC for 6 additional months versus its discontinuation in patients who achieved remission of a disease flare in the 12 months prior to enrolment (results are expected in 2023-2024).

The French MAINRITSAN 3 trial compared 2 vs. 4 years of RTX infusions for maintenance (500 mg every 6 months), and showed a minimal (but significant) superiority of the longer treatment at preventing relapses. The relapse-free survival rate at year 4 was 96% with 4 years of RTX vs. 74% when stopping RTX at 2 years (P = 0.008). Major relapse–free survival rates were 100% vs. 87%, respectively (P = 0.009). In addition to this latter difference being eventually small, some study design drawbacks limit the generalization of these results. The decision after year 2 of maintenance with RTX remains based on individualized patient characteristics (such as prior history of relapses, persistence of ANCA, especially if MPO-ANCA and/or renal disease, prior disease severity and damage). Better biomarkers for disease activity and to predict relapses remain to be identified.

Other agents might further improve the rate of sustained remission and reduce the risk of subsequent relapses. Trimethoprim–sulfamethoxazole cannot substitute for immunosuppressive treatment, but given at a high dose (320/1600 mg/day) in combination with the other treatments, could further reduce the rate of localized ENT relapse by 40% at 1 year in GPA (no such data in MPA). This effect is seen regardless of the presence or absence of *Staphylococcus aureus* on nasal swabs.

Belimumab, a monoclonal antibody directed against B-lymphocyte stimulator/B-cell activating factor (BLyS/BAFF) was investigated for maintenance in GPA or MPA, in combination with AZA or MTX (BREVAS). Published results showed no overt benefit, except maybe in the subset of patients induced with rituximab. A subsequent trial specifically combining belimimumab and rituximab has been under consideration. In the ADVOCATE trial, avacopan was given for 12 months, which would also correspond to a maintenance regimen (remission being usually achieved after 3 to 6 months). Follow-up data after the discontinuation of avacopan at month 12 are lacking (and were not collected as part of the study). Hence, the optimal duration of avacopan therapy, and the place of a combination of avacopan and RTX for maintenance, remain to be determined.

5. If the patient had been treated with rituximab for induction (1 g at days 1 and 15) instead of cyclophosphamide, what would be the options for maintenance?

In the RAVE trial, no maintenance therapy was given after the last RTX induction infusion. The relapse rates were comparable at 18 months (about 30%) in the RTX and CYC–AZA arms. In the RITAZAREM study, all patients had relapsing GPA or MPA, were re-induced with RTX, and then received RTX 1 g at month 4 then every 4 months for 2 years for maintenance (or AZA in the control

arm, which showed to be inferior at preventing relapse). Several strategies for maintenance after RTX-based induction are thus available:

- Monitor and re-treat (with RTX) only if a clinical relapse occurs (this option would not apply to a patient with history of previous relapse(s))
- Re-treat with RTX according to ANCA positivity, ANCA titre and/or CD19+/CD20+ B lymphocyte count: repeat RTX infusions (with a full induction dose regimen or a lower dosage) if there is B-lymphocyte reconstitution and/or ANCA reappearance or a significant titre increase. The reliability of CD19+ B-cell and ANCA monitoring to predict a flare in RTX-induced patients seems better than in those induced with CYC, but remains unclear. The MAINRITSAN 2 trial prospectively investigated the value of this approach and showed that the "on-demand, tailored" treatment (500 mg per infusion) was associated with a statistically comparable rate of (major or minor) relapses at 28 months of 17.3% vs. 9.9% with the fixed-schedule infusions (systematic infusions of 500 mg every 6 months).
- Systematic maintenance infusions, at regular intervals for at least 2 years, independently of ANCA status or B-cell count, using different dosages than those used for induction (500 mg every 6 months like in the MAINRITSAN trial; 1000 mg every 6 months in a UK cohort; 1000 mg every 4 months in the RITAZAREM trial), starting at 4–6 months after the last RTX induction dose. The optimal duration of maintenance with RTX is unknown. After 2 years, patients may:
  1. stop the RTX and be monitored clinically and biologically;
  2. move to yearly infusions of RTX for a couple more years, before stopping it; or
  3. continue the RTX infusions every 4-6 months for 2 more years, before having to consider again the subsequent strategy.

  The decision is based on each patient's characteristics and, sometimes, preferences as well.

Importantly, as long as the patient receives RTX, prophylaxis against *Pneumocystis jiroveci* pneumonia should be continued, and ideally for 6-12 more months after the last infusion.

The relapse rate of patients with MPA and MPO-ANCA was lower than that of patients with GPA or PR3-ANCA in most (but not all) studies. Hence, whether patients with MPA or MPO-ANCA require the same maintenance regimen as those with GPA or PR3-ANCA remains to be better evaluated in future studies (at present, there is no major difference in practice for both the induction and maintenance treatment of severe GPA or MPA).

Table 9.2. Summary of the main published randomized controlled trials of ANCA-associated vasculitis on maintenance treatment.

Study name/ acronym	Sample size	Inclusion criteria	Studied intervention	Primary endpoints	Main results/conclusions
CYCAZAREM (Jayne et al. EUVAS, 2003)	144	Newly diagnosed GPA, MPA or renal-limited disease, with at least one major organ involved (but creatinine level <500 µmol/l)	All induced with oral CYC and GC until remission (3-6 months) then randomized for maintenance with oral AZA (2 mg/kg) or continuation of oral CYC (1.5 mg/kg) until month 12 (then AZA for all until month 18)	Relapse (major or minor) and adverse events at month 18	No difference in relapse and adverse event rates at 18 months: CYC-based induction can be stopped after remission is achieved - At longer term (8.5 yr), 52% relapsed in the AZA group vs. 36% in the CYC group (subHR 1.63, 95% CI 0.99–2.71; P=0.06). Same rates of side effects or deaths
WGET (WGET research group, 2005)	180	Newly diagnosed (44%) or relapsing, limited (29%) or severe GPA	Standard therapy with GC and CYC (severe, then MTX or AZA for maintenance for 12 months) or MTX (limited, continued for 12 months after remission) with concurrent etanercept (25 mg subcutaneous, twice weekly) or placebo	Sustained remission (BVAS=0 for at least 6 months)	No significant differences between the etanercept and placebo groups (69.7% vs. 75.3% sustained remission; P=0.39) – follow-up 27 months Solid cancers developed in 6 etanercept recipients (none in placebo group)
Metzler et al. (2007)	54	Generalized GPA	Induction with oral CYC and GC then maintenance with LEF (100 mg/day loading dose for 3 days, then 20 mg/day for 1 month, then 30 mg/day) or MTX (7.5 mg/week oral for 1 month, then 15 mg/week for 1 month, then 20 mg/week)	Number of major and minor relapses	Study terminated prematurely because of high rate of major relapses in the MTX group (13 vs. 6 patients; P=0.037) – follow-up 21 months No MTX patient but 4 LEF patients had to discontinue the study because of LEF-attributable adverse events (2 hypertension, 1 peripheral neuropathy, 1 leucopenia)
WEGENT (Pagnoux et al. FVSG, 2008)	126	Newly diagnosed systemic GPA or MPA	All induced with IV CYC pulses and prednisone until remission (3-6 months) then 3 consolidation pulses before randomization for maintenance with MTX (0.3 mg/kg/week, oral or subcutaneous if not tolerated orally) or oral AZA (2 mg/kg/d) for 12-16 months	Adverse events (severe and/or leading to study drug cessation) and relapse	No difference between the groups in relapse and adverse event rates - At longer term (10 yr), relapse-free survival rates were 26.3% with AZA vs. 33.5% with MTX (P=0.29)
IMPROVE (Hiemstra et al. EUVAS, 2010)	165	Newly diagnosed systemic GPA or MPA	All induced with IV or oral CYC pulses and prednisolone until remission (3-6 months) then randomization for maintenance with oral MMF (2 g/d) or oral AZA (2 mg/kg/d) until month 42	Relapse-free survival and adverse events	MMF was less effective than AZA for maintaining disease remission (HR of relapse 1.69 [95% CI 1.06-2.70; P=0.03]) Severe adverse events did not differ significantly between groups
MAINRITSAN (Guillevin et al. FVSG, 2015)	115	Newly diagnosed (80%) or relapsing, severe GPA (76%), MPA (20%) or renal-limited disease, with ANCA (94%) or without ANCA	Induction with IV CYC and GC, then maintenance with RTX (500 mg on days 0 and 14, months 6, 12, and 18) or AZA (2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months)	Rate of major relapse (with BVAS>0 and ≥1 major organ involvement and/or life-threatening disease) at month 28	Less major relapses with RTX (5%) vs. AZA (29%; HR 6.61, 95% CI 1.56 to 27.96; P =0.002) at 28 months - At 60 months, more major relapses in both arms, but still less in the RTX group (major relapse-free survival rates of 71.9% with RTX vs. 49.4% with AZA; p=0.003)
AZA-ANCA (Sanders et al. 2016)	131	Newly diagnosed PR3-ANCA+ vasculitis	Oral CYC and GC for all then extended AZA maintenance therapy if cANCA-positive at remission (n=45; 1.5-2.0 mg/kg/day for 4 years after diagnosis then tapered by 25 mg every 3 months) or standard (1.5-2 mg/kg/day until 1 year after diagnosis then tapered by 25 mg every 3 months)	Relapse-free survival at 4 years after diagnosis	No significant difference in relapse-free survival or relapse rates between study groups (and no difference between extended treatment in those ANCA-positive at remission and standard treatment in all patients, ANCA-positive or -negative at remission) – follow-up 45 months

Study name/ acronym	Sample size	Inclusion criteria	Studied intervention	Primary endpoints	Main results/conclusions
REMAIN (Karras et al. 2017)	117	Newly diagnosed (96%) or relapsing GPA or MPA, 18–24 months after disease flare, in stable remission after CYC-GC induction followed by AZA-GC maintenance therapy	Randomized to receive continued AZA-GC until 48 months from last flare or to withdrawal by 24 months	Relapse rate at 4 years after last flare (diagnosis or relapse)	- More relapses in the withdrawal (24 months) arm (63% vs .22%; p<0.0001, OR 5.96). ANCA positivity at randomization associated with relapse risk (51% vs. 29%; p=0.017, OR 2.57) - Renal function, ANCA type or vasculitis type not predictive of relapse. Severe adverse events more frequent in the continuation arm
MAINRITSAN 2 (Charles et al. 2018)	162	Newly diagnosed or relapsing GPA or MPA in complete remission after induction with GC and CYC (61.7%) or RTX (37.6%)	- Tailored-arm: 500 mg RTX at randomization, with reinfusion only if/when CD19+B cells or ANCA had reappeared or ANCA titre rose markedly (tested q3months) until month 18 - Controls: fixed 500 mg RTX at randomization, day 14 then 6, 12 and 18 months	Number of relapses at month 28	- At month 28, relapse rates of 17.3% in the tailored-arm vs. 9.9% in the fixed-schedule arm (p=0.22) - Median of 3 infusions (IQR 2–4) in the tailored-arm (vs 5 in the fixed-schedule arm)
BREVAS (Jayne et al. 2019)	105	Newly diagnosed or relapsing, ANCA-positive, GPA (79%) or MPA (21%) in complete remission after induction with GC and CYC (74%) or RTX (26%)	Maintenance with AZA (2 mg/kg/day) for all patients and either belimumab IV (10 mg/kg, on days 1, 15 and 29 then monthly for at least 12 months – until the last enrolled patient completed the minimal 12-month study treatment) or placebo [study enrollment between 6-26 weeks after the first dose of induction therapy; patients in remission and usually already on AZA]	Time-to-first-event (relapse with BVAS≥6, or relapse with major BVAS item, or use of any study-prohibited medication)	- study truncated early at 105 patients (recruitment issues) - Adjusted HR for time-to-first-event of 1.07 (95% CI 0.44-2.59; p=0.88) and vasculitis relapse of 0.88 (95% CI 0.29-2.65; p=0.82) - In the belimumab group, all vasculitis relapses occurred in CYC-induced, PR3-ANCA patients (i.e. no relapses in the RTX-induced or MPO-ANCA patients)
MAINRITSAN 3 (Charles et al. 2020)	97	New or relapsing ANCA+ GPA (n=68) or MPA (n=29) in remission at the end of the MAINRITSAN 2 trial (all had received RTX for maintenance, either systematically every 6 months for 2 years, or based on serial ANCA testing and CD19 B-cell count for 2 years)	Randomized to continue RTX 500 mg or placebo every 6 months for 2 years more (4 infusions)	Relapse-free survival 28 months after randomization	- Relapse-free survival estimates: 96% with RTX vs. 74% with placebo groups with a HR of 7.5 (95% CI, 1.67-33.7; P=0.008) - Major relapse–free survival estimates: 100% vs. 87% (P=0.009), respectively - At least 1 serious adverse event in 12 (24%) patients in RTX vs. 14 (30%) with placebo
RITAZAREM (Smith et al. Abstract 2020; publication expected early 2023	170	Relapsing ANCA+ GPA or MPA, randomized after having achieved remission with RTX (375 mg/m^2 x4) and GC	- Randomized at month 4 to receive either AZA (2 mg/kg/day, decreased by half at month 24 and stopped at month 27) or RTX (1000 mg at month 4, then every 4 months until month 20; 5 infusions) for maintenance - GC gradually tapered and stopped at month 20	Time from randomization to disease relapse	- RTX superior to AZA with HR for relapse of 0.41 (95% CI, 0.27-0.61; P<0.001) - 22% patients with RTX had ≥1 severe adverse event vs. 36% with AZA. No differences in frequencies of hypogammaglobulinemia or infections

HR, hazard ratio; 95% CI, 95% confidence interval; subHR, subdistribution hazard ratio; IQR: interquartile

References

Jayne D et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349(1):36-44.

Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352(4):351-61.

Metzler C et al. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's Granulomatosis. Rheumatology 2007;46:1087-91.

Pagnoux C et al. Azathioprine or Methotrexate Maintenance for ANCA-Associated Vasculitis. N Engl J Med 2008;359(26): 2790-803.

Hiemstra TF et al. Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Controlled Trial. JAMA 2010;304(21):2381-8.

Flossman O et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 2011;70: 488-94.

Walsh M et al. Risk Factors for Relapse of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheum 2012;64(2):542-8.

Guillevin L, Pagnoux C et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371(19):1771-80.

Pagnoux C et al. Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. Arthritis Rheumatol 2015;67(4):1117-27.

Sanders JS et al. Extended versus standard azathioprine maintenance therapy in newly diagnosed proteinase-3 anti-neutrophil cytoplasmic antibody-associated vasculitis patients who remain cytoplasmic anti-neutrophil cytoplasmic antibody-positive after induction of remission: a randomized clinical trial. Nephrol Dial Transplant 2016;31(9):1453-9.

Karras A et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis 2017;76(10):1662-8.

Charles P et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77(8):1143-9.

Terrier B et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis 2018;77(8):1150-6.

Jayne D et al. Efficacy and Safety of Belimumab and Azathioprine for Maintenance of Remission in ANCA-Associated Vasculitis: A Randomized Controlled Study. Arthritis Rheumatol 2019; 71(6):952-63.

Charles P et al. Long-Term Rituximab Use to Maintain Remission of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Randomized Trial. Ann Intern Med. 2020;173(3):179-87.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheum 2021;48:555-66.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83.

Jayne DRW et al. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 2021;384(7):599-609.

Case 10
Relapsing microscopic polyangiitis

Mr. N, currently 68 years old, was diagnosed 8 years ago with interstitial lung disease/fibrosis (he had several suprainfections since then, but there has been no need for specific treatments, as his yearly pulmonary function tests and chest CT have shown moderate, stable abnormalities). Three years ago, he was also diagnosed with MPO-ANCA-positive microscopic polyangiitis, with fever, diffuse arthralgias and myalgias, 10-kg weight loss in 5 months, diffuse necrotic purpura on the lower limbs (biopsy: small-vessel vasculitis, with fibrinoid necrosis) and severe renal involvement (creatinine 430 µmol/l with proteinuria 2.5 g/24 hours, microscopic hematuria with granular casts, pauci-immune glomerulonephritis on biopsy with mixed lesions). He achieved remission after 6 months of oral cyclophosphamide (cumulative dose received: 27 g) combined with glucocorticoids. He was subsequently switched to maintenance therapy with azathioprine (150 mg/day) and continued prednisone (5 mg/day). His MPO-ANCA status has remained positive, although the titre decreased from >8 IU/l at diagnosis to 2.6 IU/l, at his last routine blood work, 6 months ago.

Over the past 2 weeks, he developed recurrent fever, arthralgias and myalgias, cough, shortness of breath, extreme fatigue and purpura on his legs, similar to symptoms at his disease onset 3 years previously. His first labs reveal a C-reactive protein of 120 mg/l (normal <10 mg/l), hemoglobin level of 82 g/l (normal 120-180 g/l), white blood cell count at 14,560/mm^3 (normal 4,000-10,000/mm^3), with predominant neutrophils, serum creatinine level 510 µmol/l (compared with 157 µmol/l, 3 months ago). Urinalysis shows proteinuria 3 g/l (1.8 and 1.6 g/24 hours, 6 and 12 months ago, respectively), and microscopic hematuria with casts.

1. *Can the interstitial lung disease be related to his MPO-ANCA-associated vasculitis?*
2. *How can renal disease be classified on histology in patients with ANCA-associated vasculitides (histological, prognostic classification)?*
3. *Which treatment would you consider now if relapse of the MPO-ANCA-positive microscopic polyangiitis is confirmed?*
4. *At the time of this relapse, what is the vasculitis damage index (VDI) score?*
5. *If the patient survives but progresses to end-stage renal disease, can he be considered for renal transplant?*

Learning objectives

1. To describe the relapse rate in microscopic polyangiitis (MPA), and compare it with that of granulomatosis with polyangiitis (GPA).
2. To understand the links between interstitial lung disease/fibrosis and ANCA-associated vasculitis.
3. To describe the treatment options for patients with relapsing MPA (or GPA).
4. To describe and know how to use the vasculitis damage index (VDI) score.
5. To discuss the possibility (and optimal conditions) for renal transplantation in patients with end-stage renal disease due to vasculitis.

Answers

1. Can the interstitial lung disease be related to his MPO-ANCA-associated vasculitis?

Lung fibrosis has been increasingly reported in association with and/or as a possible complication of ANCA-associated vasculitis, primarily MPO-ANCA (80–90% of cases with the two conditions). The first series originated from Japan, where MPO-ANCA prevails over PR3-ANCA vasculitis. The interstitial lung disease is often diagnosed concomitantly (43% of cases in a series from France with review of the literature by Comarmond et al, 2014) or before the vasculitis, like in this patient (45%; on average 2–5 years before [up to 24 years]). The imaging pattern is most often that of a typical (43%) or atypical (14%) usual interstitial pneumonia. Non-specific interstitial pneumonia was observed in 17% (fibrotic, 7%) of patients, and combined pulmonary fibrosis-emphysema in 21%. The fibrosis preferentially involves the lung bases (Figure 10.1).

The pathogenic mechanism of this ANCA-associated interstitial lung disease is not well understood but may relate to oxidative bursts of mononuclear inflammatory cells triggered by the ANCA, along with damage resulting from recurrent or chronic, possibly subclinical, alveolar hemorrhage. Of note, the lung fibrosis and vasculitis may have independent outcomes, with progression of the fibrosis despite sustained control of the vasculitis under treatment.



Figure 10.1. Chest CT, horizontal view of the lungs in a patient with MPO-ANCA-associated vasculitis (not active) and lung fibrosis with a usual interstitial pneumonia pattern (honeycombing changes in the bases, with reticulations or traction bronchiectases).

The mortality rate of patients with lung fibrosis with MPO-ANCA is similar to that of those with idiopathic pulmonary fibrosis, but worse than those with collagen vascular diseases without MPO-ANCA. In the series by Comarmond et al (2014), 37% of patients died after a median follow-up of 48 months, almost two-thirds from respiratory insufficiency. In the literature, the global mortality rate was 56% after a follow-up of 45 months.

2. How can renal disease be classified on histology in patients with ANCA-associated vasculitides (histological, prognostic classification)?

In 2010, a European group (Berden et al., 2010) devised a four-category classification of renal pathology in ANCA-associated vasculitis, validated by an analysis of 100 patients from the CYCAZAREM and MEPEX studies (Table 6.4), who had renal biopsies and a follow-up exceeding 12 months. This histological classification system was found to be of prognostic value for 1- and 5-year renal outcomes.

- **Focal**: ≥50% normal glomeruli (renal survival at 1 and 5 years of 93% and 93%, respectively)
- **Crescentic**: ≥50% glomeruli with cellular crescents (renal survival at 1 and 5 years of 84% and 76%)
- **Mixed**: <50% normal, <50% crescentic, <50% globally sclerotic glomeruli (renal survival at 1 and 5 years of 69% and 61%)
- **Sclerotic**: ≥50% globally sclerotic glomeruli (renal survival at 1, 5 and 7 years of 50%, 50% and 25%)

It is important to remember that these renal survival estimates were obtained in patients from two studies in which all received a combination of glucocorticoids (GC) and cyclophosphamide (CYC) for induction. Whereas a focal pathology can carry a better prognosis, it does not justify a lowering in the intensity of the induction treatment.

The prognostic value of this classification was validated in other cohorts, but has to be more thoroughly analyzed in patients treated with other induction agents, such as rituximab (RTX), or newer drugs like the complement C5a receptor antagonist avacopan. A first study on 30 patients treated with RTX rather than CYC showed that only tubular atrophy, but not the histological classification, was an independent predictor of glomerular filtration rate at 12 and 24 months post diagnosis.

3. Which treatment would you consider now if relapse of the MPO-ANCA-positive microscopic polyangiitis is confirmed?

An infection, which might have triggered the flare, must be ruled out (a bronchoscopy might be considered, if suspicion for infection is high). Adherence to treatment must also be assessed. The patient should also have a repeat chest CT to look for new lesions and/or ground-glass opacities suggestive of subclinical alveolar hemorrhage (possible as his hemoglobin level is low and he had some cough).

As this relapse is severe (major relapse with severe renal disease), the treatment to re-induce remission must include high-dose GC and another potent immunosuppressant. Currently, the choices for the latter remain CYC or rituximab. The latest 2021 ACR/VF recommendations favour RTX as the first-line option over CYC. CanVasc recommendations favour RTX in relapsing patients who had already received CYC in the past, or with a contraindication to CYC. As the patient has already received CYC for his initial flare, with a cumulative dose already high (27 g – most bladder cancers after CYC treatment were reported in patients who had received a >35 g cumulative CYC dose; a safer threshold in practice is usually set around 25 g), RTX would appear as a better choice. In addition, the results of the RAVE trial showed that relapsers achieved a better remission rate with RTX compared with CYC

(Table 6.4). The RITAZAREM study further showed that RTX achieved remission in relapsing GPA or MPA in 90% of the cases. The induction treatment could thus rely on initial methylprednisolone IV pulses (7.5-15 mg/kg/day) for 1–3 days, followed by prednisone 1 mg/kg/day (maximum 80 mg) for 2 weeks, then gradually tapered by approximately 10% every 2 weeks until reaching 5 mg/day, around the 5th month of treatment (or much faster if avacopan is used). Avacopan could also be considered instead of GC, or in combination with GC initially, in order to shorten the duration of use of high-dose GC. The optimal tapering regimen and duration of GC and/or avacopan treatment remain unknown. RTX will be given for induction at the same time, at the dose of 375 mg/m^2 every week for 4 consecutive weeks, or 1 g at days 1 and 15 (Figure 6.3).

The results of the PEXIVAS study showed that PLEX did not prolong the time to death and/or end-stage renal disease in ANCA-associated vasculitis with severe renal and/or pulmonary involvement. It might still be considered in patients with severe alveolar hemorrhage who do not respond to the conventional induction treatments, but with limited expectations. Additionally, PLEX may help (based on post-hoc analyses) improve some of the renal function in patients with more severe renal disease, but to a limited extent and with an increased risk of infection.

Due to the risk of *Pneumocystis jiroveci* pneumonia, the patient should be given prophylactic therapy with trimethoprim/sulfamethoxazole (160/800 mg 1 tablet 80/400 mg 3 times per week [dose adjusted in this case to this patient with impaired renal function]), or an alternative in case of allergy (i.e. dapsone or atovaquone) while on RTX and for an additional 6-12 months after RTX cessation. The patient should also receive treatments to limit the risk of GC-induced osteoporosis, adapted to his renal function and following the latest local/national osteoporosis guidelines. Treatment with a proton-pump inhibitor can also be considered initially to limit the risk of GC- and/or stress-induced gastro-duodenal ulcers.

4. At the time of this relapse, what is the vasculitis damage index (VDI) score?

The assessment of damage in vasculitis measures chronic changes or scarring that have resulted from the disease and/or its treatments, since the time vasculitis was diagnosed. There are a few damage scores available, including the validated Vasculitis Damage Index (VDI; Figure 10.2), the most widely used in clinical trials, the Combined Damage Assessment index (CDA), and the ANCA-associated Vasculitis Instrument of Damage (AVID). More recently, a score was also developed to specifically assess GC-related toxicity, the Glucocorticoid Toxicity Index (GTI; Figure 10.3).

The VDI was developed by the Birmingham Vasculitis Group (UK) in 1997 and was designed to be used with all types of systemic vasculitis. It comprises 64 items, each scoring 1 point, and grouped into 11 organ systems. An arbitrary time limit of ≥3 months is used as the cut off for scoring an item of damage (hence all patients should have a VDI of 0 at the time of diagnosis, and the VDI can start to increase from month 4). The VDI, CDA and AVID scores are cumulative, thus can only increase, even though the actual damage resolves (e.g. a myocardial infarction, from which the patient has recovered would still be scored and carried forward and represent permanent scarring in the myocardium).

Studies on ANCA-associated vasculitis showed that, after a mean of 7.3 years post diagnosis, 34% of patients had ≥5 VDI items and only 8% had no items of damage. The most common damage items were hypertension (42% of patients), osteoporosis (14%), malignancy (13%) and diabetes (10%).

There is a modified, pediatric version of the score now (the PVDI).

Figure 10.2. Vasculitis Damage Index form (adapted from Exley et al. 1998 and Flossmann et al. 2008 – with permission).

This is for recording organ damage that has occurred in patients since the onset of vasculitis. Patients often have comorbidity before they develop vasculitis, which must not be scored. Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS). New patients should usually have a VDI score of zero, unless: (a) they have had vasculitis for more than 3 months of onset of disease and (b) the damage has developed or become worse since the onset of vasculitis.

Date: **Patient ID:**

1. MUSCULOSKELETAL DAMAGE		**8. PERIPHERAL VASCULAR DAMAGE**	
Significant muscle atrophy or weakness		Absent peripheral pulse in one limb	
Deforming or erosive arthritis		Second episode of absent peripheral pulse in one limb	
Osteoporosis with fractures or vertebral collapse			
Avascular necrosis		Absent peripheral pulses in limbs	
Osteomyelitis		Major vessel stenosis	
2. SKIN DAMAGE		Claudication	
Alopecia		Complicated venous thrombosis	
Skin ulceration		Minor tissue loss	
Oral ulceration		Major tissue loss	
3. ENT DAMAGE		Second episode of major tissue loss	
Hearing loss		**9. OCULAR DAMAGE**	
Nasal blockage/chronic discharge/crusting		Cataract	
Nasal bridge collapse/septal perforation		Retinal change	
Chronic sinusitis/radiological evidence of bone destruction		Optic atrophy	
		Visual impairment/diplopia	
Subglottic stenosis without surgery		Blindness in one eye	
Subglottic stenosis with surgery		Blindness in both eyes	
4. PULMONARY DAMAGE		Orbital wall destruction	
Pulmonary hypertension		Significant bone destruction as seen on X-ray/CT/MRI	
Pulmonary fibrosis/cavity			
Pleural fibrosis		**10. NEUROPSYCHIATRIC DAMAGE**	
Pulmonary infarction		Cognitive impairment	
Chronic asthma		Major psychosis	
Significant chronic breathlessness		Seizures	
Impaired pulmonary function tests		Cerebrovascular accident	
Significant abnormality of pulmonary function		Second cerebrovascular accident	
5. CARDIOVASCULAR DAMAGE		Cranial nerve lesion	
Angina/coronary artery bypass		Peripheral neuropathy	
Myocardial infarction		Transverse myelitis	
Second myocardial infarction		**11. OTHER DAMAGE/DRUG TOXICITY**	
Cardiomyopathy		Premature gonadal failure	
Valvular disease		Marrow failure	
Pericarditis		Diabetes mellitus	
Hypertension		Chronic chemical cystitis	
6. RENAL DAMAGE		Malignancy	
Estimated or measured GFR <50%			
Proteinuria of >0.5 g/24 h			
End-stage renal failure		**Total VDI Score:**	
7. GASTROINTESTINAL DAMAGE			
Gut infarction		Record the number of ticked Items (1 point for each). The VDI score can either increase or remain the same over time (i.e. it cannot decrease from previous visits). Remember to carry forward any previous items of damage (even if they have currently resolved).	
Mesenteric insufficiency/pancreatitis			
Chronic peritonitis			
Esophageal stricture OR upper gastrointestinal tract surgery			

Figure 10.3. The Glucocorticoid Toxicity Index (GTI). The total composite GTI score can vary from −36 to 439. Specific list items do not score points but should be ticked when present. The composite GTI score should be scored at least at 3-month intervals, using the diagnosis (or study entry) assessment as baseline (adapted from Miloslavsky et al 2016 – with permission).

Date: **Patient ID:**

			Specific List		
Composite GTI		**Item weight**		**At baseline or before**	**New since baseline**
Body mass index (BMI)					
	Improvement in BMI	–8	Major increase in BMI		
	No change in BMI	0			
	Moderate increase in BMI	21			
	Major increase in BMI	36			
Glucose tolerance					
	Improvement in glucose tolerance	–8	Diabetic retinopathy		
	No change in glucose tolerance	0	Diabetic nephropathy		
	Worsening of glucose tolerance	32	Diabetic neuropathy		
	Worsening of glucose tolerance despite treatment	44			
Blood pressure					
	Improvement in blood pressure	−10	Hypertensive emergency		
	No change in blood pressure	0	Posterior reversible encephalopathy syndrome		
	Worsening hypertension	19			
	Worsening hypertension despite treatment	44			
Lipids					
	Improvement in lipids	−9			
	No change in lipids	0			
	Worsening hyperlipidemia	10			
	Worsening hyperlipidemia despite treatment	30			
Bone density					
	Improvement in bone density	−1	Major decrease in bone density		
	No change in bone density	0	Insufficiency fracture		
	Decrease in bone density	29			
Steroid myopathy					
	No steroid myopathy	0	Severe steroid myopathy		
	Mild steroid myopathy	9			
	Moderate steroid myopathy or greater	63			
Skin toxicity					
	No skin toxicity	0	Severe skin toxicity		
	Mild skin toxicity	8			
	Moderate skin toxicity or greater	26			
Neuropsychiatric toxicity					
	No neuropsychiatric symptoms	0	Psychosis		
	Mild neuropsychiatric symptoms	11	GC-induced violence		
	Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms		
Infection					
	No significant infection	0	Grade IV infection (life-threatening consequence)		
	Oral/vaginal candidiasis or uncomplicated zoster	19	Grade V infection (urgent intervention, death)		
	Grade III infection or greater	93			
Endocrine			Adrenal insufficiency		
Gastrointestinal			Perforation		
			Peptic ulcer disease		
Musculoskeletal			Avascular necrosis		
			Tendon rupture		
Ocular			Central serous retinopathy		
			Intraocular pressure elevation		
			Posterior subcapsular cataract		
	Total =				

5. If the patient survives but progresses to end-stage renal disease, can he be considered for renal transplant?

End-stage renal disease (ESRD) develops in up to 28% of patients at 5 years, in nephrology series. Whereas the risk of (extrarenal) relapse might be slightly lower in patients with ESRD, in whom the risk of a renal relapse is no longer a major concern, it is not null. Maintenance treatment should thus still be given to such patients, although this can be debated in patients who have strictly limited renal disease. The main cause of mortality in patients with ANCA-associated vasculitis and ESRD is infection, whose risk is of course increased by the use of long-term GC and immunosuppressive treatments, but also dialysis.

Once the vasculitis has been in sustained remission for ≥12 months, or even only ≥6 months according to the last KDIGO guidelines, under minimal and stable maintenance treatment, renal transplantation can be considered in patients without any other contraindication to the procedure. Several studies have now shown that patient and renal transplant survivals are good in ANCA-associated vasculitis, similar or even better to those of (non-diabetic) transplant recipients with other renal conditions, provided that the disease has been in sustained remission. A relapse affecting the kidney graft is of course a major concern, but should not hamper the chance for patients in sustained remission to undergo transplantation.

The vasculitis relapse rate after transplant varied from 2% to 25% in various series or registries, renal or non-renal, and was estimated at 0.02 per patient-years in a study from the Chapel Hill group on 85 renal transplanted patients with ANCA-associated vasculitis. The relapse risk was not influenced by the disease (microscopic polyangiitis or granulomatosis with polyangiitis), the ANCA subtype (PR3- or MPO-ANCA) or status at the time of transplantation (only one study found a higher relapse rate in patients with persistent ANCA positivity peri-transplantation, vs. at least three others that did not). Notably, the KDIGO guidelines mention that “persistence of ANCA should not delay transplantation”. Whereas several studies support this recommendation for PR3-ANCA patients, data on transplant patients with persistent MPO-ANCA are more limited (MPO-ANCA tends to resolve more often than PR3-ANCA under treatment, in general). Graft and patient survival rates achieved 100% and 100% at 1 year, 98% and 93% at 5 years, and 79% and 67% at 10 years, respectively. In addition, a recent study in GPA showed that receiving a renal transplant was associated with a 70% reduction in the risk of all-cause mortality (RR=0.30), largely attributed to a 90% reduction in the risk of death due to cardiovascular disease (RR=0.10).

In this patient case, one limiting parameter for renal transplant might be his underlying ILD and impaired lung function, which would impact his overall chances of survival.

References

Exley AR et al. Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). Br J Rheumatol 1998;37(1):57-63.

Flossmann O et al. Development of comprehensive disease assessment in systemic vasculitis. Postgrad Med J 2008;84(989):143-52.

Berden AE et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21(10):1628-36.

Geetha D et al. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: a multicenter experience. Transplantation 2011:91(12):1370-5.

Berden AE et al. Tubular lesions predict renal outcome in antineutrophil cytoplasmic antibody-associated glomerulonephritis after rituximab therapy. J Am Soc Nephrol 2012;23(2):313-21.

Walsh M et al. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. Trials 2013;14:73.

Moran S and Little MA. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis. Curr Opin Rheumatol 2014;26(1):37-41.

Comarmond C et al. Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. Medicine (Baltimore) 2014;93(24):340-9.

Robson J et al. Damage in the ANCA-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis 2015;74(1):177-84.

Miloslavsky EM et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76(3):543-6.

Wallace ZS et al. Improved survival with renal transplantation for end-stage renal disease due to granulomatosis with polyangiitis: data from the United States Renal Data System. Ann Rheum Dis 2018;77(9):1333-8.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheumatol 2021;48(4):555-66.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83.

Rovin BH et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int 2021;100(4):753-79.

Case 11

Eosinophilic granulomatosis with polyangiitis

A 45-year-old man presents with sudden left foot weakness on a 6-month history of progressive constitutional symptoms, sinusitis, and dyspnea due to worsening asthma. He has had some numbness and tingling sensations in his left foot and leg for the past 3 weeks. He was diagnosed 6 years ago with sinus polyposis, 4 years ago with asthma, which has become more difficult to control for the past year despite his regular puffers and the addition of oral montelukast. He was noted to have elevated eosinophils over the past 3 years, now culminating at 6580/mm^3 (N <500/mm^3) and high C-reactive protein, between 20 and 60 mg/l (N <10 mg/l). His other laboratory tests are within normal range, including serum creatinine level and urinalysis, liver enzymes, hemoglobin level, serologies for hepatitis B and C, HIV, and ova and parasite stool examination. ANCA and ANA screening tests are negative. Chest X-rays show patchy opacities in both lungs, corresponding to linear basal, posterior areas of ground-glass opacities on chest CT (Figure 11.1). CT of sinus shows bilateral sinusitis and polyposis (Figure 11.2).

1. *What are the differential diagnoses to consider?*
2. *What are the annual incidence and prevalence of eosinophilic granulomatosis with polyangiitis (EGPA), and how do they compare to those of other vasculitides?*
3. *What are the possible manifestations and most severe complications of EGPA?*
4. *If EGPA is confirmed in this patient, how would you treat him?*

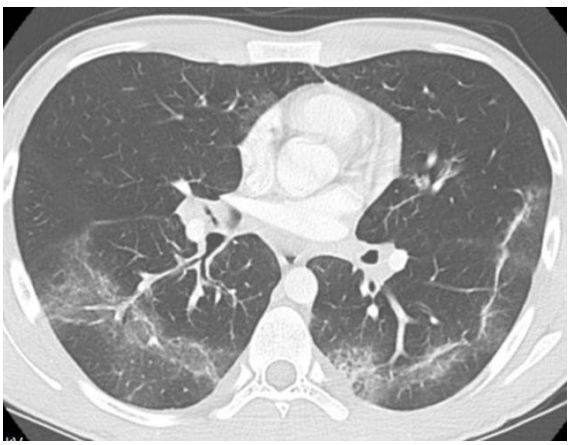


Figure 11.1. Horizontal chest CT.



Figure 11.2. Horizontal head and sinus CT.

Learning objectives

1. To describe the prevalence, typical demographics and clinical characteristics of eosinophilic granulomatosis with polyangiitis (EGPA).
2. To list the main differential diagnoses for EGPA.
3. To establish a treatment plan for patients with EGPA.

Answers

1. What are the differential diagnoses to consider?

The diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) is probable here. The patient went through the successive (Lanham's) phases of the disease: "allergic" sinusitis, sinus polyposis and asthma (phase 1), then eosinophilia with organ and tissue infiltrates (in this case, at least in the lungs; phase 2), and finally, the development of vasculitic manifestations (including mononeuritis multiplex in this case; phase 3). Not all patients go through these three phases, and some develop all these manifestations very closely in time. Only 30–40% of EGPA patients are ANCA positive, mainly with MPO-ANCA. In addition, after treatment initiation, MPO-ANCA often becomes rapidly undetectable in patients with EGPA. Therefore, the absence of ANCA does not rule out EGPA. A nerve biopsy could confirm the diagnosis in this patient, by showing eosinophilic infiltrate of the small vessel and vasa nervorum wall, with eosinophilic granulomas and fibrinoid necrosis of the vessel wall. However, in practice, whereas >60% of the nerve biopsies show some of the latter histological findings in patients with EGPA and peripheral neurologic manifestations, all 3 types of lesions are rarely present in the same sample. The presence of an isolated eosinophilic infiltrate is in keeping with a diagnosis of (possible/probable) EGPA but is not totally confirmatory.

Hence, ruling out other conditions is required in all patients with suspected EGPA, especially in those most common ones with negative ANCA testing and no absolute histological confirmation of the diagnosis (Table 11.1). Whereas some are relatively easy to exclude (e.g. allergies, infections or solid cancers), a few are more challenging (especially a primary hypereosinophilic syndrome, of lymphoid type, and lymphoma). Sometimes, only the response to treatment and follow-up will help confirm the initial diagnosis. IgG4-related disease can also mimic EGPA and, more importantly, IgG4 histological findings have been reported in patients with EGPA (and no other specific features of IgG4-related disease – see Table 3.1). Similarly, some patients with IgG4-related disease have an increased eosinophil count, along with a high serum IgE level, and some eosinophil infiltrate on histology. Hence, there may sometimes be an overlap, or a coincidental and debatable association between the two conditions. It is unclear at present whether this association should affect the definite diagnosis and management or not.

2. What are the annual incidence and prevalence of eosinophilic granulomatosis with polyangiitis (EGPA), and how do they compare to those of other vasculitides?

There is no epidemiological data on EGPA in Canada, but frequency of EGPA does not seem to drastically differ from the USA or the Western world, where the annual incidence varies between 0–4 per million inhabitants, with a prevalence of 7–32 per million. It is therefore approximately 10 times rarer than the two other ANCA-associated vasculitides combined (granulomatosis with polyangiitis and microscopic polyangiitis; see Table 11.2). A few epidemiological studies suggested that EGPA is rare in Asia, but some large series have lately been reported from Japan and Korea.

EGPA incidence has been estimated at about 34 per million patients with asthma and up to 60–64.4 per million in those requiring a leukotriene receptor antagonist or other non-leukotriene–modifying asthma drugs. Whereas asthma often clusters in families, familial cases of EGPA are exceptional.

Mean age at diagnosis of EGPA patients is about 50 years, but it can affect children and older adults. There is no sex preponderance.

3. What are the possible manifestations and most severe complications of EGPA?

The most characteristic features of EGPA include late-onset eosinophilic asthma (90–100% of patients in series), “allergic” rhinitis and/or chronic sinusitis and polyposis (30–80%), migratory and/or labile pulmonary infiltrates (40–75%), and mono- or polyneuropathy (35–75%; see Table 6.1). Skin manifestations (20–65%; cutaneous nodules, purpura, urticarial rash, nail-fold infarcts, digital ischemia) and constitutional symptoms (35–75%) are frequent.

Gastrointestinal (GI; 10–60% of patients), cardiac (10–50%), renal involvement (5–40%), and central nervous system (CNS) involvement (0–15%) are more rare but can be life-threatening, and are items in the original, prognostic 1996 Five-Factor Score (FFS). Venous thrombosis and pulmonary embolism can occur in up to 8%, mainly during the months around active phases of the disease. Several (but not all) series suggested that renal involvement, purpura, alveolar hemorrhage, and mononeuritis multiplex are more common in ANCA-positive than -negative patients, whereas cardiomyopathy and extravascular eosinophilic pulmonary infiltrates are more common in ANCA-negative patients.

Table 11.1. Main differential diagnoses of EGPA.

Other systemic vasculitides (sometimes with low-degree hypereosinophilia)
Microscopic polyangiitis
Granulomatosis with polyangiitis
Polyarteritis nodosa
Giant cell arteritis
IgA vasculitis (Henoch–Schönlein purpura)
Others: cutaneous leukocytoclastic vasculitis, cryoglobulinemic vasculitis, etc.
Hypersensitivity reactions
Hypersensitivity vasculitis (mainly drug-related)
DRESS (drug rash with eosinophilia and systemic symptoms)
Eosinophilic/hypersensitivity pneumonitis (drugs, pneumoallergens, etc.)
Allergic and/or hypereosinophilic asthma (can be associated with non-specific systemic manifestations but without vasculitis features; can be difficult to distinguish from a "forme fruste" or an early stage of EGPA)
Idiopathic chronic eosinophilic pneumonia
Allergic bronchopulmonary aspergillosis
Infections
Helminthiases/nematodoses (toxocariasis/larva migrans, strongyloides/anguillulosis, ankylostomiasis, trichinosis, ascaridiasis, oxyuriasis, trichocephalosis, etc.)
Other parasitic infections with blood and/or tissue eosinophilia (liver distomatosis, bilharziosis, filariasis, onchocerciasis, taeniases, hydatidosis, alveolar echinococcosis, myases, anisakiasis, gnathostomiasis, rarely toxoplasmosis)
HIV infection (and/or HCV infection)
Fungal infection/coccidioidomycosis
(Primary) hypereosinophilic syndrome (blood eosinophilia >1500/mm^3 for >6 months)
Lymphoid hypereosinophilic syndrome (a circulating T cell clone can sometimes be detected in EGPA patients, transiently – this presence of T cell clone is thus not totally specific)
Myeloid hypereosinophilic syndrome (FIP1L1–PDGFRA gene fusion can be detected in some patients)
Other malignant hemopathies and solid cancers
Lymphomas (mainly T cell and Hodgkin lymphomas)
Myeloproliferative neoplasms
Myelodysplastic syndromes
Acute or chronic leukemias
Solid cancers – mainly gastrointestinal tract, breast or lung cancers (blood eosinophilia and, more rarely, authentic paraneoplastic vasculitis)
Miscellanous
Eosinophilic esophagitis and/or gastritis (can sometimes be the first manifestation of EGPA)
IgG4-related syndrome (common pathogenic mechanisms and/or association with EGPA are possible)
Eosinophilic fasciitis (Shulman syndrome)
L-Tryptophan-related eosinophilia–myalgia syndrome and toxic oil syndrome
Other systemic disease, with or without associated vasculitis (rheumatoid arthritis, dermatomyositis)
Crohn's disease, ulcerative colitis
Sarcoidosis (Löfgren's syndrome)
Systemic mastocytosis
Cholesterol emboli syndrome
Gleich syndrome
Kimura disease

Table 11.2. Prevalence and annual incidence of main primary systemic vasculitides in the world (only a few studies in Canada).

Vasculitis	Prevalence (per million)	Remarks	Annual Incidence (per million)	Remarks
Giant cell arteritis	500-7500 (of population >50 years old)	Crude estimates (only a few specific studies: 144 in Reunion island in 2018 with biopsy +; 753 in Sweden with biopsy + in 2015)	80-300 (of population >50 years old)	Down to 5 in Israel in late 1960s; up to 370 in Norway in mid 1990s; at 49 in Ontario in 2015-2017
Takayasu arteritis	4-8	4.7 to 7 in the UK in early 2000s; up to 40 in Japan (no epidemiological data for India, but probably at least the same)	1-2	Down to 0.4 in Germany; up to 2.6 in Minnesota in late 1970s, and 3.3 in Kuwait
Polyarteritis nodosa	6-30	Up to >30 in late 1990s before HBV-related PAN almost disappeared	0.9- 6.8	Up to 8 in the UK, 16 in Kuwait in the late 1990s, and 77 in Alaska in late 1980s (HBV endemic area)
Kawasaki disease	-	Acute disease (in general, but damage possible)	90-500 (per million children <5 years old)	Down to 16 in Czech Republic in late 1990s; up to 2180 in Japan; in US: 91 in Caucasian vs. 320 in Asian children in the early 2000s; 196-262 in Ontario in 2000-2015
Granulomatosis with polyangiitis	50-210	Down to 23 in Paris in 2000, 30 in New York City in 1990; up to 135 in the UK in 2013 and 261 in Norway in 2013	5-30	Down to almost 0 in Japan, 2.9 in Spain; up to 11 in Australia and Minnesota, 4.6 in Saskatoon (Canada); and 34 in Germany in 2013-2016
Microscopic polyangiitis	25-50	Down to 25 in Paris in 2000; up to 94 in Sweden in 2007	5-15	Down to 2.7 in Germany; up to 15 in Japan, and 24 in Kuwait, 7.1 in Saskatoon (Canada); 13 in Germany in 2013-2016
Eosinophilic granulomatosis with polyangiitis	10-25	Down to 7 in Germany in 1994; up to 22 in Australia in 2004 and 32.9 in Norway in 2013	1-2	Down to 0 in Japan; up to 2.7 in the UK in late 1990s, and 4 in Minnesota in late 1970s
Behçet's disease	10-500	Extremely wide ethnic variations (from 6 in the UK in the 1970s to 4200 in Turkey in 2000); 100-300 in USA, mainly in immigrants; 24 in European-descent vs. 175 in Asian-descent vs. 350 in North-African-descent French population	-	No precise estimation (chronic disease and wide geographical differences); around 4 in Minnesota in mid 2000s

4. If EGPA is confirmed in this patient, how would you treat him?

There are no diagnostic criteria for EGPA. The diagnosis relies on the combination of the clinical, biological, histological, radiological findings, and requires ruling out the differentials. The 2022 ACR/EULAR classification criteria have been developed for studies and to help classify patients with established diagnoses of vasculitis (Table 11.3).

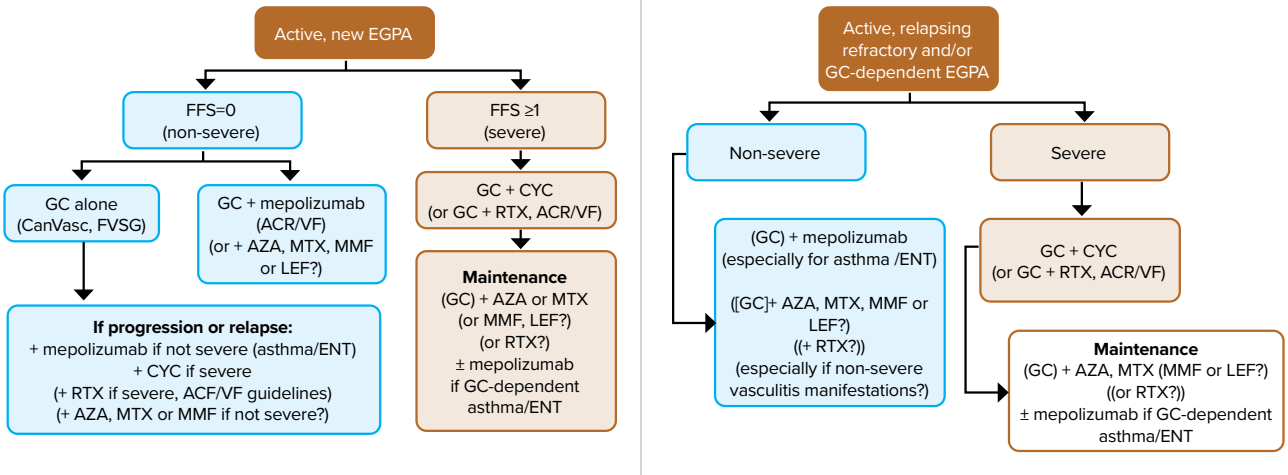
The patient has sensorimotor neuropathy, with a dropping left foot, which is considered by some groups as a severe manifestation (in patients with granulomatosis with polyangiitis, it is a major item according to the BVAS/WG – see Figure 7.3).

Patients with FFS=0 and no severe, life-threatening or major organ involvement can be treated initially with glucocorticoids (GC) alone, according to the French and CanVasc recommendations (see Figure 11.3). Initial methylprednisolone IV pulses can be given (7.5-15 mg/kg/day) for 1 to 3 days, before switching to prednisone 1 mg/kg/day (maximum 80 mg) for 2-4 weeks to patients with more concerning manifestations, although no study has ever proven the benefit of these pulses in EGPA. Prednisone is then gradually tapered by approximately 10% every 2 weeks until reaching 5 mg/day, around the 5th month of treatment. This dose should be maintained for a few months. The optimal tapering regimen and duration of GC treatment remain unknown.

Table 11.3. Summary of the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for eosinophilic granulomatosis with polyangiitis (Adapted from Grayson et al. Ann Rheum Dis 2022).

The classification criteria for eosinophilic granulomatosis with polyangiitis can be considered only in patients in whom:		
1. a diagnosis of small- or medium-sized vessel vasculitis has been made		
& 2. all alternate diagnoses and mimicking conditions have been excluded		
And have the following:		
Clinical criteria:		
	Obstructive airway disease	+3
	Nasal polyps	+3
	Mononeuritis multiplex/motor neuropathy	+1
Laboratory, imaging and biopsy criteria:		
	Maximum blood eosinophil count ≥ 1x10^9/litre	+5
	Extravascular eosinophilic-predominant inflammation on biopsy	+2
	Positive test for c-ANCA or PR3-ANCA	*-3 (subtract)*
	Hematuria	*-1 (subtract)*
A cumulative, sum score of ≥6 is needed for classification of eosinophilic granulomatosis with polyangiitis. The sensitivity of these criteria was 85% (95% CI; 77–91%) and specificity 99% (95% CI; 96–100%).		

Figure 11.3. Suggested treatment algorithms for eosinophilic granulomatosis with polyangiitis (EGPA; see text for details in Cases 11 and 12).



ACR/VF: American College of Rheumatology/Vasculitis Foundation (2021 guidelines); AZA: azathioprine; CYC: cyclophosphamide; ENT: ear, nose and throat [manifestations]; FFS: five-factor score; FSVG: French Vasculitis Study Group (guidelines); GC: glucocorticoids; LEF: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab.

In case of poor response to this treatment, worsening of the clinical manifestations of vasculitis, or disease relapse during GC dose tapering, the GC dose must be increased again and another therapeutic agent must be added. This latter situation occurs in 42% of patients. For this reason, the 2021 ACR/Vasculitis Foundation (VF) conditional recommendation is to directly initiate treatment with mepolizumab and GC, over GC alone, and even over methotrexate, azathioprine, or mycophenolate mofetil and GC in patients with active, non-severe EGPA. Strong data to support this recommendations are lacking. The CHUSPAN 2 trial did not show any benefit of a combination of GC and azathioprine over GC alone for the control of the vasculitis or the asthma or ENT manifestations. Whether other agents can achieve better results has not been thoroughly investigated yet. Mepolizumab (300 mg subcutaneously for 12 months) was effective in the placebo-controlled MIRRA trial for patients with GC-dependent, relapsing and/or refractory EGPA, mostly on asthma and ENT manifestations. Mepolizumab led to significantly more accrued weeks of remission than placebo (28% vs. 3% had ≥24 weeks of accrued remission) and was well tolerated. However, its benefit as a first-line adjunctive treatment along with GC has not yet been demonstrated to a similar extent.

If the disease continues to progress on GC alone or GC and mepolizumab, other agents must be added. Azathioprine, methotrexate, mycophenolate mofetil or leflunomide can be considered in those with persistent FFS=0 and no severe, life-threatening or major organ involvement, or an anti-IL5 agent (if not already used and) if the main issues are the asthma and/or the ENT symptoms (mepolizumab, the only approved agent so far for EGPA [in December 2017 by the FDA and in July 2018 by Health Canada]; or benralizumab, which is approved for eosinophilic asthma, but not yet for EGPA).

Cyclophosphamide (CYC) should be given to patients with any severe, life-threatening or major organ involvement and/or with an original FFS ≥1.

Based on an ungraded position from the 2021 ACR/VF recommendations, rituximab could be prescribed as an alternative to CYC in patients with active, severe EGPA. However, evidence is also scarce at present to strongly support the use of RTX in patients with severe EGPA, especially in those with cardiac involvement. A few case series of patients with refractory, GC-dependent, most of whom did not have very severe disease, showed some efficacy of RTX, maybe more in ANCA-positive patients (according to some, but not all, of these series or case reports). The French REOVAS study compared RTX and GC to GC alone in patients with non-severe EGPA, and to CYC and GC for severe disease (results presented in early 2022, but not yet published; ClinicalTrials.gov Identifier: NCT02807103). RTX-based treatment was not superior to the conventional treatments. Subgroup analyses were invariably underpowered to prove equivalence or noninferiority, or to demonstrate any preference for RTX in any subset of patients (e.g. in ANCA-positive patients). Anti-IL5 agents are not seen as being strong enough to be used instead of CYC (or RTX) for severe, active EGPA (but a study is ongoing in France, the E-merge trial, to investigate this possibility, using mepolizumab; ClinicalTrials.gov Identifier: NCT05030155).

Whether patients with EGPA and sensorimotor neuropathy should be treated directly with a combination of GC and another immunosuppressant, such as those with a FFS ≥1, remains a subject of debate and would merit prospective studies. Again, in the CHUSPAN-2 study, the combination of GC and AZA as first-line treatment did not reduce the subsequent failure or relapse rate, compared with GC (and placebo). There was no standardized study of the functional neurological recovery. Whether other agents, including CYC, can achieve better results remains to be determined. The balance between risks and benefits of more aggressive treatment such as CYC must be carefully weighed in patients with FFS=0. Whereas sensorimotor neuropathy was significantly associated in several cohort studies with the need for subsequent add-on therapy, it was not associated with higher risks of mortality in EGPA. If CYC is given in combination with GC, its dose should be similar to that used for severe GPA or MPA (Figure 6.3), and CYC duration should not exceed 3 to 6 months (followed by a maintenance treatment with a less toxic agent, such as AZA). Another French study is ongoing (MAINRITSEG; ClinicalTrials.gov Identifier: NCT03164473), and aims at comparing maintenance treatment with RTX 500 mg every 6 months versus azathioprine (results expected in late 2024).

Polyvalent IV immunoglobulins (IVIg) have also been used for the treatment of EGPA, especially in Japan and in patients with peripheral neuropathy, and might represent an alternative and temporary option in patients with severe active infection and/or pregnant women.

Finally, whether or not leukotriene receptor antagonists, such as montelukast, increase the risk of developing EGPA in asthmatic patients had been a subject of debate for a while. Meta-analyses and case-control studies have now convincingly showed that patients on these agents were indeed often able to decrease their use of GC (oral GC or puffers), thereby allowing the vasculitis manifestations to fully develop. Hence, there is no major reason to stop montelukast in patients who are already taking it, as it is unlikely to have triggered EGPA. On the other hand, as the patient in this case will receive high-dose GC, montelukast may no longer be needed.

References

Guillevin L et al. Prognostic Factors in Polyarteritis Nodosa and Churg-Strauss Syndrome: A Prospective Study in 342 Patients. Medicine (Baltimore) 1996;75(1):17-28.

Ribi C et al. Treatment of Churg-Strauss Syndrome without poor-prognosis factors. Arthritis Rheum 2008;58(2):586-94.

Pagnoux C. Churg-Strauss syndrome: evolving concepts. Discov Med 2010;9(46):243-52.

Guillevin L et al. The Five-Factor Score Revisited – Assessment of Prognoses of Systemic Necrotizing Vasculitides Based on the French Vasculitis Study Group Cohort. Medicine (Baltimore) 2011;90(1):19-27.

Samson M et al. Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) enrolled in two prospective trials. J Autoimmun 2013;43:60-9.

Comarmond C, Pagnoux C et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013;65(1):270-81.

Anderson K et al. Does geographic location affect incidence of ANCA-associated renal vasculitis in northern Saskatchewan, Canada? Rheumatology (Oxford) 2013;52(10):1840-4.

Samson M et al. Mononeuritis multiplex predicts the need for immunosuppressive or immunomodulatory drugs for EGPA, PAN and MPA patients without poor-prognosis factors. Autoimmun Rev 2014;13(9):945-53.

Groh M et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med. 2015;26(7):545-53.

Pagnoux C and Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). Expert Rev Clin Immunol 2016;6:1-9.

Mohammad AJ et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 2016;75(2):396-401.

Crickx E et al. Intravenous Immunoglobulin as an Immunomodulating Agent in Antineutrophil Cytoplasmic Antibody-Associated Vasculitides: A French Nationwide Study of Ninety-Two Patients. Arthritis Rheumatol 2016;68(3):702-12.

Danlos FX et al. Antineutrophil cytoplasmic antibody-associated vasculitides and IgG4-related disease: A new overlap syndrome. Autoimmun Rev 2017;16(10):1036-43.

Puéchal X et al. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial. Arthritis Rheumatol 2017;69(11):2175-86.

Wechsler ME et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017;376(20):1921-32.

Doubelt I et al. Outcomes of Eosinophilic Granulomatosis With Polyangiitis in North America. ACR Open Rheumatol 2021;3(6):404-12.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83.

Uzzo M et al. Novel Targets for Drug Use in Eosinophilic Granulomatosis With Polyangiitis. Front Med (Lausanne) 2021;8:754434.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheumatol 2021;48(4):555-66.

Grayson PC et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis With Polyangiitis. Arthritis Rheumatol 2022;74(3):386-92.

Case 12

Eosinophilic granulomatosis with polyangiitis – cardiac involvement and glucocorticoid dependency

Mr. K was diagnosed 3 years ago with an ANCA-negative eosinophilic granulomatosis with polyangiitis. He was 36 years old at the time. He had previously been diagnosed with asthma (8 years ago) and hypertension (6 years ago). He also had seasonal allergies, nasal polyposis and rhinitis for more than 12 years. The clinical manifestations at the time of his vasculitis diagnosis were weight loss (of 10 kg), unstable asthma, exertional dyspnea, back pain, urticarial rash on the torso and thighs, and sensory polyneuropathy in the feet (bilateral numbness). His eosinophil count was 9250/mm^3 (normal <500/mm^3) and troponin T level was high (136 ng/l; normal <10 ng/l). His chest CT showed some mediastinal lymphadenopathies and patchy ground-glass opacities. His echocardiography showed decreased left ventricular ejection fraction (LVEF) at 37%. Cardiac MRI showed a LVEF at 41%, with patchy late gadolinium enhancements in the myocardium (Figure 12.1), but no coronary lesions. He had no renal or gastrointestinal involvement.

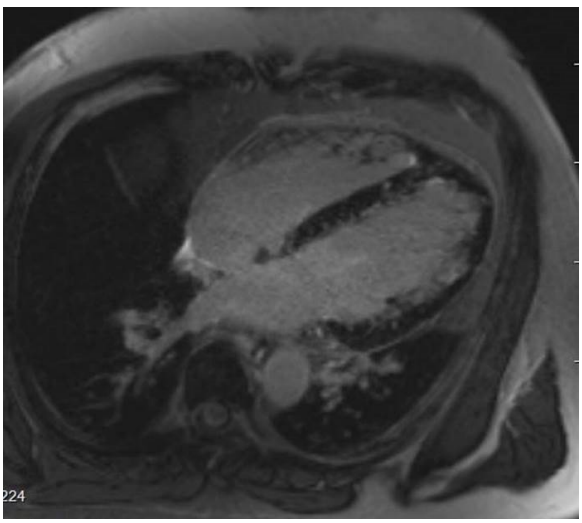


Figure 12.1. Cardiac MRI. Patchy areas of subendocardial late gadolinium enhancement at the left basal and mid-ventricular levels and at the apex (and mild pericardial enhancement).

He received treatment with high doses of glucocorticoids and IV pulses of cyclophosphamide for 4 months, and then was switched to maintenance with azathioprine. Today, he remains on azathioprine 150 mg/day and prednisone 15 mg/day, as he had been unable to taper his daily prednisone dose below 15 mg without suffering asthma or rhinitis exacerbations, with or without a concomitant increase in his eosinophil count (up to 1350/mm^3). He is also on puffers (a combination of an inhaled glucocorticoid and a long-acting β2 agonist, twice daily, and salbutamol as needed), oral beta-blockers, low-dose aspirin and an angiotensin II receptor antagonist. His recent follow-up cardiac MRI shows some persistent stable patchy late gadolinium enhancements with a LVEF at 49%. His last chest CT showed some atelectases in the lung bases but no active inflammation. His last laboratory test showed an eosinophil count at 510/mm^3, and C-reactive protein at 6 mg/l (normal <10 mg/l).

1. *What are the possible cardiac manifestations in patients with eosinophilic granulomatosis with polyangiitis, and how should these complications be diagnosed and monitored?*
2. *How often do patients with eosinophilic granulomatosis with polyangiitis relapse or become glucocorticoid-dependent because of persistent asthma or ENT manifestations?*
3. *What are the treatment options for this patient with glucocorticoid-dependent asthma and ENT manifestations?*

Learning objectives

1. To understand the negative prognostic value of cardiac involvement and the role of cardiac investigations in patients with eosinophilic granulomatosis with polyangiitis (EGPA).
2. To identify some of the therapeutic unmet needs in EGPA, especially regarding the treatment of patients with glucocorticoid-dependent asthma or ear, nose and throat (ENT) manifestations.
3. To list currently available treatment options for patients with EGPA and glucocorticoid-dependent asthma or ENT manifestations.

Answers

1. What are the possible cardiac manifestations in patients with eosinophilic granulomatosis with polyangiitis, and how should these complications be diagnosed and monitored?

Cardiac manifestations occur in 10–50% of patients with eosinophilic granulomatosis with polyangiitis (EGPA), depending on the series and definitions and/or cardiac investigations used. The mechanisms of EGPA cardiac manifestations include eosinophilic and/or granulomatous infiltration of the myocardium, eosinophil-derived protein toxicity in heart tissues, possibly leading to fibrosis, and/or coronary artery and small myocardial vessel vasculitis, causing ischemic lesions. Notably, most series (but not all) reported that ANCA-negative patients had higher rates of cardiac involvement, pericarditis and cardiomyopathy.

Cardiomyopathy (10–50% of patients) has been associated with increased mortality in earlier series and justifies an aggressive therapeutic management strategy. In some series, cardiomyopathy was even the main cause of mortality, accounting for 48% of deaths. It has been identified as a poor prognostic factor in EGPA patients, and corresponds to one of the five parameters of the five-factor score (FFS, original and revised versions – see Case 4, question/answer 3). In more recent cohort studies, cardiac involvement is not as often identified as a poor prognostic factor, likely because it is now detected and managed earlier and more aggressively. Eosinophilic pericardial effusion is frequent, in up to 20% of patients, as are conduction disorders and supraventricular arrhythmias (which can also develop years later, as a result of cardiac damage). Intraventricular thrombi, dysautonomic manifestations or cardiac valve involvement are rarer.

All patients with EGPA should undergo cardiac screening but which investigations to order at the time of diagnosis and for follow-up remains a subject of debate. The EGPA Consensus Task Force recommends "basic cardiac investigations," which include chest imaging, electrocardiography, transthoracic echocardiography, N-terminal pro-brain natriuretic peptide and troponin I measurements. The 2022 ACR/VF guidelines "conditionally recommend obtaining an echocardiogram for all patients with newly diagnosed EGPA, even in the absence of cardiac symptoms." Patients with symptoms suggestive of arrhythmia should undergo additional investigations.

The role and value of advanced cardiac imaging with MRI or positron-emission-tomography (PET) scan for example, are not well characterized. These are more sensitive investigations, but the clinical significance of abnormalities they can detect remains unclear. Asymptomatic MRI abnormalities can correspond to some cardiac involvement but, at this time, should not carry the same treatment impact as a clinically overt cardiomyopathy (that would require the use of cyclophosphamide [CYC]). A study (Dunogué et al., 2015) showed myocardial late gadolinium enhancement (LGE), usually in the subendocardial segments of the whole LV circumference, in 82% of patients with otherwise obvious cardiomyopathy, but also in 44% without obvious clinical cardiomyopathy. In patients with clinical cardiomyopathy, LGE lesions may (40% of the cases) or may not improve under treatment, and the persistence of LGE lesions during follow-up seems to be associated with a higher risk of subsequent cardiac events. In non-symptomatic patients with LGE lesions, outcomes did not differ whether or not the lesions regressed during follow-up. The value of PET scan in EGPA has to be further studied. It could help distinguish inflammation from fibrosis in those patients with abnormal MRI.

2. How often do patients with eosinophilic granulomatosis with polyangiitis relapse or become glucocorticoid-dependent because of persistent asthma or ENT manifestations?

In EGPA, it is important to distinguish vasculitis relapses (e.g. with recurrent purpura, mononeuritis multiplex and/or gastrointestinal (GI) ischemic perforation, most typically with increased eosinophil count and C-reactive protein [CRP]) from non-vasculitic, and GC-responsive and/or GC-dependent exacerbations of pre-existing and/or associated asthma or ENT manifestations. In previously published series, this distinction has not always been made. Hence, the relapse rates may vary according to the series.

Clinical remission of EGPA can be achieved in 67–92% of patients. Vasculitis/EGPA relapse rate is estimated around 14–45% (average around 25% at 5 years), often during the first year of therapy (45% of relapses). Some series also reported that the relapse rate was higher in ANCA-positive (35%) versus ANCA-negative patients (23%). In addition, in up to 84% of patients, GC cannot be stopped, because of persistent and/or recurrent asthma or ENT symptoms, as with this patient case. A series from the USA reported that 40% of patients with EGPA had severe/uncontrolled asthma at 3 years from the diagnosis of EGPA, as per the 2000 American Thoracic Society Workshop on Refractory Asthma.

In series in which the asthma and or ENT exacerbations are counted as EGPA relapses, the relapse rate reaches 81%. The 5- and 10-year survival rates are 89–97% and 79–89%, respectively.

3. What are the treatment options for this patient with glucocorticoid-dependent asthma and ENT manifestations?

The treatment of patients whose vasculitic EGPA-related manifestations have been controlled but whose asthma and/or ENT symptoms are persistent can be very challenging. Several treatment options can be tried, ideally in collaboration with physicians subspecializing in asthma management and/or ENT specialists. Inhaled asthma medications need to be optimized and patient adherence objectively assessed. Inhaled and/or nasal nebulized GC can be helpful. Whereas leukotriene receptor antagonists have been suspected to facilitate the development of full-blown EGPA in patients with early, "formes frustes" of EGPA, their use can still be considered, with close clinical monitoring.

Usual GC-sparing agents, such as azathioprine (AZA, 2 mg/kg/day, orally) or methotrexate (MTX, 15-25 mg/week), can be tried (for years, these were almost the only agents to consider). Their efficacy in eosinophilic asthma remains unclear and likely limited. The 2020 CanVasc and 2021 ACR/VF guidelines both recommended, although with low-grade evidence and/or conditionally, the preferential use of mepolizumab (anti-IL5) over these conventional agents for patients with "non-severe disease manifestations (asthma and/or sinonasal disease)".

Mepolizumab, a humanized anti-interleukin (IL)-5 monoclonal antibody, was the first anti-IL5 agent approved in Canada in July 2018 at the dose of 300 mg every 4 weeks, subcutaneously, for patients with refractory, relapsing and/or GC-dependent EGPA. In the MIRRA study, 136 EGPA patients with refractory, relapsing EGPA and/or who could not taper GC dose below 7.5 mg/day, were randomized to mepolizumab (300 mg every 4 weeks for 12 months, subcutaneously) or placebo. The results showed that mepolizumab treatment led to significantly more accrued weeks of remission (no asthma or vasculitis flare) than placebo (28% vs. 3% had ≥24 weeks of accrued remission). Over the 12 months of the study, 60% of the placebo recipients had at least one asthma exacerbation vs. 37% in the mepolizumab group.

However, at 52 weeks, only 18% of the patients were off GC (which was still better than the 3% only with placebo). After stopping mepolizumab, most patients see, within the following 3 to 6 months, their asthma and/or ENT manifestations worsen, and their eosinophil count increase again.

In routine practice, coverage for mepolizumab at the dose of 300 mg per month is still not systematic in many Canadian provinces. Several case studies, mostly conducted in Europe, suggested that the lower dosage (100 mg monthly), which is approved for hypereosinophilc asthma and easier to obtain coverage, achieves very close results to the higher dosage. In a European study, complete response rates at 3 months was 12.0% with 100 mg monthly, and 18.2% with 300 mg every 4 weeks. In a previous French study, remission rates at 12 months were 76% and 82% among patients receiving mepolizumab at 100 mg or 300 mg, respectively (the definitions of response and remission varying substantially between studies). In patients not improving with the lower dosage, an increase to 300 mg monthly can be considered. However, a few case reports also suggested that using only 100 mg monthly in some patients with EGPA can be hazardous, due to underdosing-related amplifying counteractions and/or immune-complex formation. when IL5 is not sufficiently blocked.

Other anti-IL5 agents have been approved for the treatment of eosinophilic asthma and are being investigated in EGPA, including benralizumab (and, to a lesser extent, reslizumab). A study is ongoing to compare benralizumab with mepolizumab (MANDARA; ClinicalTrials.gov Identifier: NCT04157348). Other targeted therapies are also being studied and/or considered, such as anti-IL4

(dupilumab), or anti-thymic stromal lymphopoietin (TSLP; tezepelumab). Combinations of these agents may also have a future in the therapeutic strategies for EGPA. Until recently, no animal model of EGPA was available for pre-clinical studies. A murine model had been developed, using transgenic IL-5 hypereosinophilic mice, with inhalation of IL-33 to induce vasculitic manifestations.

A few case series of patients with refractory, GC-dependent, most of whom did not have very severe disease, showed some efficacy of rituximab (RTX), maybe more in ANCA-positive patients (according to some, but not all, of these series or case reports). The French REOVAS study compared RTX and GC to GC alone in patients with non-severe EGPA, and to CYC and GC for severe disease (results presented in early 2022, but not yet published; ClinicalTrials.gov Identifier: NCT02807103). RTX-based treatment was not superior to the conventional treatments. Subgroup analyses were invariably underpowered to prove equivalence or noninferiority, or to demonstrate any preference for RTX in any subset of patients (e.g. in ANCA-positive patients, or on different disease manifestations). The 2021 ACR/VF guidelines only discuss, as an ungraded position statement, RTX as an alternative to CYC for active, severe EGPA (which is debatable; see Case 11, question/answer 4).

IVIg have also been used as GC-sparing agents in patients with refractory EGPA, with variable results. It is an option to consider especially in patients with ongoing infection, or in pregnancy.

Omalizumab, a humanized monoclonal anti-IgE antibody (225 to 375 mg subcutaneously every 2 weeks), can be considered, although its efficacy appears limited in EGPA (25%). It might be more effective in patients with elevated IgE levels (although the 2021 ACR/VF guidelines still favour, conditionally, mepolizumab over omalizumab in patients with high IgE levels). In addition, omalizumab does not seem effective for the vasculitic EGPA manifestations. Cases of EGPA vasculitic aggravations have indeed been reported in patients in whom omalizumab provided a certain degree of improved asthma control and subsequent GC tapering or withdrawal.

In this case, the patient is already on AZA and cannot taper his prednisone dose below 15 mg/day without experiencing recurrent ENT symptoms and/or worsening asthma. On the other hand, his EGPA vasculitic manifestations seem under control, his eosinophil count is close to normal and his C-reactive protein level is normal. A first step is to verify adherence to anti-asthma medications, and regular follow-up with a physician with experience in asthma management. Once this has been verified and/or optimized, options include a switch from AZA to MTX, the addition of MTX at a low dose (10-15 mg/week, in combination with AZA, possibly also at a lower dose to limit the risk of side effects), the introduction of a leukotriene receptor antagonist such as montelukast (under close monitoring), or the addition of mepolizumab, initially with AZA and GC. Both the 2020 CanVasc and 2021 ACR/VF guidelines would favour in this case the addition of mepolizumab in such a patient with non-severe, GC-dependent refractory or relapsing EGPA.

References

Guillevin L et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. Medicine (Baltimore) 1996;75(1):17-28.

Cohen P et al. Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum 2007;57(4):686-93.

Guillevin L et al. The Five-Factor Score Revisited – assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group cohort. Medicine (Baltimore) 2011;90(1):19-27.

Comarmond C, Pagnoux C et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term follow-up of the 383 patients enrolled in the French Vasculitis Study Group cohort. Arthritis Rheum 2013;65(1):270-81.

Moosig F et al. A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. Ann Rheum Dis 2013;72(6):1011-7.

Groh M et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. Eur J Intern Med 2015;26(7):545-53.

Dunogué B et al. Impact of cardiac magnetic resonance imaging on eosinophilic granulomatosis with polyangiitis outcomes: A long-term retrospective study on 42 patients. Autoimmun Rev 2015;14(9):774-80.

Wechsler ME et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017;376(20):1921-32.

Puéchal X et al. Adding Azathioprine to Remission-Induction Glucocorticoids for Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss), Microscopic Polyangiitis, or Polyarteritis Nodosa Without Poor Prognosis Factors: A Randomized, Controlled Trial. Arthritis Rheumatol 2017;69(11):2175-86.

Mukherjee M et al. Suboptimal treatment response to anti-IL-5 monoclonal antibodies in severe eosinophilic asthmatics with airway autoimmune phenomena. Eur Respir J 2020;56(4):2000117.

Doubelt I et al. Outcomes of Eosinophilic Granulomatosis With Polyangiitis in North America. ACR Open Rheumatol 2021;3(6):404-12.

Canzian A et al. Use of Biologics to Treat Relapsing and/or Refractory Eosinophilic Granulomatosis With Polyangiitis: Data From a European Collaborative Study. Arthritis Rheumatol 2021;73(3):498-503.

Chung SA et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol 2021;73(8):1366-83.

Uzzo M et al. Novel Targets for Drug Use in Eosinophilic Granulomatosis With Polyangiitis. Front Med (Lausanne) 2021;8:754434.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheumatol 2021;48(4):555-66.

Bettiol A et al. Mepolizumab for Eosinophilic Granulomatosis With Polyangiitis: A European Multicenter Observational Study. Arthritis Rheumatol 2022;74(2):295-306.

Case 13
Isolated cutaneous vasculitis

A 30-year-old female presents with a 3-day history of a skin rash that started on her lower legs. The rash initially looked like flat red spots and progressed to a more purplish colour. It was bumpy but neither pruritic nor tender. She had right otitis media 3 weeks ago and was given amoxicillin for 7 days. The rash appeared 10 days after completing the course of antibiotics. She has no other significant past medical history. She does not report any other systemic symptoms. Her physical exam is normal except for the rash (Figure 13.1).



Figure 13.1 (a and b). Diffuse maculo-purpuric rash on legs.

1. *What are the common clinical skin findings in patients with cutaneous leukocytoclastic angiitis or cutaneous arteritis?*
2. *What are the differential diagnoses and possible causes of cutaneous leukocytoclastic angiitis or cutaneous arteritis?*
3. *What investigations would you order?*

You diagnose the patient with isolated cutaneous vasculitis/leukocytoclastic angiitis on the basis of a skin punch biopsy (negative immunofluorescence study), the absence of any systemic symptoms, and otherwise normal investigations.

4. *How would you treat this patient?*

Learning objectives

1. To describe the common clinical, biological and histological characteristics of isolated cutaneous leukocytoclastic angiitis/vasculitis and cutaneous arteritis.
2. To list the differential diagnoses and causes of cutaneous vasculitis.
3. To establish diagnostic and therapeutic management plans for patients with cutaneous vasculitis.

Answers

1. What are the common clinical skin findings in patients with cutaneous leukocytoclastic angiitis or cutaneous arteritis?

The type of cutaneous lesions is closely correlated with the size of the vessel affected by vasculitis (Table 13.1). The most common clinical presentation of cutaneous vasculitis is palpable non-blanchable purpura. It can be observed in small- or medium-sized vessel vasculitides (as overlaps are common). The purpuric lesions result from the extravasation of erythrocytes through the inflamed and damaged blood vessel walls into the dermis. It is most commonly symmetrically distributed over the dependent regions of the body, especially the lower legs. Lesions may also be noted under tight-fitting clothing. The extent of cutaneous involvement is relevant to diagnostic considerations as when lesions are localized to a single site, it may suggest a secondary reaction to a local trauma or irritating factor (e.g. arthropod bite or topical agents).

The spectrum of cutaneous findings in patients with cutaneous leukocytoclastic angiitis can also include bruising, macular or ecchymotic lesions and sometimes, hemorrhagic bullae. In the most severe cases, the lesions can be necrotic, leading to painful ulcerations or gangrene. Superinfection of chronic or open lesions is a risk. Urticarial lesions can also develop, although these are more classically seen in patients with hypocomplementemic (or normocomplementemic) urticarial vasculitis (often with anti-C1q antibodies in their sera) or eosinophilic granulomatosis with polyangiitis.

Patients with cutaneous vasculitis/arteritis involving medium-sized vessels, in the deep reticular dermis and subcutaneous tissue, may present with subcutaneous nodules, erythema nodosum or livedo reticularis.

Table 13.1. Cutaneous manifestations based on the size of the vessels affected

Small-sized vessels (Superficial vessels in the upper dermis)	**Medium-sized vessels (smooth muscle wall vessels in the deep dermis, dermal-subcutaneous interface or within the subcutaneous tissue)**
• Purpura • Papules • Macules/patches • Vesiculo-bullous lesions • Pustules • Urticaria • Superficial ulcers	• Subcutaneous nodules • Livedo reticularis/racemosa • Erythema nodosum • Deep ulcers • Pitted scars

Resolution of the skin lesions can leave behind post-inflammatory hyperpigmentated spots, or fibrotic scars when ulcerations have occurred.

Arthralgias of adjacent joints are not infrequent during and/or before the flares. Frank synovitis or arthritis is rarer. With lower limb predominance of cutaneous manifestations, the ankle is the most frequent joint affected. Some patients will have low-grade fever accompanying their clinical presentation.

Table 13.2. Most common causes of isolated (or apparently isolated) cutaneous leukocytoclastic vasculitis.

Idiopathic, single-organ cutaneous vasculitis (~45-55%) and its various subsets, as defined in the 2018 dermatologic addendum
Infections (~20%)
Upper respiratory tract infections
Hepatitis B or C virus infection (HBV or HCV)
Human immunodeficiency virus (HIV)
Bacterial infections e.g. *Neisseria meningitides/gonorrhea, Streptococcus pyogenes*
Drugs (~20%)
Antibiotics (e.g. beta-lactams, minocycline)
Levamisole-tainted cocaine
Nonsteroidal anti-inflammatory drugs
Anticonvulsants (e.g. phenytoin)
Hydralazine
Allopurinol
Propylthiouracil
Granulocyte colony-stimulating factor
Connective tissue diseases (~15%)
Systemic lupus erythematosus
Sjögren syndrome
Rheumatoid arthritis
Sarcoidosis
Systemic inflammatory conditions (~10%)
ANCA-associated vasculitis
Other vasculitides: immune complex vasculitides (e.g. IgA-vasculitis, cryoglobulinemic vasculitis, urticarial vasculitis), polyarteritis nodosa, Behçet's disease, ADA2 deficiency, VEXAS syndrome
Inflammatory bowel diseases
Malignancies (<5%) – to look for, especially in adults >50 years old at vasculitis onset
Hematologic/lymphoproliferative
Solid organs

2. What are the differential diagnoses and possible causes of cutaneous leukocytoclastic angiitis or cutaneous arteritis?

Consideration of whether or not the purpuric lesions are consistent with vasculitis is a first step. Thrombocytopenia or other hemorrhagic disorders which have similar cutaneous presentations need to be excluded. The presence of palpable purpura is persuasive toward a vasculitic categorization. However, this is not entirely compelling as some infectious etiologies, including meningococcal septicemia or disseminated gonococcal infection, may result in similar clinical presentations.

A thorough history and examination will be required to exclude vasculitis mimics and to identify evidence of systemic symptomatology. Other forms of primary vasculitis will need to be considered and excluded in the differential diagnosis.

Isolated cutaneous leukocytoclastic angiitis may be associated with an identifiable underlying etiology in approximately 50% of cases (Table 13.2).

3. What investigations would you order?

Investigations will be guided by results from a thorough history and physical examination and will be selected to support the following clinical requirements:

1. To confirm the diagnosis of vasculitis
2. To rule out vasculitis mimics and identify any underlying causal etiologies related to cutaneous vasculitis (Table 13.2)
3. To better characterize the vasculitis type
4. To verify the absence and/or determine the extent and severity of any extra-cutaneous manifestation
5. To obtain baseline laboratory and test results needed to decide on the best and safest treatment options (when treatment is needed or considered)

A skin biopsy should be obtained, of relatively fresh lesions, ideally present for between 24 to 72 hours. A punch biopsy is usually sufficient (a deeper biopsy might be required for nodular lesions). Histological study should include a light microscopy analysis (with hematoxylin and eosin staining; Figure 13.2) to identify the presence and nature of cellular infiltrates within and around the vessel walls (polymorphonuclear neutrophils vs. lymphocytes or eosinophils), extravasation of nuclear dust and red blood cells, fibrinoid necrosis, presence of granulomas or giant cells, and a direct immunofluorescence study (DIF). The latter will detect immunoglobulin and/or complement deposits. The presence of perivascular IgA deposition would suggest the diagnosis of IgA-vasculitis (see Case 20). Other immunofluorescence findings may assist in identifying secondary cutaneous vasculitis, such as systemic lupus erythematosus (lupus band test, IgG and complement depositions at the dermoepidermal junction).

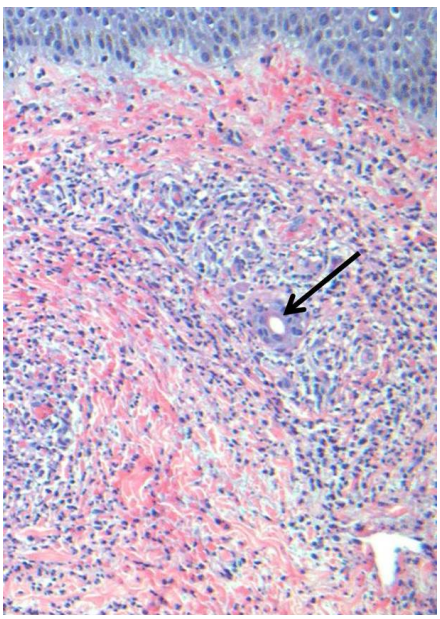


Figure 13.2. Skin biopsy, light microscopy analysis with hematoxylin and eosin stain, original magnification ×25. Diffuse perivascular, predominantly lymphocytic infiltrate with extravasation of red blood cells within the wall of a small vessel (arrow) in the papillary dermis.

Diagnostic investigations will be guided by the findings on history (Figure 13.3) and examination but will generally include:

- Complete blood cell count with WBC differential to evaluate neutrophil and eosinophil counts
- Serum creatinine level and urinalysis
- Acute phase markers: C-reactive protein and/or erythrocyte sedimentation rate
- Hepatic transaminases
- Antinuclear antibodies (ANA), extractable nuclear antigen antibodies (ENA), antineutrophil cytoplasm antibodies (ANCA), C3 and C4 complement levels, rheumatoid factor, cryoglobulins
- Serum protein electrophoresis
- Activated partial thromboplastin time
- Appropriate infectious work-up, including consideration of serologies for chronic infections (HBV, HCV, HIV, +/- syphilis with VDRL)
- Chest X-ray

Depending on the context and the results of these first investigations, other tests may be required to further evaluate potential causal associations, such as cryofibrinogen, lupus anticoagulant, antiphospholipid and anticardiolipin, anti-double stranded DNA, anti-cyclic citrullinated peptide antibodies, serum IgA levels, immunoelectrophoresis or immunofixation of serum protein, tests for celiac disease, specific bacterial serologies (e.g. rickettsioses, anti-streptolysin O), blood and/or urine culture(s), and/or genetic testing (ADA2 deficiency - see Case 4).

Age-appropriate malignancy screening may also be indicated depending on the context and associated clinical findings and preliminary results.

Figure 13.3. Diagnostic approach in a patient with suspected cutaneous vasculitis



4. How would you treat this patient?

As the vasculitic disease is generally limited to the skin, and often spontaneously regresses within weeks or months, there is no mandatory indication to treat every patient. Reassuringly, the risk of future progression from isolated, single-organ, idiopathic cutaneous vasculitis to a more systemic vasculitis is low (<10% at 5 years).

With a single episode of isolated cutaneous vasculitis, addressing and removing, when possible, the inciting etiology, triggering agent or medication may alone be therapeutically effective.

Topical treatments, including dermo-glucocorticoids, are generally ineffective. Short courses of oral GC can be prescribed for severe cutaneous flares (prednisone, 0.5 to 1 mg/kg/day for 1-3 weeks, followed by a rapid tapering over 2-6 weeks). However, the response is not universal and recurrence with tapering and GC-dependency are common. Oral glucocorticoids (GC) in severe disease may be required to speed up resolution.

Unfortunately a substantial proportion of patients (18-46% depending on the series) will develop relapsing or chronic disease. The evidence to support specific treatments in this particular patient group is not high quality. However, colchicine (0.6 mg x 2/day) is widely employed as a first-line treatment in this clinical setting. Dapsone can be utilized as an alternative agent with due caution for pre-establishment of glucose-6-phosphate dehydrogenase (G6PD) status and the propensity for hematologic toxicity (hemolytic anemia and/or methemoglobinemia). Hydroxychloroquine has been utilized in some patients with success. Azathioprine, methotrexate, mycophenolate mofetil, or leflunomide can also be considered, most often in patients refractory to the aforementioned first-line agents. An international study is ongoing to compare colchicine, azathioprine and dapsone in patients with isolated skin vasculitis (ARAMIS; ClinicalTrials.gov Identifier: NCT02939573). This is the second randomized study ever conducted in isolated skin vasculitis (the previous one compared colchicine vs. placebo, was published in 1995, included only 20 patients, and found no significant difference at 1 month).

People with chronic disease often recognize situations that can trigger a flare, such as prolonged air travel, standing up for long periods of time in overheated spaces, alcohol consumption or viral upper respiratory tract infections. Preventative measures may be beneficial in such cases.

In the event of refractory disease unresponsive to the treatments indicated above, it will be important for the clinician to re-evaluate the diagnosis and consider further investigation for underlying etiologies, including malignancies. Recently described genetic mutations (e.g. adenosine deaminase 2 [ADA2] deficiency) have also been associated with refractory cutaneous vasculitic ulcers. Other pathogenic genetic variations will likely be discovered in the years to come.

References

Sais G et al. Colchicine in the treatment of cutaneous leukocytoclastic vasculitis. Results of a prospective, randomized controlled trial. Arch Dermatol 1995;131(12):1399-402.

Carlson J et al. Cutaneous vasculitis: diagnosis and management. Clin Dermatol 2006;24:414– 29.

Atzeni F et al. Skin manifestations in vasculitis and erythema nodosum. Clin Exp Rheumatol 2006;24(1 Suppl 40):S60-6.

Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. Am J Clin Dermatol 2008;9(2):71-92.

Kluger N et al. Comparison of cutaneous manifestations in systemic polyarteritis nodosa and microscopic polyangiitis. Br J Dermatol 2008;159(3):615-20.

Pina T et al. Cutaneous Vasculitis: A Rheumatologist Perspective. Curr Allergy Asthma Rep 2013;13(5): 545-54.

Goeser MR et al. A practical approach to the diagnosis, evaluation, and management of cutaneous small-vessel vasculitis. Am J Clin Dermatol 2014;15(4):299-306.

Navon Elkan P et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med 2014;370(10):921-31.

Loricera J et al. Single-organ cutaneous small-vessel vasculitis according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides: a study of 60 patients from a series of 766 cutaneous vasculitis cases. Rheumatology (Oxford) 2015;54(1):77-82.

Bouiller K et al. Etiologies and prognostic factors of leukocytoclastic vasculitis with skin involvement: A retrospective study in 112 patients. Medicine (Baltimore) 2016;95(28):e4238.

Sunderkötter CH et al. Nomenclature of Cutaneous Vasculitis: Dermatologic Addendum to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheumatol 2018;70(2):171-84.

Beck DB et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. N Engl J Med 2020;383(27):2628-38.

Micheletti RG et al. Protocol for a randomized multicenter study for isolated skin vasculitis (ARAMIS) comparing the efficacy of three drugs: azathioprine, colchicine, and dapsone. Trials 2020;21(1):362.

Micheletti RG, Pagnoux C. Management of cutaneous vasculitis. Presse Med 2020 ;49(3):104033.

Case 14
CNS vasculitis

A 45-year-old female accountant presents with a 2-month history of progressively worsening headache and a 1-month history of rapid cognitive decline. She is now unable to work. She has no past medical history, and there is no recent history of focal neurological deficits or constitutional symptoms. Brain MRI shows subcortical and periventricular white matter changes and some patchy meningeal enhancement post-gadolinium injection (Figure 14.1). CT angiogram shows multiple irregularities in both middle cerebral arteries. Subsequent cerebrospinal fluid analysis reveals elevated leukocyte count (35/ml, with 90% lymphocytes) and a high protein level (68 mg/dl; normal <40 mg/dl).

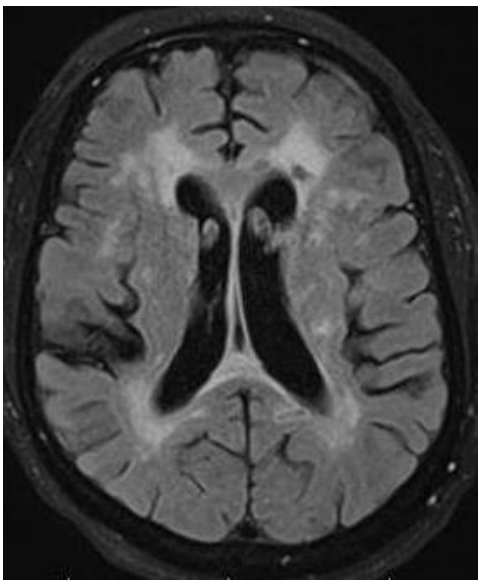


Figure 14.1. Brain MRI. T2 hyperintensity and multiple old infarcts in the periventricular, deep and subcortical white matter.

1. *What are the main differential diagnoses and mimickers of central nervous system (CNS) vasculitis?*

2. *What are the main conditions causing (secondary) CNS vasculitis?*

The patient is eventually diagnosed with primary CNS vasculitis on the basis of her clinical symptoms, imaging, investigations that ruled out mimickers and secondary CNS vasculitis, and the results of a left fronto-parietal leptomeningeal and cortical brain biopsy (lymphocytic and granulomatous vasculitis features, no sign of malignancy or infection).

3. *What is your treatment plan for this patient?*

4. *What are the expected outcomes of adult patients with primary CNS vasculitis?*

Learning objectives

1. To describe the epidemiology, clinical, biological and radiological characteristics of central nervous system (CNS) vasculitis (in adults).
2. To list the differential diagnoses and mimickers of primary CNS vasculitis in adults.
3. To establish a therapeutic plan for the treatment of adult patients with primary CNS vasculitis.

Answers

1. What are the main differential diagnoses and mimickers of central nervous system (CNS) vasculitis?

Central nervous system (CNS) vasculitis is an extremely challenging diagnostic and therapeutic condition. The definite diagnosis of primary CNS vasculitis (PCNSV) is difficult to ascertain and its pathogeny remains unknown. PCNSV is rare; there is no epidemiological study in Canada. In Minnesota (USA), the estimated annual incidence was 2.4 per million inhabitants during the period ranging from 1983 to 2003. In 1988, Calabrese and Mallek proposed a set of diagnostic criteria, which have not been validated thoroughly but remain the most used ones today and include:

1. The presence of an unexplained neurologic deficit after thorough clinical and laboratory evaluation
2. Documentation by cerebral angiography and/or tissue examination of an arteritic process within the CNS
3. No evidence of systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary

CNS vasculitis can occur at any age, with no sex predominance. Clinical symptoms are not very specific. The most common features include headaches (50-70% of patients, based on the largest cohort series), of chronic or subacute onset, cognitive changes (30-70%), and ischemic strokes (13-50%). Transient ischemic attacks (16-33%), paraparesis (3-13%), and seizures (7-29%, especially in children) can also occur. Intracranial hemorrhage (7-9%) or cranial nerve involvement are rarer. A more recent cohort of 82 patients (60% biopsy-proven) from India reported a surprisingly higher frequency of 70% of seizures at presentation, and presence of hemorrhagic changes on MRI (mostly microhemorrhages on SWI sequences).

Whereas constitutional or extra-neurological symptoms can lead to the diagnosis of a systemic disease, infection or cancer, there should be, by definition, no such symptoms in PCNSV (although a small proportion of patients may present with minor and non-specific symptoms, such as fatigue, low-grade fever, nausea and/or moderate weight loss).

In PCNSV, the sensitivity of cerebrospinal fluid examination is about 50% (mild pleocytosis, moderate protein level increase), that of brain CT scan is around 50% and that of brain MRI is around 90%. None of these examinations is specific. However, a diagnosis of PCNSV is very unlikely in a patient with normal CSF and normal brain MRI-MRA. CSF studies are important to rule out infections (beyond usual tests, next-generation metagenomic sequencing may in the future further help detect less-common infections).

CNS vessel imaging can show multiple segmental stenoses of the cerebral arteries, sometimes separated by fusiform dilatations, or can be normal in patients with small-vessel disease, only diagnosed by brain biopsy. Vascular imaging patterns can be

suggestive of CNS vasculitis but are not specific. Several other non-vasculitic causes can result in very similar vessel appearance, the most commonly debated being reversible cerebral vasoconstriction syndrome and intracranial atherosclerosis (Table 14.1). The role of more advanced vessel wall imaging (not yet available in all centres) remains to be better determined; it may help differentiate between the latter two (no vessel wall enhancement, or subtle, patchy, eccentric and non-regular enhancement) and vasculitis (more homogenous, circumferential, concentric vessel wall enhancement).

2. What are the main conditions causing (secondary) CNS vasculitis?

CNS imaging studies and cerebral and/or leptomeningeal biopsy can provide supporting evidence for the diagnosis of CNS vasculitis but do not necessarily help determine the primary versus secondary nature of CNS vasculitis. CNS vasculitis is indeed more often secondary than primary.

Among the numerous possible causes of secondary CNS vasculitis, the most common include infections and systemic diseases, including systemic vasculitides, drug abuse, and neoplasms (Table 14.2).

3. What is your treatment plan for this patient?

Mimickers and causes of secondary vasculitis have been ruled out, and the patient in this case underwent a biopsy to further support the diagnosis. In case series, only 30–50% of patients with a final diagnosis of CNS vasculitis had undergone a biopsy. Brain biopsy remained nondiagnostic in 26–50% of cases and its morbidity was relatively low, but not null (7–16% of patients presented with minor transient complications, such as transient focal deficit or abscess; mortality rate was <1.5%).

Consensus for the treatment of primary CNS vasculitis is lacking as it is extremely rare and no prospective therapeutic study has been conducted yet. Several case reports and cohort studies of adults with primary CNS vasculitis showed that aggressive regimens combining glucocorticoids (GC) and cyclophosphamide (CYC) improve patient outcomes, with a good outcome in about 80%, in contrast with the almost consistently fatal outcome of the earliest series.

GC are usually started at a high dose (1 mg/kg/day equivalent-prednisone), possibly preceded by 1 to 3 methylprednisolone pulses (7.5 to 15 mg/kg/day), and subsequently tapered by approximately 10% every 2 weeks. CYC can be given daily (2 mg/kg/d, orally) or intermittently, as IV pulses of 15 mg/kg/d every 3 to 4 weeks (dose adjusted based on age and renal function). Once the patient has improved and achieved an equivalent of remission (there are no consensus definitions for response to treatment or remission in PCNSV), usually after a maximum of 6 months, CYC can be switched to azathioprine, methotrexate, or mycophenolate mofetil, for at least 1–2 years, for maintenance, as in severe systemic vasculitides. A recent study confirmed the benefit of maintenance treatment in PCNSV.

Other treatments (tumour necrosis factor-alpha blockers, intravenous immunoglobulins, rituximab, and/or tocilizumab) can be considered for patients with relapsing and/or refractory disease, but there is very limited evidence to date. Importantly, the diagnosis of PCNSV should always be re-assessed in such cases, before considering second-line therapy.

Adjunctive and prophylactic measures must be prescribed as usual with such an immunosuppressive and GC-based treatment, including for the prevention of *Pneumocystis jiroveci* pneumonia. Treatment of any associated cardiovascular risk factors, including hypertension, hypercholesterolemia or diabetes, should be prescribed as appropriate. Antiplatelet agents can be added but evidence is lacking to demonstrate any clear benefit in adults with primary CNS vasculitis without any other cardiovascular risk factors.

Table 14.1. Main differential diagnoses and mimickers of CNS vasculitis.

Reversible cerebral vasoconstriction syndrome +++ (stereotyped onset, with thunderclap headache; most often in young women; possible triggers include pregnancy, post-partum, use of vasoactive drugs or toxins [amphetamine derivatives, pseudoephedrine, ergotamine tartrate, selective serotonin reuptake inhibitors, bromocriptin, tacrolimus, cocaine, marijuana, etc.], or exercise. Severe and/or prolonged artery spasms can cause stroke, transient in 16–54% of patients, definitive in 7%. Small cortical or convexity subarachnoid hemorrhages can occur. Vessel imaging shows multifocal segmental cerebral artery vasoconstriction, which by definition, must reverse within 12 weeks after symptom onset).		
Acute hypertension with cerebral vasospasms (with or without associated posterior reversible [leukoencephalopathy] syndrome: hypertensive emergency, pre-eclampsia/eclampsia, drug withdrawal [e.g. antihypertensive agents], medication/toxin exposure [e.g. cocaine abuse, monoamine oxidase inhibitors, combined oral contraceptives, chemotherapy with carboplatin, etoposide or some immuntherapeutic agents], pheochromocytoma, etc.)		
Intracranial atherosclerosis (can be challenging as it is very common with aging and can still be associated with vasculitis)		
Subacute subarachnoid hemorrhage (often spontaneous) **with secondary arterial vasospasm(s)**		
Other post-hemorrhagic, post-traumatic, post-neurosurgical and/or post-angiography arterial vasospasm(s)		
Intracranial dissection(s)		
Thrombotic disorders (± associated vasculopathy)		
	Antiphospholipid syndrome	Disseminated intravascular coagulation
	Sneddon syndrome	Thrombotic microangiopathy
	Degos disease	
Arterial embolisms		
	Catheterization (traumatic plaque removal)	Aortic arch atherosclerosis
	Cardiac shunt	Infectious or non-infectious endocarditis
	Cardiac myxoma	Atrial fibrillation
Miscellaneous		
	CNS lymphoma and endothelial and angiocentric lymphoma +++ or sarcoma (some of the most challenging mimickers, as an initial response to glucocorticoids, can often be observed)	
	CNS tumours	
	Paraneoplastic and/or autoimmune neurologic syndromes (including with anti-NMDAR, -NMO, -MOG, -GFPA-IgG, -Hu, -Yo, -Ri, or -amphiphysin antibodies)	Limbic encephalitis (can be paraneoplastic, with or without antibodies such as anti-voltage-gated potassium channel [VGKC] antibodies)
	Cerebral amyloid angiopathy (CAA), cerebral amyloid angiopathy with related inflammation (CAA-RI) and amyloid-β-related angiitis (ABRA)	Moya-moya disease
		Focal cerebral arteriopathy (FCA) of childhood
	Susac syndrome (most often in young women; associated encephalopathy (headache, memory impairment, cognitive changes), sensorineural hearing loss and branch retinal artery occlusion; characteristic “snowball-like” lesions in the corpus callosum on MRI)	
	Cerebroretinal vasculopathies and variants (including with *COL4A1* gene mutations), or retinal vasculopathy with cerebral leukodystrophy (RVCL) with autosomal dominant TREX1 protein mutations	Genetic vasculopathies: DADA2 (deficiency in adenosine deaminase type 2), SAVI (STING-associated vasculopathy with onset in infancy)
	CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids)	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy – *Notch3* mutations), or the rarer recessive form (CARASIL)
	MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) syndrome	Homocystinuria, vitamin B12 deficiency, porphyria
	Fabry's disease	Cerebral radiotherapy (post-radiation vasculopathy)
	Fibromuscular dysplasia, pseudoxanthoma elasticum	Neurofibromatosis
	Sickle cell anemia, thalassemia	ADEM (acute demyelinating encephalomyelitis), multiple sclerosis

MOG: myelin oligodendrocyte glycoprotein; NMDAR: N-methyl D-aspartate receptor antibody; NMO: neuromyelitis optica (usually with anti-aquaporin-4); COL4A1: collagen, type IV, alpha 1; STING: stimulator of interferon genes; GFAP-IgG: glial fibrillary acidic protein (GFAP)-IgG; TREX1: three-prime repair exonuclease 1

Table 14.2. Main causes of secondary CNS vasculitis.

Systemic vasculitides			
	Giant cell arteritis	Takayasu arteritis	
	Polyarteritis nodosa	Kawasaki disease	
	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)	Granulomatosis with polyangiitis	Microscopic polyangiitis
	Cryoglobulinemic vasculitis	Cogan syndrome	Anti-GBM disease (Goodpasture's)
	Behçet's disease	IgA-vasculitis (Henoch–Schönlein purpura)	
Other systemic diseases			
	Systemic lupus erythematosus	Rheumatoid arthritis	Sjögren syndrome
	Antiphospholipid syndrome	Dermatomyositis, polymyositis	Systemic scleroderma
	Inflammatory bowel diseases	Sarcoidosis	Celiac disease
	Mixed connective tissue disease	Relapsing polychondritis	
Infections			
	Bacteria	*Viruses*	*Fungi, parasites*
	Syphilis	Varicella zoster virus	Echinoccocosis
	Tuberculosis	Herpes simplex virus	Amebiasis
	Neisseira meningitis and other purulent meningitides	Human immunodeficiency virus (HIV)	Cryptococcosis
	Rickettsiosis, Lyme disease	Cytomegalovirus	Cysticercosis
	Bartonellosis	Hepatitis C (or B) virus	Schistosomiasis
	Brucellosis	Human T-cell leukemia virus type 1 (HTLV-1)	Trichinosis
	Endocarditis	Parvovirus B19	Toxocariasis
	Whipple's disease	COVID-19*	Candidiasis
	Leptospirosis		Mucormycosis
			Aspergillosis (invasive)
			Histoplasmosis
			Coccidioidomycosis, paracoccidioido-mycosis
			Exserohilum rostratum and spp.
Hematologic neoplasms and cancers			
	Hodgkin's and non-Hodgkin's lymphomas	Paraneoplastic (solid cancers) vasculitis	Liebow's lymphomatoid granulomatosis (EBV-induced)
	Myelodysplastic syndromes	Hairy cell leukemia	
Toxic vasculitis (these agents would most often cause reversible cerebral vasoconstriction syndrome but can also induce true vasculitis)			
	Amphetamine and derivatives	Sympathomimetic agents	Contraceptives
	Cocaine (especially if tainted with levamisole)	Marijuana	Ecstasy
	Alkaloidal "crack"		
Miscellaneous			
	Histiocytosis	Familial hemophagocytic lymphohistiocytosis (including perforin deficiency)	Buerger's disease (thromboangiitis obliterans)
	Graft-versus-host disease	Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)	Perforin or C4 complement fraction deficiency
	Eales disease		

Anti-GBM: anti-glomerular basement membrane; EBV: Epstein-Barr virus.
**COVID-19: a few, very uncertain cases of possible CNS vasculitis cases have been reported (COVID can cause several CNS manifestations, such as encephalopathy, thrombo-inflammatory stroke, or sinus thrombosis, but CNS vasculitis is not common)*

4. What are the expected outcomes of adult patients with primary CNS vasculitis?

As mentioned above, with aggressive regimens combining high-dose GC and, most often, CYC, 80% of patients with PCNSV showed some improvement in the Mayo clinic and French cohorts. However, consensus lacks regarding the definition of improvement in PCNSV, which remains partially subjective, including or not, imaging and/or functional scores, such as the modified Rankin score (Table 14.3). The mortality rate in these cohorts varies between 6% at 44 months in the French cohort (85% received a combination of GC and CYC) and 17% at 12 months in the Mayo clinic cohort (46% received GC alone). Relapses were observed in 27% of patients in both studies.

Interestingly, several subgroups of patients have been reported as possibly carrying different outcomes. Patients with PCNSV and focal neurological deficits, cognitive impairments, cerebral infarctions and/or large-vessel involvement have a high risk of death. Conversely, patients with isolated small-vessel biopsy-proven primary CNS vasculitis or gadolinium-enhanced lesions seem to have more favourable outcomes and better prognoses than those with large-vessel involvement or without gadolinium enhancement. However, despite their initial rapid therapeutic responses, these patients with small-vessel biopsy-proven PCNSV or gadolinium-enhanced lesions experience more relapses (54%). Patients with a tumoral presentation on imaging (10-15% of cases) may also relapse more often (50%) but respond well to combined CYC and GC treatment and obtain good global neurological outcomes (assessed with the modified Rankin score. However, at present, such differences between subsets in adult patients with PCNSV do not impact treatment choices.

More studies are needed, including the international pediatric BrainWorks registry and the Vasculitis Clinical Research Consortium (VCRC) cohort of PCNSV patients (more information on the CanVasc website).

Table 14.3. Modified Rankin score. *This score has regularly been used to assess patients' global outcomes in studies on primary CNS vasculitis. Other scores have or can also be used to assess different and/or complementary aspects of the neurological outcomes, such as the Montreal cognitive assessment (MoCA) or National Institutes of Health (NIH) stroke scale.*

Score	Description
0	no neurologic deficits
1	no significant disability, despite symptoms
2	slight disability
3	moderate disability
4	moderately severe disability
5	severe disability
6	death

References

Calabrese LH and Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) 1988;67:20-39.

Swartz RH et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. Neurology 2009;72(7):627-34.

Mandell DM et al. Vessel wall MRI to differentiate between reversible cerebral vasoconstriction syndrome and central nervous system vasculitis: preliminary results. Stroke 2012;43(3):860-2.

De Boysson H et al. Rituximab for primary angiitis of the central nervous system: report of 2 patients from the French COVAC cohort and review of the literature. J Rheumatol 2013;40(12):2102-3.

De Boysson H et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol 2014;66:1315-26.

Moussaddy A et al. Stroke. Inflammatory Cerebral Amyloid Angiopathy, Amyloid-β-Related Angiitis, and Primary Angiitis of the Central Nervous System: Similarities and Differences Stroke 2015;46(9):e210-3.

Salvarani C et al. An update of the Mayo Clinic cohort of patients with adult primary central nervous system vasculitis: description of 163 patients. Medicine (Baltimore) 2015;94:e738.

Salvarani C et al. Adult primary central nervous system vasculitis treatment and course: analysis of one hundred sixty-three patients. Arthritis Rheumatol 2015;67:1637-45.

Bai HX et al. Diagnostic Value and Safety of Brain Biopsy in Patients With Cryptogenic Neurological Disease: A Systematic Review and Meta-analysis of 831 Cases. Neurosurgery 2015;77(2):283-95.

Pagnoux C and Hajj-Ali RA. Pharmacological approaches to CNS vasculitis: where are we at now? Expert Rev Clin Pharmacol 2016;9:109-16.

De Boysson H et al. Tumor-Like Presentation of Primary Angiitis of the Central Nervous System. Stroke. 2016 Sep;47(9):2401-4.

Torres J et al. Diagnostic Yield and Safety of Brain Biopsy for Suspected Primary Central Nervous System Angiitis. Stroke 2016;47(8):2127-9.

de Boysson H et al. Maintenance therapy is associated with better long-term outcomes in adult patients with primary angiitis of the central nervous system. Rheumatology (Oxford) 2017;56(10):1684-93.

de Boysson H et al. Primary angiitis of the CNS and reversible cerebral vasoconstriction syndrome: A comparative study. Neurology 2018;91(16):e1468-78.

de Boysson H et al. Treatment and Long-Term Outcomes of Primary Central Nervous System Vasculitis. Stroke 2018;49(8):1946-1952

Salvarani C et al. Primary central nervous system vasculitis mimicking brain tumor: Comprehensive analysis of 13 cases from a single institutional cohort of 191 cases. J Autoimmun 2019;97:22-8.

Rocha et al. RCVS2 score and diagnostic approach for reversible cerebral vasoconstriction syndrome. Neurology. 2019;92(7):e639-47.

Agarawal A et al. Primary CNS vasculitis (PCNSV): a cohort study. Sci Rep 2022;12(1):13494.

Case 15
CNS vasculitis in children

An 8-year-old girl is admitted after experiencing several generalized seizures over the past week. She had been investigated at the age of 6 for recurrent episodes of isolated fever. Nothing was found and she has no other past personal or family medical history. On clinical examination, her blood pressure is 110/70 mmHg, and temperature is 36.9°C. She feels sleepy and drowsy, and has some minor bilateral, frontal headaches, but no sign of meningism or increased intracranial pressure (normal fundus examination). There is no obvious motor or sensory deficit. Reflexes are brisk, symmetrical. She has some livedo on the forearms and legs.

Complete blood cell count is normal, C-reactive protein is 6.5 mg/l (normal <6 mg/l), and serum creatinine is 68 µmol/l (normal <80 µmol/l). Brain MRI reveals multiple tiny areas of previous small subcortical infarcts. Cerebrospinal fluid analysis reveals mild lymphocytic pleocytosis. Conventional cerebral angiography reveals no vessel abnormalities.

1. *What are the main differential diagnoses of CNS vasculitis in children and, more specifically in this girl with associated livedo?*
2. *What are the main types of primary CNS vasculitis in children?*
3. *Which treatment is usually considered for small-vessel CNS vasculitis in children?*

Learning objectives

1. To describe the epidemiology, main clinical, biological and radiological characteristics of childhood CNS vasculitis.
2. To list the differential diagnoses and mimickers for primary CNS vasculitis in children.
3. To establish a therapeutic plan for the treatment of children with primary CNS vasculitis, according to the subtype of the disease.

Answers

1. What are the main differential diagnoses of CNS vasculitis in children and, more specifically in this girl with associated livedo?

The list of mimickers and differential diagnoses of CNS vasculitis in children is almost superimposable to that of adults (Table 14.1) except for atherosclerosis (in adults) and some more specific childhood brain inflammatory conditions, such as Rasmussen encephalitis (a T-cell-mediated inflammatory brain disease) and early onset genetic or metabolic diseases (e.g. mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS]; rolandic mitochondrial encephalomyopathy [ROME]; polymerase gamma deficiency; pediatric autoinflammatory neuropsychiatric disorder associated with streptococcal infections [PANDAS]; or posterior fossa malformations-hemangiomas-arterial anomalies-cardiac defects-eye abnormalities-sternal cleft and supra-umbilical raphe syndrome [PHACES]). Other rare mimickers include anti-myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease, central nervous system-restricted hemophagocytic lymphohistiocytosis, anti-GABA^{A} receptor encephalitis, and Aicardi-Goutières syndrome.

More recently, a recessive loss-of-function mutation in the cat eye syndrome chromosome region, candidate 1 (CECR1), the gene encoding adenosine deaminase 2 (ADA2), has been identified that can mimic polyarteritis nodosa and cause early-onset strokes, often hemorrhagic or with hemorrhagic transformation. Children with this disease are most often diagnosed before the age of 10 years (but there are rare cases diagnosed later, up to 59 years of age) and can present with skin manifestations, most commonly reticular livedo but sometimes also digital necrosis. Affected children can have hepatosplenomegaly and other visceral vessel involvement, with celiac or mesenteric aneurysms on angiography, as well as immunological or bone marrow dysfunctions. Cerebrospinal fluid (CSF) analysis can reveal mild lymphocytic pleocytosis. Treatment with anti-tumour necrosis factor (TNF)- alpha seems to be very effective in this condition. Fresh-frozen plasma infusions, which contain ADA2, or recombinant ADA2 can also be considered.

2. What are the main types of primary CNS vasculitis in children?

Primary CNS vasculitis in children can schematically be divided into three main subgroups:

- **Angiography-positive, non-progressive primary CNS vasculitis:** usually monophasic, affecting proximal CNS vessels unilaterally; possibly post-infectious, especially post-varicella zoster infection
- **Angiography-positive, progressive primary CNS vasculitis:** chronic, affecting proximal and distal vessels, uni- or bilaterally
- **Angiography-negative, small-vessel primary CNS vasculitis:** the diagnosis is made based upon brain biopsy, which shows intramural and perivascular inflammation, most often lymphocytic (fibrinoid necrosis and granulomas are rarely observed in children, as opposed to adults with primary CNS vasculitis); angiography is normal, but brain MRI usually shows lesions, infarcts and/or post-gadolinium meningeal enhancement

In the largest series of childhood primary CNS vasculitis, median age at diagnosis was 7 years, with a male:female ratio of 1.6:1. Headaches were present in 56–100% and seizures in 15% of patients (and up to 50–100% in children with small-vessel primary CNS vasculitis; more often than in adults). Hemiparesis was observed in 40–80% of children, hemisensory deficits in 79%, and fine motor deficits in 73%. More diffuse

neurologic deficits appear more common in children with small-vessel primary CNS vasculitis, including concentration difficulties in 29% of children, cognitive dysfunction in 37%, and mood or personality changes in 26%.

Like in adults, CSF analysis is often abnormal. This is the case in 90% of children with small-vessel primary CNS vasculitis, but abnormalities are mild with some pleocytosis and mildly elevated protein levels. On neuroimaging, in angiography-positive CNS vasculitis, arterial lesions are more often multifocal (76%) and proximal (86%).

3. Which treatment is usually considered for small-vessel CNS vasculitis in children?

Treatment protocols for childhood primary CNS vasculitis have been developed by the original BrainWorks team and are available online at https://cumming.ucalgary.ca/research/brainworks/brainworks.

Patients with angiography-negative (usually biopsy-proven), small-vessel primary CNS vasculitis should be treated aggressively with a combination of GC and another immunosuppressant, mostly CYC. GC are usually started at a high dose (2 mg/kg/day equivalent-prednisone; maximum 60 mg/day), possibly preceded by 1 to 3 methylprednisolone pulses (15 to 30 mg/kg/day), and subsequently tapered, by approximately 10% every 2 weeks. CYC is most often administered as IV pulses in children, at a dose of 0.5-0.75 mg/m^2 every 4 weeks (some protocols suggest a pulse at day 1, then day 15, then monthly). Oral CYC (2 mg/kg; maximum 150 mg/day) can also be used when IV pulse therapy is not feasible. Once the child has improved and achieved an equivalent of remission (there are no consensus definitions for response to treatment or remission in primary CNS vasculitis), usually after a maximum of 6 months, CYC can be switched to mycophenolate mofetil (MMF; 400 to 600 mg/m^2 twice daily), or mycophenolic acid (250-400 mg/m^2 twice daily) for at least 1 to 2 years, for maintenance. One study in children showed that the relapse rate was lower with MMF or mycophenolic acid, compared with azathioprine (0% vs. 55%). Azathioprine (2-3 mg/kg/day; maximum 150 mg/day) is thus used mostly for maintenance in children who cannot receive and/or tolerate MMF (or methotrexate).

Children with progressive primary CNS vasculitis are also usually treated with GC and CYC, and those with angiography-positive, non-progressive primary CNS vasculitis are usually treated with GC and antithrombotic agents. In all cases, early rehabilitation programs are important to limit neurological damage.

Like in adults, TNF-alpha blockers, intravenous immunoglobulins and/or rituximab can be considered for children with relapsing and/or refractory disease, based on case reports.

Whereas mortality rates today are low, only one-third of children recover without any neurological damage at 2 years. Predictors of poor neurological outcomes include neurocognitive dysfunction, headaches, multifocal and bilateral parenchymal lesions on MRI, and multiple, bilateral and/or distal stenoses on angiography at diagnosis.

References

Calabrese LH and Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) 1988;67:20-39.

Benseler SM et al. Angiography-negative primary central nervous system vasculitis in children: a newly recognized inflammatory central nervous system disease. Arthritis Rheum 2005;52(7):2159-67.

Benseler SM et al. Primary central nervous system vasculitis in children. Arthritis Rheum 2006;54(4):1291-7.

Hutchinson C et al. Treatment of small vessel primary CNS vasculitis in children: an open-label cohort study. Lancet Neurol 2010;9(11):1078-84.

Elbers J et al. Brain biopsy in children with primary small-vessel central nervous system vasculitis. Ann Neurol 2010;68(5):602-10.

Twilt M and Benseler SM. The spectrum of CNS vasculitis in children and adults. Nat Rev Rheumatol 2011;8(2):97-107.

Malik MA et al. Childhood primary angiitis of the central nervous system. J Coll Physicians Surg Pak 2012;22(9):570-4.

Batthish M et al. Refractory primary central nervous system vasculitis of childhood: successful treatment with infliximab. J Rheumatol 2012;39(11):2227-9.

Cellucci T et al. Childhood primary angiitis of the central nervous system: identifying disease trajectories and early risk factors for persistently higher disease activity. Arthritis Rheum 2012;64(5):1665-7.

Dale RC et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology 2014;83(2):142-50.

Zhou Q et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med 2014;370(10):911-20.

Cellucci T et al. Distinct phenotype clusters in childhood inflammatory brain diseases: implications for diagnostic evaluation. Arthritis Rheumatol 2014;66(3):750-6.

Navon Elkan P et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med 2014;370(10):921-31.

Twilt M and Benseler SM. Childhood inflammatory brain diseases: pathogenesis, diagnosis and therapy. Rheumatology (Oxford) 2014;53(8):1359-68.

Rodriguez-Pla A and Monach PA. Primary angiitis of the central nervous system in adults and children. Rheum Dis Clin North Am 2015;41(1):47-62.

Wilson N et al. MRI and clinicopathological correlation of childhood primary central nervous system angiitis. Clin Radiol. 2016;71(11):1160-7.

Case 16
Cryoglobulinemic vasculitis

A 52-year-old man presented a few weeks ago with sudden-onset painful tingling and numbness in his left foot, a purpuric rash, and diffuse arthralgia. He took some ibuprofen then developed painful ulcers on his right lower extremity (Figure 16.1), just proximal to the malleolus. His past medical history is significant for chronic alcohol abuse, remote heroin use, hypertension, dyslipidemia, chronic hepatitis C infection (HCV; never treated) and depression.

Investigations reveal a hemoglobin level of 122 g/l (normal 120-180 g/l), leukocyte count of 5700/mm^3 (normal 4000-10000/mm^3), and a platelet count of 93,000/mm^3 (normal 150,000 to 450,000/mm^3). Electrolytes and serum creatinine are normal, but urinalysis is positive for trace blood and protein. Transaminases are elevated, with AST 50 IU/l (normal 10-40 IU/l) and ALT 129 IU/l (normal 7-56 IU/l). Rheumatoid factor (RF) is positive at 325 IU/ml (normal <14 IU/ml). C3 is low at 0.54 g/l (normal 0.63-1.24 g/l), and C4 is <0.01 g/l (normal 0.16-0.48 g/l). Serum protein electrophoresis demonstrates a diffuse polyclonal hypergammaglobulinemia at 21 g/l (normal, 7.5 to 18 g/l). HCV DNA testing is positive. A serum cryoglobulin test is negative.

1. *What here makes you think this patient could have systemic vasculitis? What are the main differential diagnoses for such severe necrotic skin ulcerations?*
2. *What is cryoglobulinemia and what are the main causes?*
3. *Describe the clinical manifestations of cryoglobulinemic vasculitis.*
4. *What is the work-up of patients with suspected cryoglobulinemic vasculitis?*
5. *How would you treat this patient?*
6. *What is his prognosis?*

Learning objectives

1. To identify the three subtypes of cryoglobulinemia and their pathophysiologic mechanisms.
2. To describe the work-up required for cases of cryoglobulinemic vasculitis.
3. To identify the clinical manifestations and complications of cryoglobulinemic vasculitis and factors which predict a poor outcome.
4. To establish a treatment plan for patients with cryoglobulinemic vasculitis.

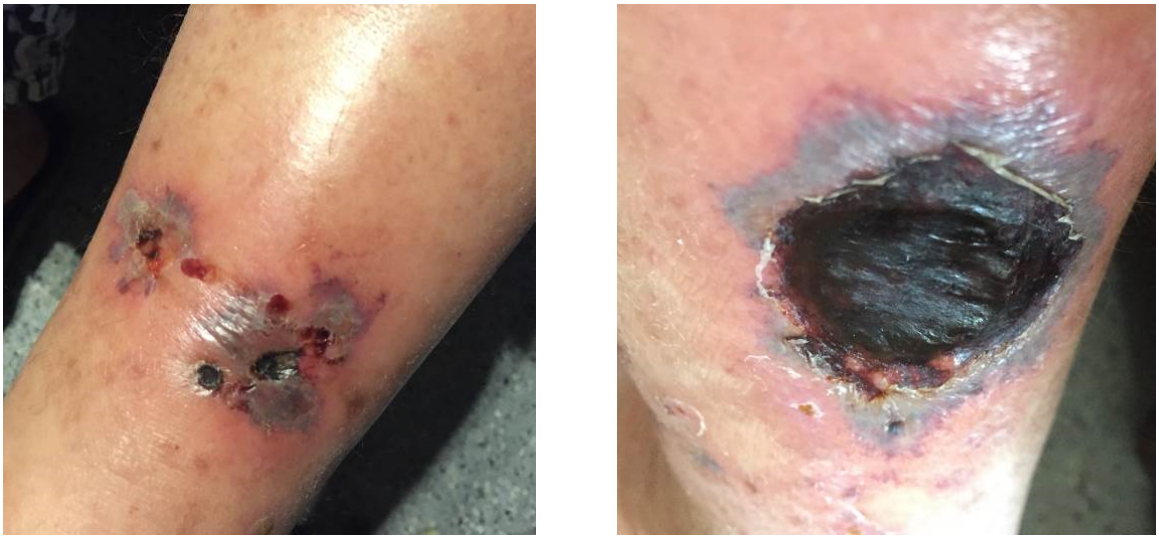


Figure 16.1 a/b. Necrotic skin ulcerations of the legs (a. anterior aspect, b. posterior aspect of the same leg).

Answers

1. What here makes you think this patient could have systemic vasculitis? What are the main differential diagnoses for such severe necrotic skin ulcerations?

Such a new onset, rapidly progressive disease affecting three different systems (skin, joints, and peripheral nervous system) and the necrotic purpura and ulcerations should raise suspicion of a systemic condition, especially vasculitis.

Various vasculitides can be considered, mostly those affecting medium- and/or small-sized vessels (polyarteritis nodosa; ANCA-associated vasculitides, immune-complex vasculitides). Secondary vasculitides can present similarly, including those due to an infection (HBV, HCV, Neisseria meningitides/gonorrhea, *Streptococcus pyogenes*) or drugs (antibiotics, levamisole-tainted cocaine). Other systemic conditions, such as lupus erythematosus, Sjögren syndrome, rheumatoid arthritis or sarcoidosis, can cause vasculitis, but exceptionally as the initial manifestation of the disease or with such severe ulcerations. Other non-vasculitic disorders potentially causing micro-thrombi in the skin vessels must also be considered in this patient, such as antiphospholipid syndrome, protein C or S deficiencies, thrombotic microangiopathy (bacterial, congenital, paraneoplastic or idiopathic), calciphylaxis, or endocarditis. Other conditions that can mimic vasculitis with very similar appearance of skin lesions include scurvy (vitamin C deficiency), sickle cell disease, or vasospams (e.g. ergotism).

2. What is cryoglobulinemia and what are the main causes?

Cryoglobulins are circulating immunoglobulins that precipitate at temperatures below 37°C and dissolve on rewarming. Despite the name, symptoms of cryoglobulinemia are rarely cold-induced. Most cryoglobulins precipitate at temperatures just below body temperature.

Three subtypes of cryoglobulins have been identified (Brouet's classification):

- Type I refers to a single monoclonal immunoglobulin; IgM is the most common subtype. The mechanism of damage in type I cryoglobulinemia is largely due to precipitation in, and subsequent occlusion of, small and medium vessels. Any lymphoproliferative disorder associated with monoclonal immunoglobulin production can cause type I cryoglobulinemia, including multiple myeloma, Waldenstrom's macroglobulinemia, B cell lymphoma, and chronic lymphocytic leukemia. Excessive production of the monoclonal immunoglobulin in these latter neoplasms can also cause hyperviscosity syndrome.
- Type II is called a mixed cryoglobulinemia because it is composed of both polyclonal IgG and monoclonal immunoglobulins. The monoclonal antibody is more often an IgM antibody against polyclonal immunoglobulins.
- Type III refers to a polyclonal IgM with rheumatoid factor activity against polyclonal immunoglobulins.

In types II and III (mixed) cryoglobulinemia, the mechanism of injury is due to immune-complex deposits and mediated vasculitis. Small and, to a lesser degree, medium vessels are the most commonly affected. Complement is typically fixed and activated, which explains the low serum levels of complement (especially C4) that are commonly seen in patients with cryoglobulinemia.

HCV-induced cryoglobulinemia is one of the most common causes of type II (90% of type II) or type III (70% of type III) cryoglobulinemia. The underlying mechanism is thought to be chronic immune stimulation by HCV E2, an HCV membrane protein, which binds directly to CD81 cell surface markers on B cells, and promotes B-cell expansion. These B cells produce immunoglobulins with RF activity. Complexes of HCV, immunoglobulins directed against HCV, RF, complement, and particles such as very-low-density lipoprotein comprise the cryoglobulin, which goes on to stimulate an inflammatory, vasculitic cascade. Most cases of HCV-associated cryoglobulinemia are asymptomatic: although over 50% of patients with HCV have detectable cryoglobulins, only about 15% of those patients will develop symptoms of cryoglobulinemia or cryoglobulinemic vasculitis.

With the recent advent of direct-acting anti-HCV antivirals leading to high rates of sustained virological response, systemic autoimmune disorders (Table 16.1), have become the main causes of mixed cryoglobulinemia in developed countries (36.5%).

The most common causes of non-HCV-related of mixed (type II or III) cryoglobulinemia are autoimmune diseases (mainly Sjögren syndrome [20% of patients may have cryoglobulins, but only a small fraction will develop associated symptoms], followed by systemic lupus erythematosus), and lymphoproliferative disorders. Human immunodeficiency virus (HIV) infection can also cause cryoglobulinemia. Numerous other infectious agents (cytomegalovirus, Epstein-Barr virus, parvovirus B19, pyogenic bacterial infections, parasitic infections, leprosy and candidiasis) have been associated with cryoglobulinemia in case reports and series, but the strength of these associations is unclear. Although hepatitis B virus (HBV) has been associated with cryoglobulinemia, most studies reporting that link were done in the early 1980s, before HCV had been identified. HBV as a cause of cryoglobulinemia appears to be extremely rare.

Although rheumatoid arthritis has been linked to mixed cryoglobulinemia, it is possible that most cases were actually due to HCV infection, as the latter can cause a symmetric polyarthritis and positive RF.

Finally, cryoglobulinemia can be unprovoked, "idiopathic" or "essential".

Table 16.1. Characteristics of patients with cryoglobulinemic vasculitis, asymptomatic cryoglobulinemias or other vasculitis without cryoglobulinemia (adapted from Quartuccio et al. 2014).

	Cryoglobulinemic vasculitis	Asymptomatic cryoglobulinemia	Other vasculitides without cryoglobulinemia
Cryoglobulinemia type:			
I	5%	4%	—
II	58%	40%	—
III	9%	29%	—
Not typable	28%	28%	—
RF positivity	81%	58%	32%
Low C4	72%	27%	10%
Monoclonal component	69%	46%	7%
HCV infection	72%	58%	—
Sjögren syndrome	12%	28%	13%
Other associated connective tissue disease	2%	8%	12%

3. Describe the clinical manifestations of cryoglobulinemic vasculitis.

Clinical manifestations of cryoglobulinemia can be divided mechanistically according to whether they occur via direct occlusion (as in the case of type I cryoglobulinemia) or immune mediated (as in type II and III).

Manifestations of type I cryoglobulinemia include Raynaud's phenomenon, arterial thrombosis, distal ulcers and necrosis, and hyperviscosity syndrome, characterized by bleeding, vision changes, and neurologic symptoms.

Manifestations of type II and III cryoglobulinemia are due to immune-mediated vasculitis, and as such, they can affect almost any organ with small or medium vessels. Skin, renal, nervous system, and articular symptoms are especially common.

Arthralgias are common but (non-erosive) synovitis and/or arthritis are rarer. Patients with cryoglobulinemia will commonly describe exquisite joint pain.

Skin manifestations of cryoglobulinemic vasculitis include purpura, more commonly occurring on the lower extremities, and may be palpable or not, retiform or not (retiform refers to the way the purpuric lesions are distributed along vessels in the extremities).

Other skin lesions can occur, such as urticaria, livedo racemosa, and, if medium vessels are involved, deep, necrotic skin ulcers, usually above the malleoli and with purple borders. If digital vessels are affected, digital necrosis can occur.

Membranoproliferative glomerulonephritis is the most common renal manifestation of cryoglobulinemia. Patients typically present with microscopic hematuria or proteinuria, although nephrotic-range proteinuria or nephritic syndrome can occur. Kidney injury often causes hypertension. Renal failure is the most common cause of death in patients with cryoglobulinemic vasculitis.

Cryoglobulinemia can affect the vasa nervosum and cause painful distal symmetric sensory or, less often, sensorimotor polyneuropathy of insidious

or abrupt onset. Mononeuritis multiplex can be seen as well. Symptoms often persist long after the cryoglobulinemia has been treated. Central nervous system involvement is rare (stroke), and has a poor prognosis.

4. What is the work-up of patients with suspected cryoglobulinemic vasculitis?

Diagnoses of cryoglobulinemia and cryoglobulinemic vasculitis are typically made by identifying the presence of serum cryoglobulins and confirming the presence of vasculitic manifestations.

False-negative cryoglulin tests are common. If clinical suspicion is high, the test should be re-ordered and carried out in the proper conditions (the blood vials must ideally be kept at 37°C until processed, rapidly). In types II and III cryoglobulinemia, the cryoglobulins may be present in small quantities, and take a long time to precipitate (up to 7 days, in the case of type III). Finally, levels of serum cryoglobulins may vary during the course of the disease. In some patients, the evidence for cryoglobulinemic vasculitis (clinical symptoms, positive RF, disproportionately low C4 compared with the near normal C3 levels, mono- or oligoclonal gammopathy with or without HCV infection) may be so compelling that initiation of treatment can be considered even without a positive cryoglobulin test.

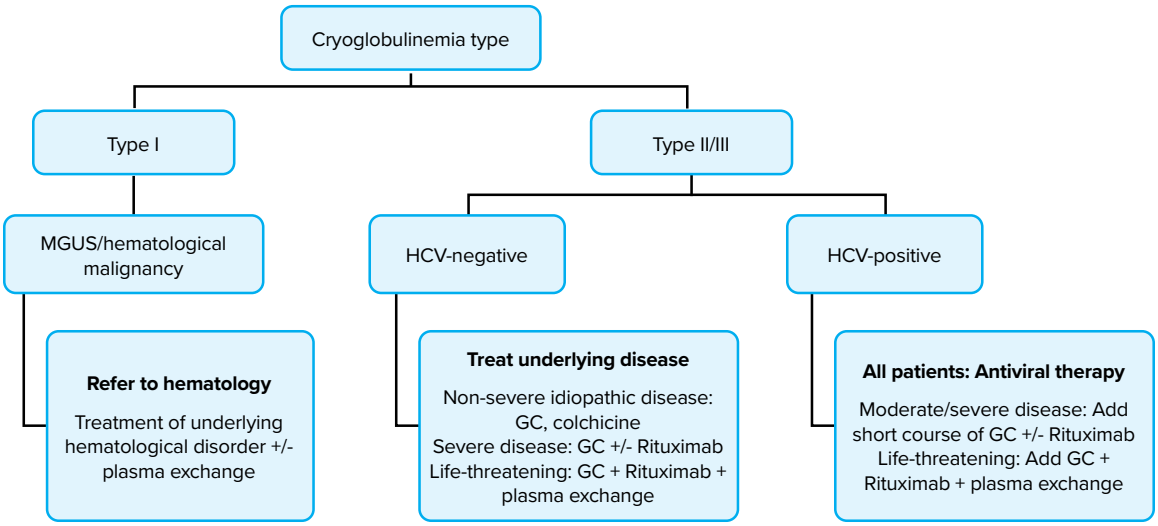
The proportion of cryoglobulins among immunoglobulins or “cryocrit” can be used to measure cryoglobulinemia disease activity, but the variability between laboratory assays limits its reliability in practice.

Because so many cases of cryoglobulinemia are secondary, a search for causes is essential. All patients should be screened for HCV, HBV and HIV infections (and other infectious agents according to the patient’s history). Other autoantibodies are common in cryoglobulinemia, including antinuclear antibody, anti-smooth muscle, antiphospholipid, and antineutrophil cytoplasm antibodies (ANCA). Their significance is unclear but they usually do not translate into any additional disease or clinical manifestations (bystanders). A work-up for possible hematologic malignancy should be done, and may include a complete blood count with blood film, flow cytometry, serum protein electrophoresis, urine protein electrophoresis, serum free light chains, and, when indicated, bone marrow biopsy.

In parallel, investigations targeted at all possibly affected organs should be considered. A serum creatinine and urinalysis are essential. Imaging of painful joints is rarely helpful except to rule out alternative causes of arthralgia. Nerve conduction studies with electromyography can be helpful in typing and assessing the extent of nerve damage. Biopsies of affected organs can also provide useful information. Hematoxylin and eosin (H&E) staining of skin biopsies can show leukocytoclastic vasculitis and intravascular thrombi, due to direct occlusion of the microvasculature. Immunofluorescence studies can show immunoglobulin and C3 deposition. Renal biopsy can reveal membranoproliferative glomerulonephritis in patients with renal involvement, with or without associated small-vessel microthrombi. Most suggestive histological findings are large deposits filling the capillary lumen, sometimes with a fibrillar or crystalloid structure by electron microscopy, as well as exudative infiltration of monocytes, diffuse thickening of the glomerular basement membrane, with a double-contoured appearance mainly due to the peripheral interposition of monocytes, and sometimes vasculitis in small- and medium-sized renal arteries, usually without crescents (or only a few). Bone marrow or liver biopsies may show clonal B-cell expansion.

In patients with HCV, it is also important to determine the extent of liver fibrosis by ultrasound, sonographic elastography or biopsy. The presence of severe liver fibrosis is independently associated with a poorer prognosis.

Figure 16.2. Management of cryoglobulinemic manifestations (vasculitis or other) according to the type of cryoglobulin (adapted from Terrier B et al. Curr Opin Rheum 2013; see text for details)



GC: glucocorticoids; MGUS: monoclonal gammopathy of undetermined significance.

5. How would you treat this patient?

The treatment of cryoglobulinemic vasculitis has undergone two paradigm shifts in the past 10 years. One is due to the introduction of well-tolerated curative treatments for HCV infection. The other is due to increased use of rituximab (RTX).

The mainstay of therapy for cryoglobulinemic vasculitis is treatment of the underlying cause (see Figure 16.2).

Patients diagnosed with a lymphoproliferative neoplasm should be referred to hematology in order to receive the most appropriate chemotherapy. The mainstay of therapy for cryoglobulinemic vasculitis caused by HCV was previously an interferon-based regimen, which often exacerbated cryoglobulinemia, had tolerance issues and only worked in a fraction of patients. Modern interferon-free direct-acting antiviral regimens (including sofosbuvir and ledipasvir, daclatasvir, ribavirin or simeprevir) for HCV are well tolerated and almost universally associated with complete clearance of the virus in >90% of cases. The clearance of cryoglobulins is however lower (only 44-46% in some studies). Referral to a liver and HCV specialist is mandatory for patients with HCV-associated vasculitis.

A small number of patients may still have persistent cryoglobulinemia and HCV-associated vasculitis. In these patients, as well as for patients with very severe initial vasculitis manifestations, other options detailed below for non-HCV-associated vasculitis can be considered (in combination with antiviral drugs).

Several options exist to treat non-HCV cryoglobulinemia and its clinical manifestations. High-dose glucocorticoids (GC) are typically used for severe disease. Typical dosing is prednisone-equivalent 1 mg/kg/day with a taper as quickly as possible to the minimum dose that will safely suppress disease activity without causing harm. Plasma exchange is highly effective in type I cryoglobulinemia. It can effectively remove the circulating antibodies causing hyperviscosity syndrome. It is typically followed by chemotherapy

if there is an underlying malignancy. In types II and III cryoglobulinemias, the evidence is weaker. Plasma exchange has been used in life-threatening disease and in patients with severe leg ulcers. Some reports mention a risk of rebound cryoglobulin overproduction after its use.

RTX should now be considered in patients with moderate-to-severe disease. Typical dosing is 375 mg/m^2 every week for 4 consecutive doses, or, sometimes but preferably not for patients with the highest cryocrits, 1 g at days 1 and 15; lower doses such as 250 mg/m^2 at days 1 and 15 might be as effective in cryoglobulinemic vasculitis. RTX can be used safely in patients with active HCV (in combination with or, most often, a few weeks after the initiation of antiviral drugs). The efficacy of RTX is usually durable, although relapse occurs in around 20% of cases, between 7-18 months after the initial RTX course. B-cell reconstitution typically precedes relapse, but not all patients with a biochemical relapse will have a clinical relapse. Relapses can be treated with a repeat induction course of RTX.

Other agents are now rarely used, such as cyclophosphamide (2 mg/kg/day orally or 750 mg/m^2 IV monthly) for severe cases, colchicine for cutaneous disease, or methotrexate, mycophenolate mofetil, or azathioprine. Low-dose interleukin-2 for patients with HCV-associated cryoglobulinemia resistant to antivirals and RTX has also been investigated in a small, prospective, phase I open-label trial, which showed it was safe and efficacious at reducing cryoglobulin burden and vasculitic symptoms.

In this patient's case, a quick start of antiviral therapy would be highly recommended if there are no contraindications, in combination with prednisone 1 mg/kg/day to treat his moderate-to-severe manifestations (leg ulcers, peripheral nerve involvement). Prednisone will be tapered rapidly. The addition of rituximab can also be considered.

6. What is his prognosis?

In general, the prognosis of patients with cryoglobulinemia is relatively good. If it is due to a secondary cause which can be then eradicated, relapse is not expected. Relapse after treatment with direct-acting antiviral agents in HCV cryoglobulinemic vasculitis occurs in up to 12.6% of patients, with death occuring in 9.6% of relapsing patients, mostly due to infection from immunosuppression.

A number of risk factors are associated with poorer prognosis, including male gender, older age, HCV infection, liver fibrosis, elevated cryocrit, low C3, and elevated creatinine. The presence of alveolar hemorrhage, cardiac or central nervous system involvement, and/or intestinal ischemia is associated with 80% mortality. The presence of glomerulonephritis is associated with a 33–49% mortality rate.

Many patients suffer complications, such as secondary malignancy. Lymphoma develops in up to 20% of patients within 10 years of diagnosis. B-cell lymphoma is the most common type. Hepatocellular carcinoma and papillary thyroid cancer have also, but more rarely, been associated with cryoglobulinemia.

References

Brouet JC et al. Biologic and clinical significance of cryoglobulins: a report of 86 cases. Am J Med 1974;57:775–88.

Monti G et al. Incidence and characteristics of non-Hodgkin lymphomas in a multicenter case file of patients with hepatitis C virus-related symptomatic mixed cryoglobulinemias. Arch Intern Med 2005;10;165(1):101-5.

Saadoun D et al. Increased risks of lymphoma and death among patients with non-hepatitis C virus-related mixed cryoglobulinemia. Arch Intern Med 2006;166(19):2101-8.

Dammaco F et al. Pegylated interferon-alpha, ribavirin, and rituximab combined therapy of hepatitis C virus-related mixed cryoglobulinemia: a long-term study. Blood 2010;116(3):343-53.

Saadoun et al. Regulatory T-cell responses to low-dose interleukin-2 in HCV-induced vasculitis. N Engl J Med 2011;365(22):2067-77.

Terrier B et al. Prognostic factors in patients with hepatitis C virus infection and systemic vasculitis. Arthritis & Rheumatism 2011;63:1748–57.

De Vita S et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum 2012;64(3):843-53.

Terrier B. Cryoglobulinemia vasculitis: an update. Current opinion in rheumatology. 013;25(1):10–8.

Quartuccio L et al. Validation of the classification criteria for cryoglobulinaemic vasculitis. Rheumatology 2014;53(12):2209-13.

Visentini M et al. Efficacy of low-dose rituximab for the treatment of mixed cryoglobulinemia vasculitis: Phase II clinical trial and systematic review. Autoimmun Rev 2015;14(10):889-96.

Terrier B et al. Non HCV-related infectious cryoglobulinemia vasculitis: Results from the French nationwide CryoVas survey and systematic review of the literature. J Autoimmun 2015;65:74-81.

Ferri C et al. International diagnostic guidelines for patients with HCV-related extrahepatic manifestations. A multidisciplinary expert statement. Autoimmun Rev 2016; 15(12):1145-60.

Rocatello D et al. Improved (4 Plus 2) Rituximab Protocol for Severe Cases of Mixed Cryoglobulinemia: A 6-Year Observational Study. Am J Nephrol 2016;43(4):251-60.

Haq SA and Pagnoux C. Infection-associated vasculitides. Int J Rheum Di 2019; 22(Suppl 1):109-15.

Boleto G et al. Cryoglobulinemia after the era of chronic hepatitis C infection. Seminars in arthritis and rheumatism. 2020;50(4):695–700.

Fayed A, et al. Relapse of HCV-Cryoglobulinemic Vasculitis Following Sustained Viral Response after Interferon-free Direct-Acting Antiviral. Am J Gastroenterol; 2022 Jan 29.

Case 17

Anti-glomerular basement membrane antibody disease

Mr. J is a 57 year-old man with medical history of type 2 diabetes, hypertension, and smoking (currently still smokes; 25 pack-years). There is no known specific family disease, but his father died in his 70s from end-stage renal disease, without any further precision available. He is a construction worker, and has not travelled outside his urban hometown in Kingston (Ontario) for the past 2 years.

A month ago, he started to feel more fatigued than usual, and then developed some shortness of breath on exercise, then at rest, with chills, and over the past couple of days, has spat up some red-tinged material. He also noticed some redness and frothiness in his urine over the past few days. He denies any skin rash, muscle or joint pain, or fever.

At triage in the emergency department, he is found to have low oxygen saturation at 82% on room air (92% on 6 l nasal prongs), regular tachycardia at 110/minute, blood pressure at 148/87 mmHg. He has bilateral leg edema to mid-calf and diffuse, bilateral crackles on lung auscultation. His labs show a hemoglobin level at 98 g/l (N: 110-180), a white blood cell count of 14500/mm^3 (N: 4000-10000), a normal platelet count and ALT level, serum creatinine at 952 µmol/l (N<125), and an active urine sediment, with protein >3 g/l, and red blood cells >80 per field (N<3). C-reactive protein is 125 mg/l (normal <10 mg/l).

Chest X-ray reveals diffuse infiltrate, and chest CT without contrast medium shows diffuse ground-glass opacities, septal thickening, some nodularities in the bases, but no cavitary lesions, in keeping with possible alveolar hemorrhage and/or superimposed infection. Bedside point-of-care echocardiography shows normal cardiac ejection fraction at 59% and left atrial dilatation.

The patient is found to have anti-GBM antibodies, and no ANCA, ANA or lupus anticoagulant antibodies.

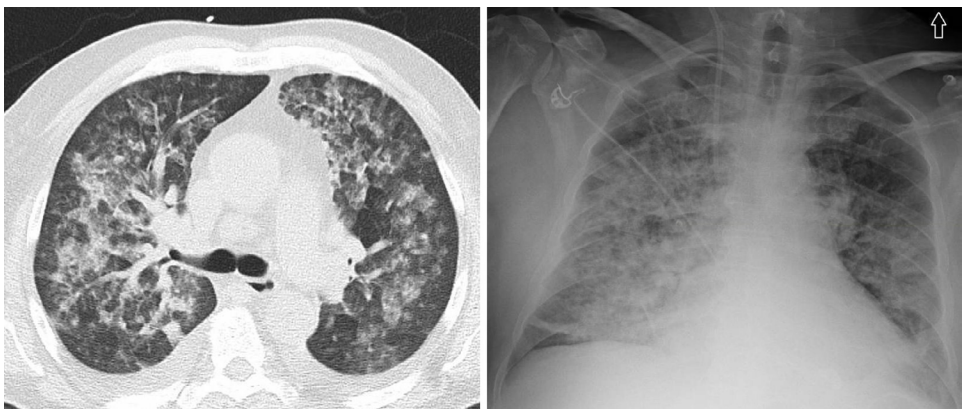


Figure 17.1. Chest CT (right) and X-ray (left). Diffuse, bilateral infiltrate, with ground-glass opacities, in keeping with diffuse alveolar hemorrhage, septal thickening, and some nodularities in the bases.

1. *What is anti-GBM disease?*
2. *What is the impact of being double-positive (for both ANCA and anti-GBM antibodies)?*
3. *What are the possible treatment options for this patient?*

Learning objectives

1. To identify anti-GBM disease as an additional vasculitis in the 2012 Chapel Hill nomenclature.
2. To be aware of this subset of patients with both ANCA and anti-GBM antibodies.
3. To list the main treatment options and steps for anti-GBM disease.

Answers

1. What is anti-GBM disease?

Anti-glomerular basement membrane (GBM) disease is a rare, autoimmune and small-vessel vasculitis. It was previously known as Goodpasture disease; whereas Goodpasture syndrome referred more broadly to pulmonary-renal syndromes (severe renal disease and alveolar lung hemorrhage), depending on the causative condition. Of note, anti-GBM disease was only added to the revised Chapel Hill consensus conference nomenclature of vasculitides in 2012, within the group of small-sized-vessel, immune-complex mediated vasculitis.

The annual incidence of anti-GBM disease is 1-2/million in European populations, and it has a bimodal age distribution, with peaks in the 3rd and 7th decades, a male preponderance in early adulthood, but a slight female preponderance in those with a later disease onset.

Anti-GBM antibodies (Abs) bind to the non-collagenous (NC) 1 domain of the alpha-3 chain (and/or, less often, alpha-1 or -4) of type IV collagen, and can damage the GBM, resulting in rapidly progressive glomerulonephritis with crescent formation (80-90% of patients), but also the alveolar basement membrane, resulting in alveolar hemorrhage (50% of patients, occasionally without renal disease). The direct pathogenicity of anti-GBM antibodies was shown by adoptive transfer experiments, wherein anti-GBM from humans administered to primates resulted in glomerulonephritis. However, anti-GBM disease is more considered as a T-cell, rather than a primary B-cell disease, as evidenced by strong HLA-associations: HLA-DR15 and *DRB1**1501 are associated with disease susceptibility in Caucasian and Asian populations, whereas *DRB1**01, DR7 and DR9 are negatively associated with disease risk. Anti-GBM disease is also sometimes considered a "conformeropathy" because a primary event in the pathogenic cascade would be the perturbation of the quaternary structure of the alpha-hexamer of NC1 collagen.

Environmental triggers may contribute to disease pathogenesis, through "molecular mimicry" with some infections, such as influenza, and/or pulmonary irritants, including smoking, hydrocarbon, or inhaled recreational drugs. Temporal and spatial clustering of cases have

been reported. Anti-GBM disease has also been reported with the use of alemtuzumab for relapsing-remitting multiple sclerosis (but not when used for other conditions, to date).

Extrarenal or pulmonary manifestations are uncommon.

The diagnosis relies on the presence of anti-GBM in the patient sera, and/or on renal biopsy. However, around 10-18% of patients with anti-GBM disease do not have circulating antibodies by conventional assays. A kidney biopsy, when performed, may show the characteristic linear deposition of the auto-Ab on the GBM on direct immunofluorescence study. Lung biopsy is rarely performed.

Treatment and outcomes are discussed below (Question 17.3).

2. What is the impact of being double-positive (for both ANCA and anti-GBM antibodies)?

Twenty-one to 47% of patients with anti-GBM disease also have ANCA, mostly MPO-ANCA. Conversely, a few studies showed that up to 5% of patients with ANCA-associated vasculitis have detectable anti-GBM Abs. This double positivity is most often not caused by a simple cross-reactivity.

It is therefore important here to order the classical ANCA and not forget to order the anti-GBM Ab testing (usually by ELISA or bead-based immunoassays) in patients with pulmonary-renal syndrome like in this case.

These double-positive patients are often older, more often males, and less often smokers, than those with anti-GBM positivity alone. They also can present with longer prodromes and more extrarenal disease manifestations. The severity of renal and lung disease at presentation seems to be comparable between double-positive and single-anti-GBM-positive cases, but more severe (and rapidly progressive) than in patients with ANCA-associated vasculitis (without anti-GBM). One-year renal survival is also worse in patients with double-positive disease than in ANCA-associated vasculitis without anti-GBM Abs (at 27% vs. 64%, respectively, in a French cohort of 33 double-positive patients, and 45 patients with ANCA-associated vasculitis). Conversely, double-positive cases have similar renal recovery to single-anti-GBM-positive patients, but they have more frequent relapses, especially when they are both PR3-ANCA-positive. This relapse rate in double-positive patients is similar to that of patients with ANCA-associated vasculitis. To summarize, double-positive patients carry the poorer renal outcomes of anti-GBM disease, and the higher relapse risk of ANCA-associated vasculitis.

3. What are the possible treatment options for this patient?

Other causes of pulmonary-renal syndrome should still be considered, especially ANCA-associated vasculitis (and ANCA and anti-GBM double-positive cases), but also lupus, antiphospholipid syndrome, and a (superimposed) infection, which would need to be treated as well (see also Case 9, Table 9.1).

Treatment for anti-GBM disease includes plasmapheresis, to rapidly remove anti-GBM Abs, cyclophosphamide (CYC, mostly oral, at a dose of 2 mg/kg/day adjusted to age and kidney function) and glucocorticoids (GC). Plasma exchanges (PLEX) should be done daily, with large volume exchanges initially, and then gradually spaced out for at least a total of 14 days or, ideally, until anti-GBM Abs become undetectable. Fresh frozen plasma should be used for the exchange in patients with alveolar hemorrhage and/or to prevent (or help treat) bleeding complications of renal biopsy. An early rebound of the disease can occur after the cessation of PLEX. Fifty to 80% of the patients also require dialysis initially, especially if double-positive ANCA and anti-GBM.

Rituximab (RTX) has been used in a few patients, with variable outcomes. As explained above, autoreactive T cells contribute to disease pathogenesis, and are not the targets of RTX. RTX may be considered as an alternative (in case of formal contraindication to CYC) or an adjunct agent in severe, refractory disease, and/or in double-positive patients. There are also case reports with mycophenolate mofetil (MMF) and cyclosporin A. Imlifidase, an IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS), has also been investigated in a small open-label trial in 15 patients with severe, rebounding disease, in combination with GC, CCY and PLEX. Six hours after imlifidase administration, anti-GBM were undetectable or within the reference range. At 6 months, 10 patients were dialysis independent.

Once remission is achieved, after 2 to 6 months of CYC, and after 4 to 9 months of GC, there is usually no need for maintenance therapy in single-positive anti-GBM patients. In double-positive patients, the relapse risk is higher, and maintenance is recommended (with RTX, MMF or azathioprine).

Whereas survival at 5 years is nowadays >85%, end-stage renal disease is frequent in anti-GBM disease (only 10-15% renal survival rate at 5 years in patients with an initial creatinine level >500 µmol/l and requiring dialysis). Renal transplantation should not be performed in patients with persistent serum anti-GBM Abs, because of their higher risk of recurrent disease.

References

McAdoo SP, Pusey CD. Antiglomerular Basement Membrane Disease. Semin Respir Crit Care Med 2018;39(4):494-503.

Marques C et al. Prognostic Factors in Anti-glomerular Basement Membrane Disease: A Multicenter Study of 119 Patients. Front Immunol 2019;10:1665.

Uematsu-Uchida M, Ohira T, Tomita S, Satonaka H, Tojo A, Ishimitsu T. Rituximab in treatment of anti-GBM antibody glomerulonephritis: A case report and literature review. Medicine (Baltimore) 2019;98(44):e17801.

Marques C, Plaisier E, Cacoub P, Cadranel J, Saadoun D. [Review on anti-glomerular basement membrane disease or Goodpasture's syndrome]. Rev Med Interne 2020;41(1):14-20.

Philip R et al. ANCA and anti-glomerular basement membrane double-positive patients: A systematic review of the literature. Autoimmun Rev 2021;20(9):102885.

Rovin BH et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int 2021;100(4):753-79.

Kant S, Kronbichler A, Sharma P, Geetha D. Advances in Understanding of Pathogenesis and Treatment of Immune-Mediated Kidney Disease: A Review. Am J Kidney Dis 2022;79(4):582-600.

Clerte M et al. Renal and overall outcomes of double-positive (ANCA and anti-GBM antibodies) patients compared to ANCA-associated vasculitis patients with severe renal involvement: A multicenter retrospective study with systematic renal pathology analysis. Scand J Rheumatol 2022;51(3):205-13.

Case 18
Behçet syndrome

A 23-year-old male of Turkish descent, living in Canada since the age of 9 years, presents with a 1-year history of multiple recurrent painful scrotal ulcers, which have tested negative for herpes simplex virus. Following a search on the internet, he wondered if he might have Behçet's disease as he also had recurrent oral aphthous ulcers since his childhood.

On clinical examination, besides some current oral and scrotal ulcers, some possible folliculitis-type lesions are observed on his thighs, arms and forearms, but not centered by hair (Figure 18.1). He also has some grossly decreased visual acuity in the right eye but without any redness or obvious ophthalmoplegia, and with preserved, symmetrical pupillary reflexes.



Figure 18.1. Small pustular lesion on the arm, with appearance of folliculitis but not centered by hair.

1. *What investigations would you order for this patient's work-up?*
2. *What therapies can be used in the treatment of the muco-cutaneous manifestations of Behçet's disease?*

You refer the patient to ophthalmology. He is found to have reduced visual acuity and evidence of mild posterior uveitis in both eyes, right more than left.

3. *What treatment will you now consider for this patient?*
4. *What are the possible neurological manifestations of Behçet's disease?*
5. *What are the possible cardiovascular complications of Behçet's disease?*

Learning objectives

1. To describe the epidemiology, main clinical characteristics and possible complications of Behçet's disease (BD).
2. To list the different treatment options for BD, according to the disease manifestations.
3. To discuss some of the still controversial areas in the management of BD.

Answers

1. What investigations would you order for this patient's work-up?

The diagnosis of Behçet's disease (BD; or Behçet syndrome, as different subsets may exist) is almost entirely clinical. The investigations in this patient are thus aimed at ruling out differential diagnoses, establishing a good baseline assessment of the disease and every organ involved, and obtaining general test results prior to initiating therapy, which might include at some point immunosuppressants.

BD is most prevalent in its classical form in countries along the "Silk Road", from Far East Asia to northern Mediterranean countries. It is also common in South American countries, and people originating from all those areas. It is rare in white Canadians, in whom the frequencies of each possible disease manifestation may slightly differ (more frequent gastrointestinal and neurological manifestations). The prevalence thus varies throughout the world (see Table 11.2 in Case 11). In Turkey, it was reported to be as high as 4200 per million inhabitants. In the USA, the prevalence is around 25-400 per million, higher in people originating from the above-mentioned areas.

Different criteria have been developed for the diagnosis or classification of Behçet's disease, including the International Criteria for Behçet's Disease (ICBD) and, for children, the Consensus Classification Criteria for Pediatric Behçet's Disease (PEDBD). With the ICBD, a point score ≥4 indicates a diagnosis of BD:

- **Ocular lesions**, 2 points: chronic and/or relapsing uveitis (most often posterior, with retinal necrotico-hemorrhagic vasculitis, but also anterior with or without hypopion, intermediate or pan-uveitis), most common in young, male patients and usually within the first 3–5 years after disease onset
- **Genital aphthosis**, 2 points: ulcers on the scrotum (rarely the shaft or glans penis) or labia majora/minora, taking 2–4 weeks to heal and often leaving scars
- **Oral aphthosis**, 2 points: recurrent, multiple, aphthous ulcers
- **Skin lesions**, 1 point: acneiform lesions, pseudo-folliculitis (as not centered by hair), papulopustular lesions (mainly on the face, upper chest, upper back, legs, arms), erythema nodosum and superficial phlebitis
- **Neurological manifestations**, 1 point (detailed in question/answer 18.4, below)
- **Vascular manifestations**, 1 point (detailed in question/answer 18.5, below)
- **Positive pathergy test**, 1 point: pathergy test is optional; when conducted, 1 point may be assigned for a positive result

(manifested by papule or pustule 24-48 hours after a needle prick; often positive in patients from Turkey or Asia, rarer in white North American patients)

The ICBD has an estimated sensitivity of 94.8% and specificity of 90.5%. Pathergy test is not totally sensitive and is not specific.

Inflammatory arthritis and arthralgia involving the knees, ankles, wrists and elbows are also frequent. Gastrointestinal symptoms (5–30% of patients; may be higher in Caucasian patients from nonendemic areas for BD) include nausea, vomiting, diarrhea, and abdominal pain, which can be secondary to mucosal ulcerations, mostly in the ileo-cecal region. It is often difficult to distinguish between inflammatory bowel disease (Crohn's disease mainly) and gastrointestinal involvement of BD. Crohn's disease can also cause oral ulcers, and some extra-digestive manifestations. Renal involvement is rare in BD.

Differential diagnoses to consider include reactive and seronegative arthritis (associated with HLA B27 or not), inflammatory bowel disease, sarcoidosis, systemic lupus, other systemic vasculitides, immune deficiency syndromes, and autoinflammatory syndromes, such as A20 haplo-insufficiency (HA20). Recurrent fever, more severe GI disease, and/or auto-antibodies may help differentiate BD from these latter conditions. Patients must also be screened for infections, such as syphilis, herpes simplex virus or tuberculosis. Rarer conditions, which can cause similar ocular problems, can also be considered (e.g. Vogt-Koyanagi-Harada syndrome). Patients with recurrent venous thromboses should likely be tested for thrombophilia and antiphospholipid antibodies.

Blood work should thus include complete blood count with differential, C-reactive protein (often mildly increased during flares), serum creatinine level and urinalysis, liver enzymes, serum protein electrophoresis, and antinuclear antibody screening test. Other infectious serologies (hepatitis B and C virus, human immunodeficiency virus [HIV]) or autoimmune (antineutrophil cytoplasm antibodies [ANCA] and/or anti-*Saccharomyces cerevisiae* antibodies [ASCA]) can also be ordered, depending on the clinical manifestations. Chest X-ray will help rule out sarcoidosis and tuberculosis, but also detect possible, large pulmonary artery aneurysms. Skin biopsy of a pseudo-folliculitis or pathergic lesion can reveal characteristic aspects with leukocytoclastic vasculitis, with predominant neutrophilic infiltrate and fibrinoid necrosis.

Imaging studies are ordered to diagnose complications of the diseases, and may include chest X-ray to look for pulmonary artery aneurysm(s), chest CT to rule out pulmonary embolism, and/or other imaging based on clinical findings. Increased common femoral vein wall thickness (≥0.5 mm) on US Doppler would be a more distinctive feature of BD, and is being evaluated as a diagnostic test (sensitivity and specificity would be >80%).

Every patient with BD should be referred to ophthalmology at diagnosis, then on a regular basis for follow-up, at least during the first 3 to 5 years. Other investigations are ordered depending on the clinical signs and results of these initial tests.

Whereas HLA B51 allele is present in up to 55–70% of patients with BD from areas with the highest prevalence of the disease, it is less common in other populations with BD (35–40% in North American or North European patients), and is also present in healthy general populations (10–18% in the USA, up to 22% in some Middle Eastern areas). It is therefore not a diagnostic test and has no validated place in the diagnostic work-up of patients with suspected BD.

2. What therapies can be used in the treatment of the muco-cutaneous manifestations of Behçet's disease?

No local remedy to alleviate pain and to expedite the healing of oral aphthous lesions has been validated. Their efficacy varies and remains limited. Mouth rinses with diluted and/or effervescent aspirin tablets, diluted oxygenated water and/or other antiseptic mouthwash solution, local application of lidocaine viscous gel before meals, local contact application of glucocorticoid (GC) such as triamcinolone acetonide ointment, sucralfate and/or aspirin tablets are among the most often cited in textbooks. A retrospective study showed that a combination of soluble betamethasone, doxycycline, and nystatin oral suspension dissolved in 10 ml of water could reduce ulcer severity, frequency and pain.

Several systemic drugs can also be used, with variable efficacy. During flares, short courses of oral GC can be tried (10 to 40 mg/day for 2–7 days). Colchicine at 1–2 mg/day has been shown to be useful for reducing genital ulcers and erythema nodosum in women. Its efficacy is less clear for oral aphthous lesions, but can be tried (0.6-1.2 mg/day during flares, then 0.6 mg/day as background therapy to limit the frequency and severity of flares). The most common and limiting side effect of colchicine is diarrhea.

Apremilast, an oral phosphodiesterase-4 inhibitor, was shown in a large multicentre randomized controlled trial of 2047 patients with BD to reduce the number and the pain of oral ulcers in BD, when given at a dose of 30 mg twice daily. It may also be beneficial for genital ulcers. Like colchicine, a common side effect of apremilast is diarrhea. It is available in Canada, but not yet approved for BD by Health Canada (it is approved only for patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy, and patients with psoriatic arthritis).

If the former options fail and the patient is debilitated by the severity and/or recurrences of the oro-pharyngeal or genital ulcers, other options can be considered, with careful consideration of their pros and cons (e.g. risk of serious side effects, cost, route of administration and need for sustained and regular use). Azathioprine (2-3 mg/kg/day) can reduce the frequency and/or severity of oral and genital ulcers. Thalidomide (100 mg/day) has also been shown to reduce the frequency and/or severity of oral and genital ulcers as well as papulopustular lesions, but its access is restricted due to its potential side effects (neuropathy, sedation, constipation, teratogenicity). Interferon-alpha-2α (6 million IU subcutaneously three times weekly) can reduce the duration and pain of oral ulcers and the frequency of genital ulcers and papulopustular rash. In a small double-masked trial, cyclosporine A (10 mg/kg/day) alleviated oral aphthous ulcerations in 70% of patients with BD compared with 20% with colchicine, but with numerous side effects (including hypertension). Tumour necrosis factor (TNF)-alpha blockers, including etanercept (25 mg subcutaneously twice weekly) or adalimumab (40 mg subcutaneously every other week) can also improve oral ulcers and erythema nodosum, and are often used next, in practice, if the second-line therapy with azathioprine fails or is contraindicated.

3. What treatment will you now consider for this patient?

Ocular involvement is reported in half of patients with BD and is usually more severe in males and young patients. Left untreated, it can lead to synechiae and/or blindness. Besides topical treatments, as prescribed by the ophthalmologist, this patient thus requires systemic treatments, with oral GC, initially at a high dose (prednisone-equivalent 1 mg/kg/day) for 2 to 4 weeks followed by a gradual taper, and another immunosuppressive drug. Azathioprine (2–3 mg/kg/day) is the first-line agent of choice

for anterior uveitis. It can decrease hypopyon, uveitis flares, stabilize visual acuity and decrease the development of new eye disease.

In a patient with refractory eye disease and/or severe retinal involvement, cyclosporine A or infliximab should be used in combination with azathioprine and GC. Cyclosporine A (2–5 mg/kg/day) is relatively fast acting, but can cause hypertension and nephrotoxicity. It should also be avoided in patients with central nervous system (CNS) manifestations, as it could exacerbate these latter. Infliximab (5–10 mg/kg per infusion, at day 1, 15 then every 4 to 8 weeks) is therefore more often used, after having checked for the absence of (or treated if needed) latent or active tuberculosis. Adalimumab can also be considered. Interferon-alpha (IFNα), alone (not with azathioprine) or in combination with GC, could be a subsequent choice for the treatment of eye disease.

Ocular disease treatment and duration are guided by the ophthalmologist but should be continued for at least 18-24 months. Relapses are frequent, and vision loss is observed in 10–15% of patients with BD and eye involvement.

4. What are the possible neurological manifestations of Behçet's disease?

Neurological involvement occurs in 3–25% of patients with BD.

CNS involvement can affect the parenchyma (70–80% of cases), most commonly and typically the brainstem and/or pons (Figure 18.2). Patients can present with pyramidal signs, hemiparesis, sphincter disturbances, headaches and/or behavioural changes (which can mimic early-onset dementia). Benign intracranial hypertension, migraines and aseptic meningitis or meningoencephalitis are other possible CNS manifestations classified as parenchymal neuro-BD. Non-parenchymal BD involvement relates to vascular manifestations, mainly dural sinus thrombosis (strokes are rare in BD). Dural venous sinus thrombosis can present with intracranial hypertension, headaches and papilledema.

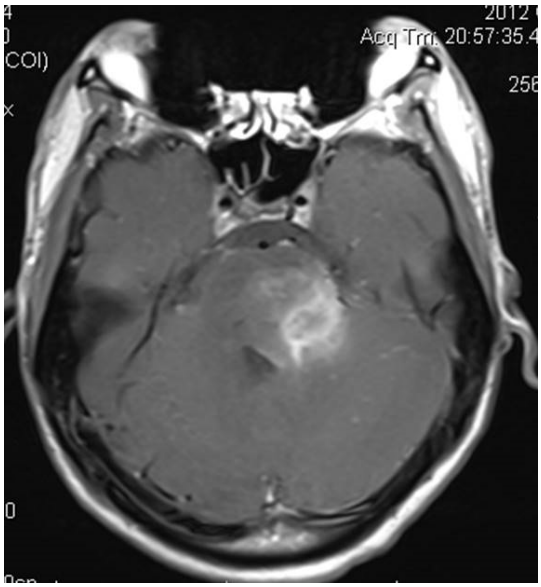


Figure 18.2. MRI of the brain (FLAIR sequence) in a young male patient with BD and CNS involvement, with enhancing brainstem/pons lesion.

Peripheral nervous system involvement is unusual in BD (rare cases of peripheral neuropathy, often debatable). However, diffuse pain syndrome or fibromyalgia is not uncommon, especially in Caucasian female patients, of uncertain mechanisms.

Patients with BD and severe parenchymal CNS involvement require aggressive treatment with high-dose GC (often with methylprednisolone IV pulses of 0.5-1 g/day for 1-3 days, followed by prednisone 1 mg/kg/day for 2-4 weeks with a subsequent taper) and cyclophosphamide (CYC), given as per the treatment for CNS vasculitis or severe ANCA-associated vasculitis (see Cases 6 and 15). Once remission is achieved, usually after a maximum of 6 months of CYC, the patient is usually switched to maintenance therapy, most often with azathioprine. For less severe cases, azathioprine can be used instead of CYC.

Anti-TNF-alpha antibodies can also be considered for patients with contraindications or with CYC-refractory disease.

For dural sinus thrombosis, GC are recommended; the need for associated anticoagulation to treat this type of inflammatory thrombosis remains a subject of debate.

Cyclosporine A should be avoided in patients with BD and a history of CNS involvement and should be stopped in patients who develop neurological features suggestive of parenchymal CNS involvement, as per the international consensus recommendations on Neuro-BD. On the other hand, a survey looking at the 20-year outcomes of 387 patients with BD found that disease activity and severity decreased over time, mainly in patients with muco-cutaneous, articular and/or ocular manifestations.

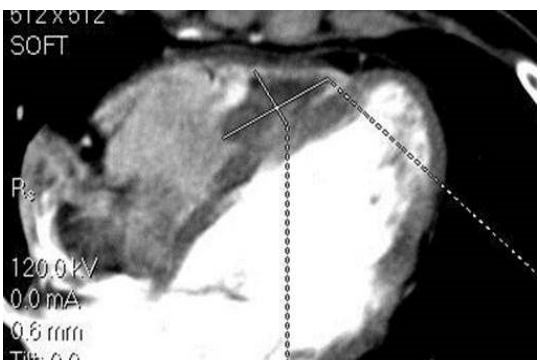


Figure 18.3. Cardiac MRI in a young male patient with BD. Right intraventricular thrombus (cross-marked).

5. What are the possible cardiovascular complications of Behçet's disease?

Cardiac manifestations are rare in BD, (observed 1–8% of cases), and include pericarditis (half the cases with cardiac manifestations), aseptic endocarditis, intracardiac (mostly right) intraventricular thrombus (Figure 18.3), coronary artery aneurysm and/or thrombosis (BD is a cause of myocardial infarction to consider in young patients; mortality is >15%), and cardiomyopathy (inflammatory, ischemic and/or fibrotic).

In contrast, vascular involvement is frequent and occurs in 7–40% of patients with BD, mostly males. BD can involve both the venous (superficial and/or deep venous thromboses, pulmonary embolism, Budd-Chiari syndrome when hepatic veins are affected) and arterial systems (aneurysms and/or occlusions of the abdominal aorta, carotid, femoral, popliteal, coronary, and/or pulmonary arteries – Figure 18.4).

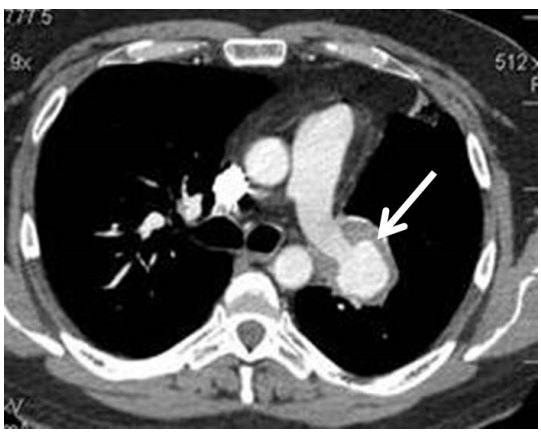


Figure 18.4. Chest CT in a young male patient with BD. Left pulmonary artery aneurysm, with associated arterial wall thickening (arrow).

Patients with cardiovascular involvement should be treated aggressively, like those with CNS disease, with high-dose GC and AZA or CYC for the most severe cases (including pulmonary artery aneurysms; with a switch to maintenance AZA 3 to 6 months after having achieved remission). Anti-TNF-alpha antibodies (infliximab, 5-10 mg/kg per infusion at days 1, 15 then every 4 to 8 weeks) can also be considered for patients with contraindications or with CYC–refractory disease.

For deep venous thromboses, GC are recommended; the need for associated anticoagulation to treat this type of inflammatory thrombotic event remains debated (their use

can be particularly challenging and hazardous in patients with associated aneurysms, especially on pulmonary arteries). Superficial vein thromboses can be treated with topical nonsteroidal ointments; the role of aspirin is a topic of debate and evidence to support its use in preventing recurrences is lacking.

BD is a chronic disease for which there presently is no cure. Global mortality is 5% at 7 years, with poor prognostic factors, including male sex, arterial involvement and frequent disease flares

Major organ involvement, in particular pulmonary artery aneurysms, Budd-Chiari syndrome, and CNS involvement also carry poorer prognostic values.

References

Kural- Seyahi E. et al. The long- term mortality and morbidity of Behcet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. Medicine 2003;82:60–76.

Hatemi G et al. EULAR recommendations for the management of Behçet disease. Ann Rheum Dis 2008;67(12):1656-62.

de Menthon M et al. HLA-B51/B5 and the risk of Behçet's disease: a systematic review and meta-analysis of case-control genetic association studies. Arthritis Rheumatol 2009;61(10):1287-96.

Saadoun D et al. Mortality in Behçet's disease. Arth Rheumatol 2010;62(9):2806–12.

Maldini C et al. Relationships of HLA-B51 or B5 genotype with Behcet's disease clinical characteristics: systematic review and meta-analyses of observational studies. Rheumatology (Oxford) 2012;51(5):887-900.

Sibley C et al. Behçet syndrome manifestations and activity in the United States versus Turkey -- a cross-sectional cohort comparison. J Rheumatol 2014;41:1379–84.

Kalra S et al. Diagnosis and management of Neuro-Behçet's disease: international consensus recommendations. J Neurol 2014;261(9):1662-76.

International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol 2014;28(3):338-47.

Davatchi F et al. Combination of pulse cyclophosphamide and azathioprine in ocular manifestations of Behcet's disease: longitudinal study of up to 10 years. Int J Rheum Dis 2014;17(4):444-52.

Nava F et al. Biologics, colchicine, corticosteroids, immunosuppressants and interferon-alpha for Neuro-Behçet's Syndrome. Cochrane Database Syst Rev 2014;(12):CD010729.

Hamuryudan V et al. Pulmonary artery involvement in Behçet's syndrome: Effects of anti-TNF treatment. Semin Arthritis Rheum 2015;45(3):369-73.

Davatchi F et al. Adult Behcet's disease in Iran: analysis of 6075 patients. Int J Rheum Dis 2016;19(1):95-103.

Koné-Paut I et al. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis 2016;75(6):958-64.

Seyahi E and Yazici H. To anticoagulate or not to anticoagulate vascular thrombosis in Behçet's syndrome: an enduring question. Clin Exp Rheumatol 2016;34(1 Suppl 95):S3-4.

Aeschlimann FA et al. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF-kB-mediated autoinflammatory disease. Ann Rheum Dis 2018;77:728–735.

Hatemi G et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis 2018;77(6):808-18.

Hatemi G. et al. Trial of apremilast for oral ulcers in Behcet's syndrome. N Engl J Med 2019;381(20):1918–28.

Alibaz-Oner F et al. Femoral vein wall thickness measurement: A new diagnostic tool for Behçet's disease Rheumatology 2021;60(1):288–29.

Case 19

Cogan syndrome, Susac syndrome, and relapsing polychondritis

Mrs. EC is a 37-year-old female accountant and mother of 3 healthy children, with no significant past medical history. Four months ago, she started to feel excessive and lingering fatigue. One month ago, she developed left ear tinnitus and gradual sensorineural hearing loss. She had no headaches, and no sign suggestive of chondritis or any other ear, nose or throat (ENT) symptoms. Two weeks ago, she woke up with a painful right eye and was diagnosed with interstitial keratitis. At that time, her laboratory tests showed a C-reactive protein of 177 mg/l (normal <10 mg/l), leukocyte count of 12,000/mm^3, (normal 4000-10,000/mm^3) with neutrophils 9800/mm^3 (normal 2000-7000/mm^3), hemoglobin 92 g/l (normal 110-160 g/l), creatinine normal at 85 µmol/l, and normal urine analysis. Infectious work-up (serologies for hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], syphilis) was negative and chest X-ray was normal. Brain MRI was unremarkable.

She received IV methylprednisolone (500 mg/day for 5 days) but did not recover any hearing from her left ear. Her keratitis resolved and now she only uses prednisolone acetate 1% eyedrops.

She is referred to rheumatology for suspicion of vasculitis. Her C-reactive protein is now at 32 mg/l.

1. *Which vasculitis could be considered and which test(s) will you order to investigate these hypotheses?*
2. *What are the most typical manifestations and complications of Cogan syndrome?*
3. *What are the differences between Cogan syndrome, Susac syndrome and relapsing polychondritis?*
4. *How would you treat this patient?*

Learning objectives

1. To describe the epidemiology, main clinical characteristics and possible complications of Cogan syndrome (CS).
2. To list the main differential diagnoses to consider in patients suspected of having CS (as CS is a diagnosis of exclusion).
3. To list treatment options for patients with CS according to the disease manifestations.

Answers

1. Which vasculitis could be considered and which test(s) will you order to investigate these hypotheses?

The main vasculitis that can cause sensorineural hearing loss and interstitial keratitis and has to be considered in this patient is Cogan syndrome (CS). The differential diagnosis of CS includes antineutrophil cytoplasm antibodies (ANCA)-associated vasculitides (mostly but not exclusively granulomatosis with polyangiitis [GPA], as it can frequently cause ENT symptoms and variable eye manifestations, mostly episcleritis, scleritis or uveitis). Urticarial vasculitis, rheumatoid arthritis-associated vasculitis and cryoglobulinemic vasculitis are more often associated with scleritis and/or, for the latter two, with peripheral ulcerative keratitis or retinal vasculitis. Behçet's disease can cause anterior, intermediate, posterior or pan-uveitis. Another systemic disease to consider in patients with interstitial keratitis is sarcoidosis.

Infections can also cause keratitis, including syphilis, tuberculosis, Lyme disease, chlamydial infection, herpes simplex (HSV), varicella zoster virus (VZV), measles, mumps, Epstein-Barr virus (EBV) or human T-lymphotropic virus 1 (HTLV1). Other causes include lymphomas and lens contact-related keratitis.

The association of ophthalmological and cochleo-vestibular manifestations should also raise the possibility of Vogt-Koyanagi-Harada disease (anterior and/or posterior uveitis, tinnitus, sensorineural hypoacousia, vitiligo, poliosis, and meningitis) and Susac syndrome (see Table 19.1).

2. What are the most typical manifestations and complications of Cogan syndrome?

CS is a rare vasculitis (<1/5000 inhabitants) of unknown pathogenesis that can affect the eyes, internal ears (sensorineural hearing loss) and, in around 10–20% of patients, large vessels. As all these manifestations rarely develop concomitantly (only in 5% of patients), the diagnosis can be challenging and delayed, sometimes for up to 2 years before all the suggestive clinical features are present. Most affected patients are Caucasians; there is a slight female predilection, and mean age at diagnosis is around 30-32 years old. Patients often report a flu-like viral illness prior to disease onset. The disease can be monophasic or, most often (in 75% of cases), with multiple recurrent flares.

The most frequent (80% of patients) and classical ocular manifestation is interstitial keratitis, unilateral initially then bilateral, sometimes transient and spontaneously resolving in the first weeks or months of the disease. After a few months, keratitis recurs, worsens and/or progresses, but still with a relative sparing of the central portion of the cornea, leading to the appearance of a ring of peripheral corneal scarring. Conjunctival hyperemia is also common; anterior non-granulomatous uveitis and/or retinal vasculitis have also been described. Glaucoma and cataract are common in patients with CS receiving long-term topical treatments.

Hypoacousia can be unilateral initially, and then becomes bilateral. Vestibulo-cochlear manifestations (imbalance, vertigo, nausea) are common. When isolated, before the occurrence of ocular manifestations, these auditori-vestibular symptoms can mimic Ménière's disease. The hearing loss can progress to deafness within 1 to 3 months in the most severe cases.

The frequency of medium- and/or large-vessel vasculitis in patients with CS varies between 10–20%. Aortitis and aortic insufficiency are the most typical and severe complications of CS. Large-vessel disease in CS can mimic Takayasu arteritis. The coronary arteries can also be involved.

Table 19.1. Main characteristics of Cogan syndrome, Susac syndrome and relapsing polychondritis

Most typical characteristics	Cogan syndrome	Susac syndrome	Relapsing polychondritis
Epidemiology	Prevalence <1 case/5000 inhabitants (~400 cases reported in series); mean age at diagnosis 30-32 years old; slight female predominance; mostly Caucasians	Very rare (~300 cases reported); mean age at onset 30 years old; clear female predominance (80%); pregnancy possibly associated with higher risk of disease flare	~3.5 new cases/million/year (USA); mean age at diagnosis 45-55 years; possible female predominance in some series; mainly Caucasians (and Asians)
Ophthalmological	Interstitial keratitis (80%); conjunctival hyperemia; less often non-granulomatous uveitis and/or retinal vasculitis	Branch retinal artery occlusion, most often peripheral and resulting in visual field deficits; blurry vision, photopsia, scintillation, diplopia; fluorescein angiography shows multifocal lesions (infarcts) and vessel leakage, and sometimes yellow retinal arterial wall plaques (Gass plaques)	>50% of patients, mainly scleritis, episcleritis and conjunctivitis; uveitis in 25%, corneal ulceration (10%); more rarely, retinal vasculitis, adnexal inflammation, ophthalmoplegia due to extraocular muscle vasculitis
Ear, Nose and Throat	Sensorineural hypoacousia; vestibulo-cochlear manifestations (imbalance, vertigo, nausea); can progress to deafness within months	Sensorineural hearing loss, most often sudden (can be more insidious) and due to occlusion of cochlear arterioles and cochlear apex infarcts; vertigo, roaring tinnitus	• Auricular chondritis (most patients), possibly leading to flabby pinna; auricular collapse causing hearing loss; sensorineural hearing loss and vestibulo-cochlear involvement rare, due to vestibular inflammation of vasculitis of internal auditory arteries • Nasal chondritis (25–50%) with pain, epistaxis, saddle-nose deformity • Laryngotracheal involvement with tracheal collapse or subglottic stenosis
Cardiovascular	Medium- and/or large-vessel vasculitis in 10–20% of patients; mostly aortitis and aortic insufficiency; coronary arteritis	None	Small-, medium- and/or large- vessel vasculitis in 25-50% of patients (leukocytoclastic vasculitis; thoracic or abdominal aorta aneurysmal dilation; aortic or mitral valve regurgitation; coronary arteritis)
Other manifestations	Headaches (40%), arthralgias (40%), fever (25%), myalgias, diarrhea and abdominal pain	• Encephalopathy: migraine and headaches (50%), mood disorders (manic attack, delirium), vigilance disturbance, seizure; sometimes cerebellar features, pyramidal syndrome, hemiparesia and/or cranial nerve involvement. Cerebrospinal fluid (CSF): increased protein level up to 2 g/l, mild lymphocytic pleocytosis (usually <20 cells/µl). Brain MRI: T2 and T2-FLAIR white matter hypersignals, suggestive "snow balls" central in corpus callosum; possible leptomeningeal contrast enhancement; normal brain vessel imaging • Myalgias, non-specific skin rashes (livedo or erythematous)	• Episodic, asymmetrical and non-erosive arthralgia-arthritis (35-75%), mainly metacarpophalangeal, proximal interphalangeal, wrists and knees • Costochondritis, possible costo-chondral dislocation, impairing chest wall motion • Headaches, cranial neuropathies (including optic neuritis), aseptic lymphocytic meningitis • Renal involvement (<10%), mostly with mesangial proliferation (different glomerulonephritis types reported) • Skin lesions (35%) such as purpura, livedo, oral ulcers
Other comments	• No specific diagnostic test • Possible auto-antibodies against inner ear antigens; imaging of the brain normal (or calcification of the labyrinth or cochlea)	• Can be monophasic (over a 2-year period), polycyclic (relapses beyond >2 years) or chronic and continuous • No specific diagnostic test, but the triad of hearing loss, branch retinal artery occlusion and "snow balls" in the corpus callosum is pathognomonic (all 3 develop simultaneously in only 15% of patients; delay before completion of the triad can take up to 3 years) • Biopsy of brain lesion (not required) shows focal microangiopathy with arteriole wall proliferation, lymphocyte infiltrate and basal lamina thickening, and gliosis • Anti-endothelial cell antibodies found in 20–40% patients	• No specific diagnostic tests. Biopsy of affected ENT tissue can show non-specific granulation in the perichondral areas with loss of cartilage matrix proteoglycans and mixed cellular infiltrate • Associated with HLA DR4 allele; possible antibodies against cartilage tissue elements like collagen types II, IX and X or matrilin-1 • Can overlap and coexist with granulomatosis with polyangiitis, Behçet's disease

Finally, patients with CS can have non-specific systemic symptoms, such as headaches, arthralgias (40% of patients), fever (up to 25%), myalgias, diarrhea or abdominal pain.

Importantly, CS has been reported in association with, or as a rare manifestation of, other systemic conditions, including polyarteritis nodosa, GPA, rheumatoid arthritis, Crohn's disease and relapsing polychondritis.

There is no specific diagnostic test for CS. Screening tests for antinuclear antibodies, ANCA or rheumatoid factor are usually negative. There might be some specific auto-antibodies, possibly against inner ear and vestibulo-cochlear antigens, but none have yet been identified. Anti-heat shock protein (HSP)-70 antibodies are present in 50–90% of patients. Magnetic resonance imaging (MRI) or positron emission tomography (PET)-scan of the brain are normal, or may show some internal ear damage (calcification of the labyrinth or cochlea).

3. What are the differences between Cogan syndrome, Susac syndrome and relapsing polychondritis?

The main manifestations and differences between CS, Susac syndrome (a retino-cochleo-cerebral vasculopathy) and relapsing polychondritis are listed in Table 19.1. All three diseases can cause ocular and auditory manifestations and may require systemic treatment with glucocorticoids (GC) and (grossly the same) immunosuppressants. This patient had no history of chondritis, and relapsing polychondritis causes episcleritis or scleritis more commonly than keratitis.

4. How would you treat this patient?

Local treatments for the keratitis or other eye manifestations are mandatory and must be left to the ophthalmologist (usually topical GC and cycloplegic eye drops).

Systemic treatments are relatively effective for eye manifestations, but much less for the sensorineural hearing loss. In patients with acute, sudden hearing loss, pulses of methylprednisolone are usually prescribed, followed by oral prednisone, rapidly tapered after 2 to 4 weeks if hearing improves. Cochlear implants are often needed. For GC-dependent cases, patients with more severe eye disease and/or when large vessels are involved, a combination of systemic GC and other immunosuppressants, including cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine A is recommended. Biologics such as infliximab, rituximab and tocilizumab have also been used in some patients with refractory and/or relapsing CS, and might be more effective for hearing loss than the former conventional immunosuppressants. In most series, biologics have been included in the treatment regimen for CS as third- or fourth-line options. Of all biologics, infliximab is most often used to treat CS, as it led in some studies to an improvement in hearing or to remission (as can be defined) in >86% of cases. Infliximab also enabled GC tapering. As such, some experts recommend using infliximab as the first-line option, combined with GC, in patients with CS. Vascular surgery can be required (preferentially when the disease is quiescent clinically and biologically) in patients with severe aortic insufficiency.

For the patient in this case, the work-up will help direct the most appropriate treatment. If there is no large-vessel disease and if the eye inflammation has resolved under topical treatments, a combination of GC and azathioprine, methotrexate or mycophenolate mofetil can be considered, although the hearing loss is unlikely to recover. In case of refractory or severe eye disease and/or large-vessel involvement, the mandatory treatment would consist of GC and a potent immunosuppressant, possibly cyclophosphamide or infliximab. Consensus guidelines and randomized controlled studies are lacking to further determine the best first-line treatment.

References

Gluth MB et al. Cogan syndrome: a retrospective review of 60 patients throughout a half century. Mayo Clin Proc 2006;81(4):483-8.

Kessel A et al. Cogan syndrome--pathogenesis, clinical variants and treatment approaches. Autoimmun Rev 2014;13(4-5):351-4.

Tayer-Shifman OE et al. Cogan's syndrome--clinical guidelines and novel therapeutic approaches. Clin Rev Allergy Immunol 2014;47(1):65-72.

Espinoza GM and Prost A. Cogan's syndrome and other ocular vasculitides. Curr Rheumatol Rep 2015;17(4):24.

Durtette C et al. Cogan syndrome: Characteristics, outcome and treatment in a French nationwide retrospective study and literature review. Autoimmun Rev 2017;16(12):1219-23.

Padoan R et al. Cogan's syndrome: new therapeutic approaches in the biological era. Expert opinion on biological therapy. 2019;19(8):781–8.

de Montmollin N et al. Tracheobronchial involvement of relapsing polychondritis. Autoimmun Rev 2019;18(9):102353.

Ferrada M et al. Defining Clinical Subgroups in Relapsing Polychondritis: A Prospective Observational Cohort Study. Arthritis Rheumatol 2020;72(8):1396-402.

Marrodan M et al. Susac syndrome: challenges in the diagnosis and treatment. Brain 2022;145(3):858-71.

David C et al. Susac syndrome: A scoping review. Autoimmun Rev 2022;21(6):10309.

Case 20
IgA vasculitis

A 26-year-old man of Asian descent presents to the emergency department with a 2-week history of postprandial abdominal pain and bilateral ankle arthralgias. One week ago, he developed purpura on his buttocks and both lower extremities as well as two bullous lesions adjacent to his medial malleoli (Figure 20.1). Some of the purpuric lesions have begun to ulcerate.

A complete blood count, electrolytes, serum creatinine level, and liver function tests are normal. Urinalysis shows 1+ blood and 2+ protein.

Computerized tomography (CT) of his abdomen shows edematous changes consistent with diffuse thickening of the small bowel (Figure 20.2). A skin biopsy of one of the purpuric lesions shows a perivascular lymphocytic infiltrate consistent with a leukocytoclastic vasculitis on hematoxylin and eosin (H&E) staining. Immmunofluorescence study shows linear deposits of immunoglobulin A (IgA).



Figure 20.1. Purpura and ecchymotic bullous lesions.

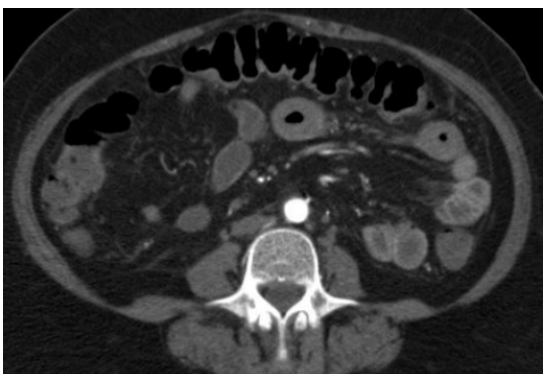


Figure 20.2. CT of the abdomen.

1. *Describe the epidemiology and pathophysiology of IgA vasculitis.*
2. *Describe the main clinical manifestations of IgA vasculitis.*
3. *What further investigations would you order?*
4. *How would you treat this patient?*

Learning objectives

1. To describe the epidemiology and pathophysiology of IgA vasculitis (IgAV).
2. To describe the main clinical manifestations of IgAV.
3. To describe the work-up of IgAV.
4. To identify different treatment options for IgAV.
5. To identify differences between the disease course in children and adults.

Answers

1. Describe the epidemiology and pathophysiology of IgA vasculitis.

IgA vasculitis (IgAV; formerly Henoch-Schönlein purpura) is an immune-complex small-vessel vasculitis. It is the most common form of vasculitis to affect children, with an incidence of up to 26 per 100,000 children under 18 years old. The disease is rarer in adults, occurring only in up to 2 per 100,000. Men are slightly more likely to develop the disease than women, and black children have a lower incidence than Caucasian or Asian children. IgAV appears to have a seasonal predisposition. In children, it is more common in fall and winter. In adults, it is more common in winter and summer.

The IgA1 subtype of IgA is implicated in the development of IgAV. IgA is an important factor in mucosal immunity, and many cases or flares of IgA vasculitis follow a respiratory infection. Patients with IgAV appear to have overproduction, impaired clearance, and aberrant glycosylation of IgA1, whose level is commonly elevated in their blood. Infections and malignancy have been theorized to trigger the disease in genetically prone individuals, such as those with HLA-DRB1. IgAV has also been reported in association with other conditions (e.g. in up to 10% of patients with familial Mediterranean fever) and with malignancies in adults, as well as in association with some medications such as anti-TNF-alpha (in patients with inflammatory bowel disease or spondylarthropathies).

2. Describe the main clinical manifestations of IgA vasculitis.

The classic triad of IgAV symptoms consists of purpura, arthralgias, and abdominal pain. Renal involvement is also common.

Palpable purpura is the most common manifestation, occurring predominantly in the lower extremities and the buttocks. The purpuric lesions increase in number toward the feet and may coalesce into plaques. In some cases, they may even become hemorrhagic and bullous or ulcerated. Purpura often worsens while standing.

Up to 80% of children with IgA vasculitis have some form of articular complaint. Joint involvement is less frequent in adults (61%). Arthralgias in the lower extremities often precede the purpuric rash by a few days to a week. Patients often complain of joint swelling, due to true synovitis in the ankles and knees or periarticular soft tissue edema.

The gastrointestinal (GI) manifestations of IgAV can be dramatic and severe. They can be the first manifestation of IgAV and precede

the development of purpura by up to 14 days. Patients may complain of abdominal pain or rectal bleeding and may even present with a surgical acute abdomen. Children may develop small bowel intussusception requiring surgery.

Renal involvement is common in IgAV. Some patients may present with only renal involvement (renal-limited IgAV, or IgA glomerulonephritis). In patients with other manifestations, renal involvement may appear quite late, i.e. months or years later. Up to 50% of patients with renal involvement may develop chronic renal abnormalities, such as persistent proteinuria and/or microscopic hematuria, although only about 1–2% of children (but up to 5-10% of adults) progress to end-stage renal disease. Women who had IgAV as children (or later) may go on to develop gestational hypertension and proteinuria, even if their renal disease was mild. Whether IgAV and IgA nephropathy represent different extremities of a continuous spectrum of the same disease (is probable but) remains debated.

Other rarer organ involvement has been reported, including episcleritis, alveolar hemorrhage, orchitis, and myocarditis.

3. What further investigations would you order?

The work-up for IgAV involves a thorough exploration of alternative diagnoses and good baseline assessment of every organ or system possibly affected.

The initial work-up must include a complete blood count, electrolytes, serum creatinine and urinalysis.

Abdominal imaging is often non-specific but may show thickening of the small bowel and the terminal ileum in patients with GI involvement. Rarely, the large bowel can be involved. Endoscopy may demonstrate mucosal redness, petechiae, erosions, and ulcers anywhere within the GI tract.

Skin biopsies of recent purpuric lesions should be sent for conventional microscopic pathology but also for immunofluorescence (IF) study. Non-specific leucocytoclastic vasculitis can be observed on microscopy; linear and/or granular IgA deposits in vessel walls in IF carry a better diagnostic value. The absence of this IgA staining does not rule out the diagnosis of IgAV.

Renal biopsy may be helpful, although the diagnosis can often be made without it. Similar to skin biopsies, IF study can demonstrate IgA deposition in the mesangium. The renal biopsy also allows for a staging of the disease using the Oxford classification of IgA nephropathy, which takes into account mesangial hypercellularity (M), segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T) lesions, and crescent (C). This MEST-C score can help predict clinical outcome.

Other small-vessel vasculitides can cause cutaneous purpura and renal disease, and so testing for antinuclear antibodies (ANA) and antineutrophil cytoplasm antibodies (ANCA) should also be ordered. IgAV can also be triggered by an underlying infection, including parvovirus B19 and human immunodeficiency virus (HIV). Malignancies are risk factors for IgAV in adults, including myeloproliferative and lymphoproliferative disorders, or small-cell lung cancer. Age-appropriate cancer screening is warranted. An IgA paraproteinemia can be observed in a few adults with IgAV, however, the diagnostic and prognostic values are unclear (monoclonal gammopathy of unknown significance).

4. How would you treat this patient?

Disease onset is usually acute and rapid, followed by a disease course that is often self-limited to less than 3 months. As a general rule, the older the patient, the longer the course of the disease. While children may have self-limited disease courses of less than 1 month, in some adults the

disease may take years to resolve. Recurrences occur in one-third of children within the first 4 months. Subsequently, more delayed relapses are rare in children but occur in about 20% of adults.

In addition, patients with recurrent IgAV from countries where Mediterranean fever is prevalent should be screened for MEFV gene.

There are only a few guidelines available for the treatment of IgAV, mostly developed by pediatric groups, including the European SHARE and the Egyptian consensus-recommendations. For mild cases without multiple organ involvement, symptomatic treatment may be sufficient. In patients with more severe or relapsing disease, systemic GC and immunosuppression may be required.

Although nonsteroidal anti-inflammatory drugs are often used to treat the arthralgias of IgAV, it seems prudent to restrict their use when possible given that they are contraindicated in patients with renal disease and may precipitate GI bleeding. Angiotensin-converting enzyme inhibitors are often used for mild renal disease, with proteinuria.

A number of treatments can be effective at treating the cutaneous component of IgAV disease. Colchicine (0.6 to 2 mg per day) and dapsone (after excluding G6PD deficiency; 50 to 150 mg/day) have both been used, although the evidence for their use is limited to case reports. Montelukast has also been used to treat children. It may alleviate purpura, abdominal pain, proteinuria, and hematuria. No data exist for adults.

High-dose GC pulses with or without another immunosuppressant may be given to patients with severe disease manifestations. These treatments should be considered in patients with relapsing disease, evidence of severe GI disease (including perforations), pulmonary involvement, or poor prognostic factors for renal progression. The latter category includes proteinuria in excess of 1 g/day, frank nephrotic syndrome, or crescentic glomerulonephritis involving a majority of the glomeruli.

GC appear to be more effective at treating arthralgias, abdominal pain, and renal manifestations than they are at treating skin disease. In a prospective study of 86 patients with IgA nephropathy as the sole clinical manifestation, patients randomized to a 3-day course of 1 g of pulse methylprednisolone followed by additional pulses at 2 and 4 months, as well as prednisone 0.5 mg/kg every other day for 6 months, 10-year survival was significantly better in the treatment group than in a control group treated with supportive therapy alone. Azathioprine, mycophenolate mofetil, cyclosporine A, and cyclophosphamide have also been used, but no compelling data exist to direct a particular choice of drug or dose, or even the need for maintenance therapy. Although a number of small trials have compared these agents to treatment with GC alone, none showed clear evidence of superiority for any approach. In trials in which patients with high-risk, severe disease features were randomized to either GC therapy alone or with a combination of cyclophosphamide for induction and azathioprine for maintenance, there was no difference in outcomes (decline in glomerular filtration rate) at 3 years. There are also anecdotes and case reports supporting the use of intravenous immunoglobulin (IVIg) at a dose of 2 g/kg monthly for 3 months followed by 0.35 mg/kg every 15 days given intramuscularly.

Rituximab has been used in several case series or reports to treat both visceral and cutaneous manifestations of the IgAV disease. Two regimens that have been described include 375 mg/m^2 weekly for 4 weeks, or 1 g IV given as two doses, 2 weeks apart, with reinduction as needed. A small randomized controlled trial compared rituximab vs. standard therapy in 34 adult patients with biopsy-proven IgA nephropathy and proteinuria >1 g/d, also given angiotensin-converting enzyme inhibitors or angiotensin

receptor blockers. Rituximab did not significantly improve renal function or proteinuria and failed to reduce serum levels of galactose-deficient IgA1 and antigalactose-deficient IgA1 antibodies. More studies may be needed. Similarly, plasma exchange has been reported to work as an adjunct to GC in (only) small, uncontrolled case series and case reports.

Patients who develop end-stage renal disease may ultimately require transplant. In patients requiring renal transplant, the prognosis is guarded. At 5 years, renal recurrence is reported in up to 25% and graft loss reported in 11 %.

References

Foster BJ et al. Effective therapy for severe Henoch-Schonlein purpura nephritis with prednisone and azathioprine: A clinical and histopathologic study. J Pediatr 2000;136:370–375.

Pillebout E et al. Henoch-Schönlein purpura in adults: outcome and prognostic factors. J Am Soc Nephrol 2002;13:1271–8.

Iqbal H and Evans A. Dapsone therapy for Henoch-Schönlein purpura: a case series. Arch Dis Child 2005;90:985–86.

Pillebout E et al. CESAR study group. Addition of cyclophosphamide to steroids provides no benefit compared with steroids alone in treating adult patients with severe Henoch Schönlein Purpura. Kidney Int 2010;78:495–502.

Jauhola O et al. Cyclosporine A vs. methylprednisolone for Henoch–Schönlein nephritis: a randomized trial. Pediatr Nephrol 2011;26:2159–66.

Ren P et al. The combination of mycophenolate mofetil with corticosteroids induces remission of Henoch-Schönlein purpura nephritis. Am J Nephrol 2012;36:271–7.

Augusto J et al. Addition of Plasma Exchange to Glucocorticosteroids for the Treatment of Severe Henoch-Schönlein Purpura in Adults: A Case Series. Am J Kid Dis 2012;59:663–9.

Audemard-Verger A et al. IgA vasculitis (Henoch–Schönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev 2015;14:579–85.

Rauen T et al. Intensive Supportive Care plus Immunosuppression in IgA Nephropathy. N Engl J Med 2015;373:2225-36.

Fenoglio R et al. Rituximab therapy for IgA-vasculitis with nephritis: a case series and review of the literature. Immunol Res 2017;65(1):186-92.

Trimarchi H et al. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. Kidney Int 2017;91(5):1014-21.

Audemard-Verger A et al. Characteristics and Management of IgA Vasculitis (Henoch-Schönlein) in Adults: Data From 260 Patients Included in a French Multicenter Retrospective Survey. Arthritis Rheumatol 2017;69(9):1862-70.

Lafayette RA et al. A Randomized, Controlled Trial of Rituximab in IgA Nephropathy with Proteinuria and Renal Dysfunction. J Am Soc Nephrol 2017;28(4):1306-13.

Maritati F et al. Brief Report: Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schönlein). Arthritis Rheumatol 2018;70(1):109-14.

Ozen S et al. European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative. Rheumatology (Oxford) 2019 Sep 1;58(9):1607-16.

Villatoro-Villar M et al. Clinical Characteristics of Biopsy-Proven IgA Vasculitis in Children and Adults: A Retrospective Cohort Study. Mayo Clin Proc. 2019 Sep;94(9):1769-80.

Abu-Zaid et al. Consensus evidence-based recommendations for treat-to-target management of immunoglobulin A vasculitis. Ther Adv Musculoskelet Dis 2021;13:1759720X211059610.

Pillebout, E. IgA Vasculitis and IgA Nephropathy: Same Disease? J. Clin. Med 2021;10:2310.

Case 21
Retinal vasculitis

Mr. J is a 47 year-old man with no specific past medical history, other than mild hypertension, on amlodipine 5 mg/day, and seasonal, allergic rhinitis. He started to notice worsening floaters in his bilateral visual fields for the past 6 months, and then some decreased, blurry vision, mostly in his left eye. He denies any headache, jaw, muscle or joint pain, or any other systemic manifestations. He went to see his eye specialist, and after several investigations, including a fluorescein angiography (Figure 20.1), was told he had retinal vasculitis or possible Birdshot chorioretinopathy (BCR). He was started on anti-inflammatory eye drops, referred to you for further investigations, and possible systemic immunosuppressive treatment.

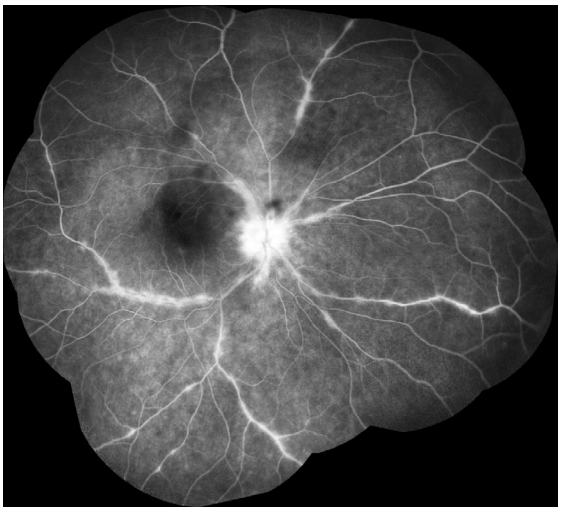


Figure 20.1. Fluorescein angiography of the retina showing arterial beading appearance and leakage of the contrast dye, and several patchy choroidal ovoid lesions.

1. *What is retinal vasculitis?*
2. *What are the causes of retinal vasculitis and thereby, the investigations to order usually in such a patient?*
3. *Which systemic treatment can be considered in this patient, if this is indeed an isolated, primary retinal vasculitis or BCR?*

Learning objectives

1. To understand the clinical concept and definition of retinal vasculitis.
2. To list the causes of retinal vasculitis.
3. To understand the place of systemic treatments for isolated retinal vasculitis.

Answers

1. What is retinal vasculitis?

Retinal vasculitis is defined as an inflammation of retinal arterioles, venules and/or capillaries. As biopsy of the retina is not a routine investigation, retinal vasculitis is more of a clinical diagnosis, based on fundus examination and retinal imaging with fluorescein angiography (and/or other imaging modalities, such as optical coherence tomography angiography [OCTA] and indocyanine green angiography [ICGA]) showing perivascular infiltrate/leakage/permeability.

Hence, whereas ophthalmologists can be very assertive in their diagnosis of retinal vasculitis, several rheumatologists and/or internal medicine specialists may challenge such diagnoses in the absence of proven, histological evidence of vessel wall inflammatory infiltrates. Some conditions classically listed as causes of retinal vasculitis are indeed due to vasculopathy, rather than true vessel wall inflammation, as seen in primary systemic vasculitis.

On retinal examination and imaging, sheathing, perivascular cuffing and exudation, vascular occlusion leading to capillary non-perfusion, pre-retinal hemorrhages, and/or neovascularization can be observed. If the disease continues to progress, it can lead to tractional retinal detachments, vitreous hemorrhage, and/or glaucoma due to neovascularization of the iris/retina. Eventually, patients can become blind.

Posterior uveitis (or choroiditis) is the inflammation of the choroid, the back part of the uvea, and may also affect the retina. Retinal vasculitis is commonly associated with (posterior, or pan-) uveitis.

There is no accepted classification of retinal vasculitis, but it is generally categorized based on etiology (infectious versus noninfectious), vascular caliber (large, medium, or small-sized vessels) and type (arteriole- or venule-predominant, or both), location of the lesions (close to the macula or peripheral), and whether it is occlusive (known as ORV) or non-occlusive.

2. What are the causes of retinal vasculitis and thereby, the investigations to order usually in such a patient?

Retinal vasculitis can be associated with many systemic, infectious and non-infectious, diseases, and several, "purely" ophthalmic diseases (Table 21.1). In the largest published cohorts of retinal vasculitis, primary, idiopathic retinal vasculitis represented only around 5-20% of the cases. Hence, a thorough search for a cause is mandatory in all patients, even in the absence of obvious extraocular clinical manifestations.

Investigations are mostly aimed at ruling out infections, and looking for underlying systemic conditions. They are adjusted based on the patient demographics, medical and socio-professional history, and clinical findings.

General and immunological laboratory investigations should include complete blood count, serum creatinine, lytes, calcium and albumin levels, CRP (and/or ESR), urinalysis, ALT, complement C3 and C4, antinuclear antibody, and ANCA screening test. Other immunological tests can include angiotensin converting enzyme (ACE), anti-phospholipid antibody, extractable nuclear antigens (ENA), rheumatoid factor (RF) and anti-CCP, HLA-B51, and HLA-A29.

Infectious laboratory tests should include quantiFERON-TB Gold, if available, and/or tuberculin skin test otherwise, HSV, VZV and CMV IgG/IgM, HBV, HCV and HIV serologies, VDRL-FTA Abs, and as, elicited by history, toxoplasmosis, bartonella, HTLV-1, Lyme, and/or West Nile virus IgG/IgM serologies.

Table 21.1. List of conditions associated with, or causing, retinal vasculitis.

Infectious diseases		
Bacterial • Syphilis • Tuberculosis • Cat scratch disease *(Bartonella henselae)* • Rickettsial diseases (including Mediterranean spotted fever, rocky Mountain spotted fever) • Lyme/Borreliosis *(Borellia burgdorferi)* • Brucellosis • Endophthalmitis • Leptospirosis • Whipple's disease	**Viral** • Acute retinal necrosis due to HSV or VZV • Cytomegalovirus retinitis • Epstein–Barr virus • Human immunodeficiency virus • Human T cell lymphoma virus type 1 (HTLV-1) • Rift Valley fever (Bunyaviridae) • West Nile virus • Chikungunya virus • Dengue fever • Hepatitis • COVID-19 (rare cases, mostly with retinal vein occlusions)	**Parasitic/fungal** • Toxoplasmosis • Histoplasmosis • Coccidioidomycosis • Candidiasis • Toxocariasis • Amoebiasis
Non-infectious		

Systemic and/or CNS immune or inflammatory diseases
• Systemic/Primary Vasculitis +++
  • *Behçet's disease +++*
  • *ANCA-associated vasculitis (EGPA>GPA>MPA)*
  • *Takayasu arteritis*
  • *Polyarteritis nodosa*
  • *CNS vasculitis*
• Sarcoidosis +++
• Systemic lupus erythematosus +
• Antiphospholipid syndrome
• Crohn's disease
• Dermatomyositis
• Sjögren syndrome
• Polymyositis
• Relapsing polychondritis
• Rheumatoid arthritis
• HLA-B27-associated uveitis
• Systemic sclerosis
• Multiple sclerosis
• Susac syndrome
• RVCL (retinal vasculopathy with cerebral leukodystrophy, due to mutation in TREX1 gene)
• A20 haploinsufficiency (Behçet's-like disease, due to mutations in TNFAIP3)
• Vogt-Koyanagi-Harada disease
	Isolated ocular diseases
	• Birdshot chorioretinopathy
	• Acute multifocal hemorrhagic retinal vasculitis
	• Eales disease (hypersensitivity to mycobacterial antigen), Frosted branch angiitis
	• Idiopathic recurrent branch retinal arterial occlusion (IRVAN)
	• Intermediate uveitis
	• Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV; due to mutations in Calpain 5 [CAPN5] gene)
		Other
		• Drug-induced vasculitis (methamphetamine, trimethoprim-sulfamethoxazole, checkpoint inhibitors, hepatitis C treatments, interferon)
		• Intravitreal medications (vancomycin, anti-VEGF-A brolucizumab, aminoglycosides, mitomycin-C, cefuroxime, rituximab)
		• Vaccination-associated vasculitis
		• Tattoo-related vasculitis

Masquerade/Mimickers		
• Leukemia • Ocular lymphoma (B- or T-cell) • Angiotropic lymphoma (often with occlusive-like features) • Paraneoplastic syndromes • Amyloidosis		

ANCA: antineutrophil cytoplasm(ic) antibodies; CNS: central nervous system; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; HSV: herpes simplex virus; MPA: microscopic polyangiitis; TNFAIP3: tumour necrosis factor alpha-induced protein 3; VZV: varicella-zoster virus.

Imaging should include a chest X-ray and/or CT, and often some CNS imaging (ideally a brain-orbit MRI).

Aqueous fluid analysis with PCR (for HSV, VZV, CMV, toxoplasma) and cytology is often performed by eye specialists. Chorioretinal biopsies are rarely performed (mostly to diagnose lymphoma). New metagenomic deep sequencing testing is another promising technique to look for infections, especially in small amounts of aqueous fluid.

Other investigations may be needed, after the first rounds of tests, such as a CSF analysis (lumbar puncture).

3. Which systemic treatment can be considered in this patient, if this is indeed an isolated, primary retinal vasculitis or BCR?

BCR is a chronic, bilateral, autoimmune posterior uveitis with a strong association with HLA-A29. The disease is often progressive and can lead to irreversible visual loss. BCR is most prevalent in Caucasian populations, but rare, with estimated prevalence within 0.2–1.7 cases/100,000 population. BCR is mostly diagnosed in middle-aged individuals and with a slight female preponderance. Criteria for the diagnosis of BCR include (1) bilateral disease, (2) ≥3 characteristic BCR lesions inferior or nasal to the disk in one eye, (3) low-grade anterior chamber inflammation (≤1+ cells in the anterior chamber on the SUN score), and (4) low-grade vitreous inflammation (≤2+ on the NEI/SUN vitreous haze score). Additional supportive findings include the presence of HLA-A29, retinal vasculitis, and cystoid macular edema. In up to 20 % of patients, BCR is self-limiting, with eventual complete remission. Other patients require more intensive treatments with local and systemic glucocorticoids, at least initially, and steroid-sparing immunosuppressive agents.

Options for steroid-sparing agents include methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), cyclosporine A or tacrolimus, intravenous immunoglobulin (IVIg; with controverted results in BCR) and biologics, especially anti-TNF agents, such as infliximab or adalimumab, for refractory cases. Some case series suggested a possible place of tocilizumab (anti-IL6-R) or daclizumab (anti-IL2-R). Data on secukinumab (anti-IL17A) are also encouraging, but very preliminary. Data on rituximab are sparse. Cyclophosphamide (CYC) can also be tried in refractory cases of idiopathic retinal vasculitis also, but rarely in BCR.

Local treatments are needed in parallel, and managed by eye/retina specialists, and may include GC injections, implants, and photocoagulation, anti-VEGF injections and/or surgery (pars plana vitrectomy) in case of neovascularization. Cataract and glaucoma are frequent complications of the disease itself and the treatments. Close collaboration and communication between the eye specialist and the rheumatologist/internal medicine physician are mandatory to help adjust treatments, based on disease severity, response to the initial treatments, and tolerance to medications.

References

Pagnoux C, Thorne C, Mandelcorn ED, Carette S. CNS involvement in acute posterior multifocal placoid pigment epitheliopathy. Can J Neurol Sci 2011;38(3):526-8.

Rothschild PR et al. Ophthalmologic manifestations of systemic necrotizing vasculitides at diagnosis: a retrospective study of 1286 patients and review of the literature. Semin Arthritis Rheum 2013;42(5):507-14.

Evangelos Minos et al. Birdshot chorioretinopathy: current knowledge and new concepts in pathophysiology, diagnosis, monitoring and treatment. Orphanet J Rare Dis 2016;11(1):61.

Hsu et al. Update on Retinal Drug Toxicities. Curr Ophthalmol Rep 2021;9(4):168-77.

Ghazala A Datoo O'Keefe, Narsing Rao. Retinal vasculitis: A framework and proposal for a classification system. Surv Ophthalmol 2021;66(1):54-67.

Agarwal A et al. A Comprehensive Update on Retinal Vasculitis: Etiologies, Manifestations and Treatments. J Clin Med 2022;11(9):2525.

Arepalli SR, Thomas AS. Occlusive retinal vasculitis: novel insights into causes, pathogenesis and treatment. Curr Opin Ophthalmol. 2022;33(3):147-56.

Silpa-Archa S, Sapthanakorn W, Foster CS. Isolated Retinal Vasculitis: Prognostic factors and expanding the role of immunosuppressive treatment in retinal vasculitis associated with positive QuantiFERON®-TB Gold Test. Retina 2022 Aug;42(10):1897-1908.

Case 22

Vasculitis and risk of late cancers and cardiovascular disease

Mrs. H was diagnosed in 1995, at the age of 58 years, with a severe pneumo-renal myeloperoxidase (MPO)-antineutrophil cytoplasm antibodies (ANCA)-positive microscopic polyangiitis. She received 12 months of daily, oral cyclophosphamide (cumulative dose of 54 g), then 3 years of weekly, subcutaneous methotrexate (25 mg/week). She also received glucocorticoids between 1995 and 2002 and underwent hemodialysis for 4 months in 1995. She recovered well, with a recent glomerular filtration rate of 50 ml/min (normal >60 ml/min). Prior to the vasculitis, she had no significant medical history, but she has been a smoker since her 20s (cumulative, 30 pack-years). She does not drink alcohol. She has two healthy daughters, and one grandson.

She was referred for possible enrollment in a study, as her second daughter read on the Internet that several cohort and genetic studies on vasculitis are actively recruiting patients in Canada.

1. *What are the risks of late cancer in patients with a history of ANCA-associated vasculitis?*
2. *Is there an increased risk of cardiovascular disease in patients with a history of ANCA-associated vasculitis?*
3. *Is there a higher risk for their daughters to suffer microscopic polyangiitis?*
4. *Is there any study in which this patient could participate in Canada?*

Learning objectives

1. To discuss the risk of late cancers in patients with a history of vasculitis.
2. To discuss the risk of cardiovascular disease in patients with a history of vasculitis.
3. To discuss the risk of vasculitis in first-degree relatives of patients with ANCA-associated vasculitis.
4. To identify CanVasc as a possible source of information on ongoing studies in vasculitis in Canada and understand the place and role of CanVasc vasculitis reference centres.

Answers

1. What are the risks of late cancer in patients with a history of ANCA-associated vasculitis?

Several studies have demonstrated a mild increased risk of cancer (1.2–2.8-fold higher) in patients with a history of ANCA-associated vasculitis who had been treated with conventional (non-rituximab-based) immunosuppressive therapy, compared to the general population. The increased risk was lower in the most recent series and has been primarily driven by non-melanoma skin cancer (4-10 fold). The risk of bladder cancer, associated with high cumulative exposure to cyclophosphamide (CYC), has decreased with recommendations to limit the use of CYC and switch to less toxic immunosuppressants after remission is achieved. The risk of bladder cancer was found to be increased by up to 2.4–5-fold in studies on granulomatosis with polyangiitis (GPA) or other necrotizing systemic vasculitides, in patients who had received CYC for ≥7 months and most often a cumulative CYC dose >35 g (average 50 g [range, 8 g to >210 g]). The use of mesna in patients receiving IV pulse CYC can limit the incidence of hemorrhagic cystitis but has no proven impact on the risk of urothelial cancer. Higher incidence of myeloid leukemia has been seen, mostly among patients exposed to cumulative CYC doses >36 g. The increased incidence of lymphoma found in a few earlier studies has not been replicated in subsequent studies.

The changing treatment algorithms with use of a lower dose and shorter exposure to cyclophosphamide and increasing use of rituximab will likely demonstrate decreased incidence of malignancy in the future.

2. Is there an increased risk of cardiovascular disease in patients with a history of ANCA-associated vasculitis?

Patients with a history of ANCA-associated vasculitis have been shown in several cohorts to have an increased risk for cardiovascular disease. A European Vasculitis Society (EUVAS) study showed that at 5 years post diagnosis, 14% of patients with ANCA-associated vasculitis had a cardiovascular event, especially after 1 year post diagnosis and in older patients, with diastolic hypertension (42% of patients) and proteinase 3 (PR3)-ANCA. In a cohort of GPA patients from British Columbia (Canada) with >5,000 person-years of follow-up, the age- and sex-adjusted all-cause mortality hazard ratio (HR) was 3.12 (95% confidence interval [CI] 2.35-4.14), with excess mortality due to cardiovascular-disease-related causes, but not cancer. In this cohort, the HRs were 1.86 ([95% CI 1.05-3.31) for myocardial infarctions and 1.50 (95% CI 0.78-2.89) for ischemic stroke, especially during the first year after GPA diagnosis.

This risk appears to be greater than could be explained through traditional cardiovascular risk factors alone, which are common in patients who have been treated with high-dose and long-term glucocorticoids (GC). Some recent publications including patients with newly diagnosed AAV reported treatment-related damage at 7 year follow-up. Hypertension was seen in 41.5% and diabetes in 10.4%. These are both associated with increased cardiovascular events and underscore monitoring and treatment of these to mitigate CV risk.

As mentioned in the CanVasc recommendations for the management of patients with ANCA-associated vasculitides, “as part of their lifelong annual follow-up, cardiovascular risk factors (including smoking status, diabetes, hypercholesterolemia, hypertension, and

obesity) [...] should be systematically assessed, with treatment as needed according to the current respective guidelines for each of these conditions."

3. Is there a higher risk for their daughters to suffer microscopic polyangiitis?

Familial forms and clustering of ANCA-vasculitis are extremely rare. Whereas there are known genetic associations with ANCA-associated vasculitides (for PR3-ANCA-associated vasculitis with HLA-DP, the genes encoding alpha1-antitrypsin (SERPINA1) and PR3 (PRTN3); for MPO-ANCA-associated vasculitis with HLA-DQ), these are not hereditary diseases. Environmental factors, infections and drug exposures are also likely to play a role in the pathogenesis of ANCA-associated vasculitis and may cluster in the same family and geographical area. Hence, the risk of developing vasculitis might be slightly higher (1.5–2-fold) in first-degree relatives of patients with ANCA-associated vasculitis than in the general population (annual incidence of microscopic polyangiitis is 5-10 per million), which remains very low.

4. Is there any study in which this patient could participate in Canada?

There are and will always be various ongoing vasculitis studies in Canada. CanVasc was founded in 2010 and now includes more than 20 affiliated centres across Canada, with expertise and an interest in vasculitis, and many more collaborators (updated list is available on the CanVasc website – https://canvasc.ca/). CanVasc aims at optimizing the management of vasculitis patients in Canada, through the development of recommendations, educational and awareness programs for health care providers, and studies on vasculitides.

CanVasc core members have developed several tools to promote studies in Canada and help recruit patients, including its Internet website with regular updates on active studies recruiting patients and information on how and where to enroll in them. There are different, simple observational cohort studies, including the CanVasc database for adults with vasculitis, or the pediatric ARCHiVe database for children with vasculitis. Genetic research studies are also ongoing in Canada. There are several therapeutic studies, ongoing or planned, which involve several Canadian and CanVasc centres (patients should be referred to those centres to be enrolled, if eligible). The North American Vasculitis Clinical Research Consortium (VCRC) has strong connections with several CanVasc centres, which also participate in the VCRC cohort, genetic and therapeutic studies.

Finally, patients can enroll themselves online in the VCRC network contact registry and/or the Vasculitis Patient-Powered Research Network (VPPRN), and then participate in various and simple online scientific surveys on vasculitis (links on CanVasc website (https://canvasc.ca/).

References

Pankhurst T et al. Malignancy is increased in ANCA-associated vasculitis. Rheumatology (Oxford) 2004;43(12):1532-5.

Mahr AD et al. Epidemiology of Wegener's granulomatosis: Lessons from descriptive studies and analyses of genetic and environmental risk determinants. Clin Exp Rheumatol 2006;24(2 Suppl 41):S82-91.

Knight A et al. Risks and relative risks of Wegener's granulomatosis among close relatives of patients with the disease. Arthritis Rheum 2008; 58: 302–30.

Le Guenno G et al. Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. Arthritis Rheum 2011;63(5):1435-45.

Morgan MD et al. CD4+CD28- T cell expansion in granulomatosis with polyangiitis (Wegener's) is driven by latent cytomegalovirus infection and is associated with an increased risk of infection and mortality. Arthritis Rheum 2011 Jul;63(7):2127-37.

Flossmann O et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis 011;70(3):488-94.

Heijl C et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. Ann Rheum Dis 2011;70(8):1415-21.

Robson J et al. Damage in the anca-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. Ann Rheum Dis 2015;74(1):177-84.

Shang W et al. Incidence of Cancer in ANCA-Associated Vasculitis: A Meta-Analysis of Observational Studies. PLoS One 2015;10(5):e0126016.

Xie G et al. Association of granulomatosis with polyangiitis (Wegener's) with HLA-DPB1*04 and SEMA6A gene variants: evidence from genome-wide analysis. Arthritis Rheum 2013;65(9):2457-68.

Rahmattulla C et al. Incidence of Malignancies in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Diagnosed Between 1991 and 2013. Arthritis Rheumatol 2015;67(12):3270-8.

Faurschou M et al. Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis. Rheumatology (Oxford) 2015;54(8):1345-50.

Prendecki M et al. Familial vasculitides: granulomatosis with polyangitis and microscopic polyangitis in two brothers with differing anti-neutrophil cytoplasm antibody specificity. Clin Kidney J 2016;9(3):429-31.

Aviña-Zubieta JA et al. Risk of Myocardial Infarction and Stroke in Patients With Granulomatosis With Polyangiitis (Wegener's): A Population-Based Study. Arthritis Rheumatol 2016;68(11):2752-59.

Tan JA et al. All-Cause and Cause-Specific Mortality in Patients With Granulomatosis With Polyangiitis: A Population-Based Study. Arthritis Care Res (Hoboken) 2019;71(1):155-63.

Mendel A et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheumatol 2021 Apr;48(4):555-66.

Evaluation Cases

After having read this book, you can test and further increase your knowledge in vasculitis by reviewing these two additional cases. For some of the questions, you may need (on purpose) to search for additional information in other sources than the previous sections of this book.

Case A

A 24-year-old woman, with no significant past medical history, recently married but without any children, has been suffering for the past 6 months from gradually increasing bilateral chest pain and shortness of breath on exertion. Other associated symptoms include general fatigue, and more recently, worsening frontal headache, crusting rhinitis and burning, painful sensation and redness in her right eye. Her family physician has ordered some investigations (Table A.1), a chest X-ray (Figure A.1) and referred her to an ophthalmologist. The latter diagnosed her with right eye nodular scleritis (Figure A.2) and called you to see her urgently.

Table A.1. Main laboratory results

Variable	Results	Normal values
Hemoglobin, g/l	95	110-160
Neutrophils, /mm^3	12260	2000-7000
Eosinophils, /mm^3	450	0-500
Serum creatinine, µmol/l	180	60-110
C-reactive protein, mg/l	208	<10
Aspartate transaminase, IU/l	53	<45
Protein, Urine dipstick	2+	0
Red blood cell, Urine dipstick	2+	0
Antinuclear antibodies	Negative	Negative
Anti-glomerular basement membrane antibodies	Negative	Negative
Proteinase-3 antineutrophil cytoplasm antibodies (PR3-ANCA), IU/l	>8	<1
Myeloperoxidase (MPO)-ANCA, IU/l	<1	<1

1. *What is the most likely diagnosis?*
2. *Have animal models been able to support the pathogenic role of PR3-ANCA and MPO-ANCA?*
3. *Which induction treatment strategy would you suggest for this patient?*
4. *Once remission is achieved, what laboratory monitoring would you order?*
5. *The patient then asks you about risks of infertility and for pregnancy with her condition. What can you tell her?*

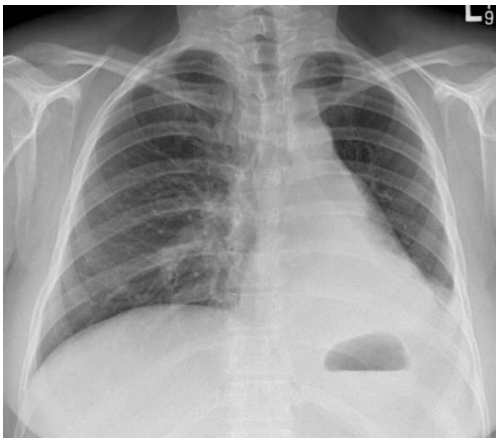


Figure A.1. Chest X-ray, antero-posterior view.



Figure A.2. Right eye nodular scleritis.

Case B

Mr. AB is a 76-year-old man with a history of dyslipidemia, hypertension, and peptic ulcer (he completed a treatment for *Helicobacter pylori* eradication 6 years ago). He woke up this morning with left eye blindness. For the past 2 weeks, he had noticed some left temporal dull pain and tenderness when combing his hair or when laying his head on the pillow.

In the emergency department, besides the complete loss of left eye vision, with a normal optic nerve on funduscopy, there is some left temporal artery prominence, but pulse is present and the artery is not particularly tender to the touch. Laboratory investigations reveal a low hemoglobin level of 88 g/l (normal 120-180 g/l), platelet count 468 G/l (normal 150-450 G/l), creatinine 95 µmol/l (normal 60-120 µmol/l), erythrocyte sedimentation rate at 1st hour at 87 mm (normal <38 mm), and normal liver function tests. An urgent brain computerized tomography (CT) scan is ordered, which does not show any acute change.

1. *What is the most likely diagnosis? How do you explain the normal funduscopy?*
2. *What are the possible cardiovascular complications of giant cell arteritis?*

The patient is promptly started on the appropriate treatment. Ten months later, he is considered in remission but still on prednisone 5 mg/day (along with a statin, a calcium-channel blocker, low-dose aspirin, calcium and vitamin D supplementation). He never recovered his left eye vision but otherwise is doing well. His last C-reactive protein level is 5 mg/l and erythrocyte sedimentation rate is 85 mm at 1st hour.

3. *What could be the cause(s) of the increased erythrocyte sedimentation rate?*
4. *Should this patient be vaccinated against shingles?*
5. *Will you now add methotrexate or tocilizumab?*

Answers — Case A

1. What is the most likely diagnosis?

The clinical manifestations (ear, nose and throat [ENT] manifestations with crusting rhinitis, scleritis), radiological (right middle lobe lung nodule, possibly cavitary) and the laboratory findings (inflammation, increased serum creatinine with proteinuria and micro-hematuria, PR3-ANCA) are highly suggestive of a PR3-ANCA+ granulomatosis with polyangiitis (GPA), in a severe, systemic form (eye disease and renal involvement).

An infection (tuberculosis, fungal) or another systemic condition (rheumatoid arthritis, sarcoidosis) can also cause scleritis and affect the lungs, and should be ruled out, but they are less likely. Such a patient should also be systematically tested for anti-glomerular basement membrane (GBM) antibodies (as overlaps with GPA and anti-GBM disease are possible), which is negative in this patient.

2. Have animal models been able to support the pathogenic role of PR3-ANCA and MPO-ANCA?

Animal models (mice and rats) of MPO-ANCA vasculitis have been developed and suggest a pathogenic role of MPO-ANCA. Conversely, there is no good and simple model to provide evidence for the pathogenic role of PR3-ANCA. Some murine models of PR3-ANCA vasculitis have been developed, but they require extensive changes (i.e. humanization) of the murine immune system and the use of very specific murine strains. The reasons for these discrepancies are not well known, and may include the lower homology between human and murine PR3 compared with that of MPO and the need for additional conformational changes for the PR3 or PR3-ANCA to become, potentially, pathogenic *in vivo*. The reasons why ANCA develop and/or may become pathogenic in humans remain unknown. Other components of the immune system are also implicated, and their role might even prevail over that of ANCA.

3. Which induction treatment strategy would you suggest for this patient?

This young female patient has a severe, systemic form of PR3-ANCA+ GPA with progressive renal involvement. Nodular scleritis is also considered a major organ involvement, which requires the use of a strong immunosuppressant, such as cyclophosphamide or rituximab (rather than methotrexate) or mycophenolate mofetil for induction, in combination with glucocorticoids (GC) and/or avacopan (although data are lacking on the efficacy of avacopan for severe GPA-related scleritis). Local treatments should be combined, managed by a specialized ophthalmologist.

Because she is young, recently married and may have plans to become pregnant in the next few years (not now!) because the disease must be in sustained remission for at least 6 months before considering a pregnancy, rituximab could be favoured for induction (1 g at days 1 and 15), in combination with GC (safety data with avacopan for future pregnancies, in pregnancy, and for breastfeeding are lacking to date). As her eye and renal disease is severe, one should consider initial methylprednisolone IV pulses (7.5–15 mg/kg/day) for 1–3 days, followed by prednisone 1 mg/kg/day (maximum 80 mg) for 2 weeks, then gradually tapered by approximately 10% every 2 weeks until reaching 5 mg/day around the 5th month of treatment.

The use of cyclophosphamide (instead of rituximab) would expose this patient to an additional risk of infertility, although relatively limited if it is given at the appropriate dosage and for no more than 3 months. Cyclophosphamide can be used as a bridging option, for a few weeks,

if the approval (and coverage) of rituximab takes some time to be obtained.

Trimethoprim/sulfamethoxazole (800/160 mg 1 tablet DS 3 times per week, or 400/80 mg daily) to limit the risk of *Pneumocystis jiroveci* pneumonia, must be co-prescribed. In the presence of an allergy or a contraindication, dapsone may be an alternative in the absence of glucose phosphate dehydrogenase deficiency (G6PD deficiency), or atovaquone.

With a long GC course, calcium and vitamin D supplementation are required.

4. Once remission is achieved, what laboratory monitoring would you order?

Patients with GPA in remission, under maintenance therapy and thereafter, need to be seen in clinic on a regular basis, at least every 3 months for the first few years, then every 6 months for several years, and, finally, every year. Relapses can occur decades later, although the risk of relapse seems to decrease in patients in sustained remission over time.

Patients should have regular monitoring laboratory tests (blood cell count, creatinine, urinalysis, C-reactive protein, and other tests depending on the ongoing treatments). The role of serial ANCA measurement remains a topic of debate. Persistent ANCA or increasing ANCA titres are associated with a higher risk of relapse, especially in patients with PR3-ANCA disease, renal disease and/or treated with rituximab, but the predictive value of ANCA is not absolute. Relapses can occur in patients who had become ANCA-negative, and not all patients with persistent or increasing ANCA titres relapse. Under rituximab maintenance therapy, the control of immunoglobulin levels (IgA, M and G) has been recommended by several groups (before each infusion and, more certainly, in case of infection), and the monitoring of CD19 B cells can be considered (B-cell reconstitution is associated with a higher, non-systematic risk of relapse). The search for better biomarkers of disease activity and/or to diagnose a relapse early is still underway in ANCA-associated vasculitides. Repeat imaging should be ordered as needed, parsimoniously (in this patient, a control chest CT could be considered at the time of remission, then 6 to 12 months later).

5. The patient then asks you about risks of infertility and for pregnancy with her condition. What can you tell her?

As stated already, plans to become pregnant should be considered only once the disease has been in sustained remission for at least 6 months. Whereas CYC can induce hypo- or infertility (dose- and age-dependent relationships), and sufficient data on avacopan and pregnancy in humans are lacking, exposures to GC, RTX and/or AZA don't cause fertility issues. Many agents are teratogenic and can induce pregnancy loss or miscarriages, such as CYC, LEF, MMF or MTX. The latter are therefore contraindicated during conception (need for wash-out periods, variable according to the agent, most often around 6 months) and pregnancy. Some agents can be continued during pregnancy if needed, including AZA, or low-dose GC. RTX can also be given, if that is really needed during the pregnancy.

If the pregnancy is planned, with a disease in sustained remission for >6 months, and in a patient who has not developed end-stage organ damage, such as renal or cardiac insufficiency, the pregnancy outcome is usually good. Risks of a flare of GPA during the pre-partum, pregnancy, post-partum and breastfeeding remain small, and close to that of any patient with GPA over a period of 9 months or a few more months (i.e. still between 10-25%, most often limited). Hence, maintenance treatments should not be stopped abruptly because of the pregnancy, and expertise in vasculitis and obstetrical medicine are needed

to adjust treatments as needed, and follow the pregnancy.

A slight increase in the rate of preterm deliveries (average around 20%) has been found in several series in GPA, usually without any further consequence for both the mother and newborn (low birth weight in 10-30%; stillbirth rate <2%). Although comparative data are lacking, low-dose aspirin is therefore often given during pregnancy, especially during the last trimester, to limit the risk of preeclampsia and, hypothetically, placental vascular complications. In GPA, the presence of subglottic or endobronchial stenosis (as damage) can also complicate the peri-partum anesthesiologic management (increased need for C-sections and/or ventilation difficulties). An international registry has been collecting data on pregnancy in patients with vasculitis (more information on the CanVasc website https://canvasc.ca/links).

References

Xiao H et al. Overview of the Pathogenesis of ANCA-Associated Vasculitis. Kidney Dis (Basel) 2016;1(4):205-15.

Nakazawa D et al. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol. 2019;15(2):91-101.

Mendel et al. CanVasc Consensus Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitis: 2020 Update. J Rheumatol 2020;48(4):555-66.

Ross C, D'Souza R, Pagnoux C. Pregnancy Outcomes in Systemic Vasculitides. Curr Rheumatol Rep 2020;22(10):63.

Shochet L, Kitching AR. Animal models of vasculitis. Curr Opin Rheumatol 2022;34(1):10-7.

Massicotte-Azarniouch D et al. Mechanisms of vascular damage in ANCA vasculitis. Semin Immunopathol 2022 ;44(3):325-45.

Ross C, Makhzoum JP, Pagnoux C. Updates in ANCA-associated vasculitis. Eur J Rheumatol 2022;9(3):153-66.

Answers — Case B

1. What is the most likely diagnosis? How do you explain the normal funduscopy?

The clinical presentation (sudden-onset temporal headaches and vision loss in a subject >50 years old, temporal artery abnormalities and biological results (inflammatory syndrome) are highly suggestive of giant cell arteritis (GCA).

Unilateral visual loss in GCA is most often due to anterior optic ischemic neuritis (80% of cases; bilateral in 30% of patients), but can also, more rarely, result from central retinal artery occlusion, or posterior optic ischemic neuritis (normal fundus examination initially, then optic atrophy).

2. What are the possible cardiovascular complications of giant cell arteritis?

GCA can affect the aortic arch and its branches (aortic arch syndrome). Aortitis can occur in up to 10–30% of patients associated with a risk of subsequent aortic aneurysm and/or dissection, plus or minus aortic valvular insufficiency. These can develop years after the diagnosis, when the disease is otherwise in remission. Coronary arteritis is exceptional.

In the long term, whether or not the risk of other cardiovascular diseases (stroke, coronary artery disease) is increased in patients with GCA remains controversial, with contradictory studies (most, but not all, suggesting an increased risk of cardiovascular disease with a hazard ratio [HR] around 1.5–2.8). In the British Columbia (Canada) cohort of >800 GCA patients (follow-up >2,000 person-years), the age- and sex-adjusted hazard ratios were 2.75 (95% CI 2.16-3.50) for myocardial infarction and 2.21 (95% CI 1.68, 2.91) for stroke, especially during the first year after diagnosis.

3. What could be the cause(s) of the increased erythrocyte sedimentation rate?

Erythrocyte sedimentation rate (ESR) may be increased in this patient due to the GCA-related systemic inflammation. However, it is important to remember that ESR increases with age and is physiologically higher in women (normal upper limit of ESR in men = age/2; in women = [age + 10]/2). ESR also increases in cases of anemia or hemodilution, including during pregnancy, or spherocytosis. Finally, ESR increases in patients with high serum viscosity, especially those with poly- or monoclonal gammopathy (benign or due to myeloma). C-reactive protein is more specific of inflammation, but up to 5% of patients with biopsy-proven GCA can have normal C-reactive protein and/or ESR. Of course, neither ESR nor CRP are specific of GCA (infections, cancers and any other inflammatory condition can lead to their increase).

4. Should this patient be vaccinated against shingles?

Patients >50 years of age are clearly at increased risk of shingles, even more so when they are on high-dose glucocorticoids (GC). The live attenuated vaccine against varicella zoster virus (VZV) is not advisable in patients receiving >20 mg/day of prednisone-equivalent (and its efficacy is limited in older patients). The recombinant shingles vaccine is more effective and can be offered to patients taking immunosuppressants and/or GC, like the one in this case, without any emergency.

In the early 2010s, a few studies suggested a possible role of VZV infection in the pathogenesis of GCA. One group found some expression of VZV in the temporal arteries of >65% of patients with GCA, biopsy proven or not. At least 2 other

groups failed to reproduce these findings. Thus far, there has been no study reporting a decrease in the incidence of GCA since the VZV vaccine has been used.

Other vaccinations, including against COVID-19, seasonal flu viruses, and/or pneumococcal vaccinations should also be considered.

5. Will you now add methotrexate or tocilizumab?

There is still no right or wrong answer to this question.

The use of adjunct methotrexate (MTX; 15-25 mg/week orally or subcutaneously) can be considered for its GC-sparing effect and in relapsing patients. It is rarely used as a first-line treatment, especially since a meta-analysis of three small randomized controlled trials (RCT) showed that the benefit of MTX (15 mg/week) was modest. One RCT is ongoing in France to compare MTX at a higher dosage of 20 mg/week versus tocilizumab, in combination with GC - METOGiA; ClinicalTrials.gov Identifier: NCT03892785).

GiACTA (251 patients) evaluated subcutaneous tocilizumab for 12 months in GCA (and GC for 6 months only), as a first-line treatment or for relapsers, versus GC alone (and a placebo of tocilizumab) for 6 or 12 months. At 12 months, the sustained remission rate was 53% in the tocilizumab group compared with 14% in patients treated with GC alone for 6 months and 18% in those treated with GC alone for 12 months. Serious infections occurred in 6% of patients on tocilizumab and a 6-month course GC versus 12% in those on GC alone for 12 months. Based on these positive results, the Food and Drug Administration (FDA) granted tocilizumab with a breakthrough therapy designation for GCA in October 2016, and Health Canada granted approval in October 2017. Whether tocilizumab should be used in all patients with newly diagnosed GCA or only in those who are GC-dependent or who relapse, instead or after failure of MTX, remains to be determined. However, the 2021 American College of Rheumatology/Vasculitis Foundation Guideline "conditionally recommends, for patients with newly diagnosed GCA, [...] the use of oral GC with tocilizumab over oral GCs alone."

If the relapse of GCA is confirmed or, at least, strongly suspected (for now, this patient "only" has isolated, elevated ESR), adding tocilizumab (subcutaneously, 162 mg/week, for at least one year) can be considered, in the absence of contraindication (such as history of diverticulitis, elevated liver enzymes, or any ongoing infection). After one year, data are lacking to define the best option. After stopping tocilizumab at month 12, only around 40% of patients remain in remission for the 2 following years. Many other agents (such as abatacept, guselkumab, secukinumab, mavrilumab, or JAK-inhibitors) are also under investigation in GCA (hence, none of them is approved yet).

References

Mahr AD et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56:2789-97.

Tomasson G et al. Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. Ann Intern Med 2014;160(2):73-80.

Udayakumar PD et al. Cardiovascular risk and acute coronary syndrome in giant cell arteritis: a population-based retrospective cohort study. Arthritis Care Res (Hoboken) 2015;67(3):396-402.

Ungprasert P et al. Cerebrovascular accident in patients with giant cell arteritis: A systematic review and meta-analysis of cohort studies. Semin Arthritis Rheum 2016; 46(3):361-6.

Lo Gullo A et al. Venous Thromboembolism and Cerebrovascular Events in Patients with Giant Cell Arteritis: A Population-Based Retrospective Cohort Study. PLoS One 2016;11(2):e0149579.

Bienvenu B et al. Management of giant cell arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). Rev Med Interne 2016;37:154-65.

Amiri N et al. Increased risk of cardiovascular disease in giant cell arteritis: a general population–based study. Rheumatology 2016;55(1):33–40.

Stone JH et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med 2017;377(4):317-28.

Hellmich et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79(1):19-30.

Maz M et al. Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Rheumatol 2021;73(8):1349-65.

Stone JH et al. New-onset versus relapsing giant cell arteritis treated with tocilizumab: 3-year results from a randomized controlled trial and extension. Rheumatology (Oxford) 2022;61(7):2915-22.

Pugh D et al. Large-vessel vasculitis. Nat Rev Dis Primers 2022 Jan 6;7(1):93.

Vasculitides are relatively rare but potentially life-threatening diseases, which can basically affect any organ in the body. Their management requires some knowledge of their pathogenesis, clinical presentations and therapeutic strategies.

This book, based on practical clinical case scenarios, was developed by physicians participating in the Canadian Vasculitis research network (CanVasc). This 3rd Edition is intended to provide any physician interested or involved in the care of patients with vasculitides up-to-date and directly useful information on the main clinical situations for these complex diseases.



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