Systemic vasculitides: an overview

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Abstract

The systemic vasculitides are a rare but serious group of multisystem autoimmune diseases characterized by inflammation of the blood vessels. Diagnosis requires careful clinical assessment in combination with immunological testing, imaging and often tissue biopsy. Prompt treatment is vital to prevent irreversible organ damage and decrease mortality and morbidity. Immunosuppressive drugs are the mainstay of treatment and have significantly improved outcomes in recent decades. However, relapses are common, and individuals with vasculitis have a higher risk of infections, cardiovascular diseases and cancer compared with the general population. The toxicity of treatments, especially glucocorticoids, contributes to these complications.

Keywords Anti-neutrophil cytoplasm antibody-associated vasculitis; cryoglobulinaemic vasculitis; giant cell arteritis; granulomatosis with polyangiitis; IgA vasculitis; microscopic polyangiitis; polyarteritis nodosa; systemic vasculitis; Takayasu arteritis

Key points

- Vasculitis is a group of heterogeneous disorders that is best categorized according to the size of the blood vessels involved
- The pathological hallmark is immune-mediated injury of the blood vessels
- Clinical assessment of suspected vasculitis aims to confirm the diagnosis and define the disease extent and severity, while considering secondary causes and excluding disease mimics
- Prompt recognition of vasculitis and early initiation of therapy is required to prevent irreversible organ damage and potentially life-threatening complications
- Patients require careful follow-up to monitor disease activity and manage disease- and treatment-related complications

Introduction

The systemic vasculitides are a group of heterogeneous disorders characterized by immune-mediated inflammation of blood vessels. They may manifest clinical features because of:

- lost vessel wall integrity, aneurysmal change and bleeding
- more commonly, compromise of lumen patency because of vessel wall swelling or scarring, thrombosis or dissection giving rise to tissue ischaemia
- tissue inflammation and injury in affected organs.

The exact manifestations depend upon the size, type and location of the affected vessels. Vasculitis can occur as a primary process or secondary to another disease. Although each vasculitis is rare, these conditions are often serious and sometimes fatal, requiring prompt recognition and treatment.

Classification

The Chapel Hill Consensus Conference (CHCC) Nomenclature (Figure 1)[1] categorizes the vasculitides primarily based upon the size of the blood vessels predominantly involved (and on organ involvement and associated systemic diseases or probable underlying cause). Large vessel vasculitis (LVV) is characterized by the involvement of the aorta and its major branches; medium vessel vasculitides affect the main visceral arteries; and in small vessel vasculitis (SVV), inflammation of the intraparenchymal arteries, arterioles, capillaries and their analogous veins predominates.

CHCC nomenclature has replaced some eponymous syndromes with nomenclature descriptive of the underlying pathophysiology. Although CHCC nomenclature provides names and descriptions for the various vasculitides, it does not give criteria by which a specific disease can be identified in an individual (i.e. diagnostic criteria).

Epidemiology

Each type of vasculitis is a rare disease, and each demonstrates distinct demographic and epidemiological patterns. Accurate estimations of the incidence and prevalence of the vasculitides have been hampered by the absence of reliable diagnostic criteria, the rarity of these conditions and a lack of data from many parts of the world, including the Indian subcontinent, China, Africa and South America.[2]

Some vasculitides (e.g. Takayasu arteritis (TA), giant cell arteritis (GCA)) more commonly affect female than male patients, a feature of many other autoimmune diseases. However, not all demonstrate significant differences in sex distribution (e.g. anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV)).

Vasculitis may affect any age group; however, it is more common at ends of the age spectrum, and certain conditions show marked age tropism. Kawasaki disease and immunoglobulin (Ig) A vasculitis predominantly affect children. TA occurs almost exclusively in people aged <50 years. Conversely, GCA predominantly affects those >50 years, and the incidence of AAV increases with advancing age. Anti-glomerular basement membrane (GBM) vasculitis has a bimodal age distribution, with younger patients (aged 20–30 years) being predominantly male and a peak of individuals at 60–70 years of age being more frequently female.

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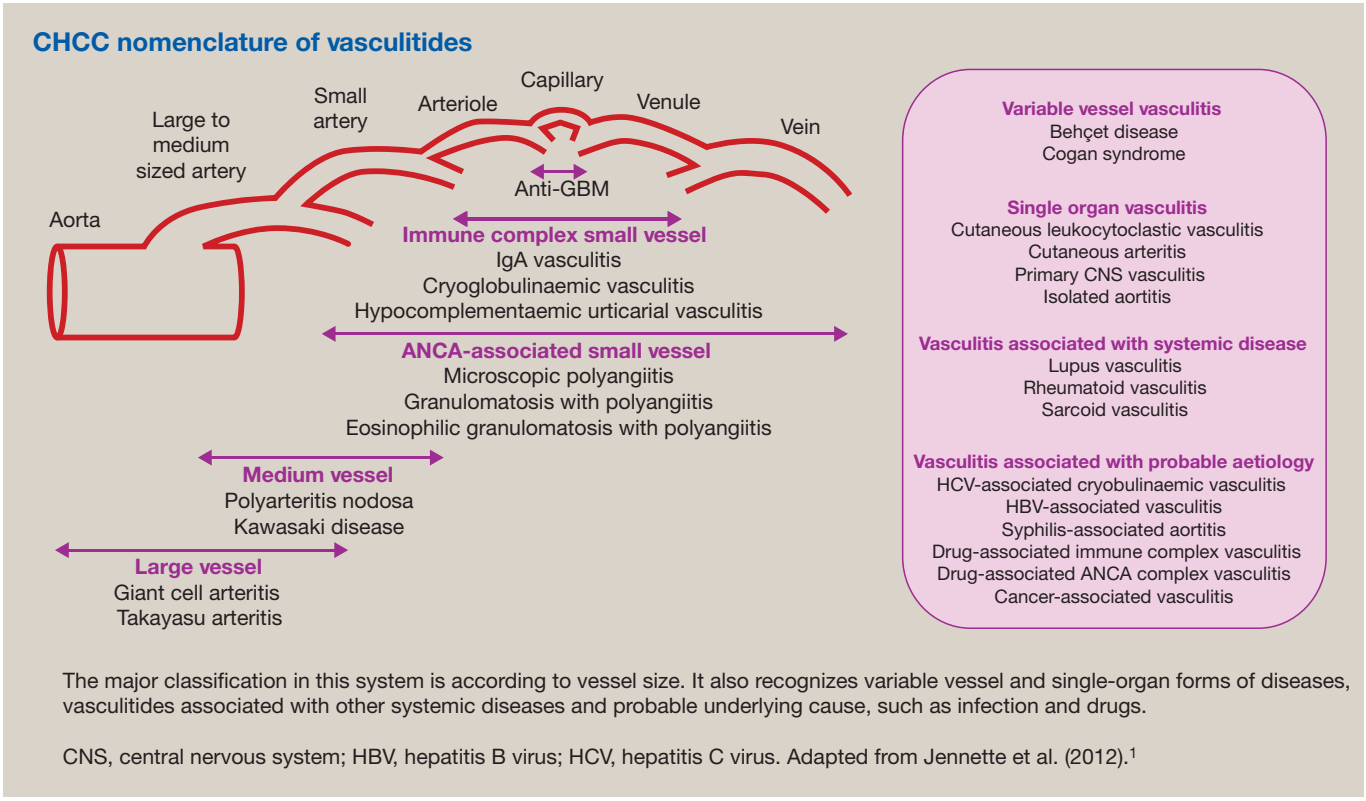

The major classification in this system is according to vessel size. It also recognizes variable vessel and single-organ forms of diseases, vasculitides associated with other systemic diseases and probable underlying cause, such as infection and drugs.

CNS, central nervous system; HBV, hepatitis B virus; HCV, hepatitis C virus. Adapted from Jennette et al. (2012).[1]

Figure 1

Geographical variation in patterns of disease is also well recognized. This is exemplified by Behçet syndrome, which has its highest prevalence along the ancient Silk Road, stretching from the Mediterranean through to East Asia. There is considerable global variation in GCA incidence, with the highest estimates in Northern Europe. Strikingly, there is a particularly high prevalence among in individuals with Scandinavian ancestry, both within Northern Europe and in Americans of Scandinavian descent, suggesting a shared genetic risk across these populations.

There are also global patterns in the incidence of AAV subtypes; for example, in Southern Europe and Japan, microscopic polyangiitis (MPA) is more common than granulomatosis with polyangiitis (GPA), whereas in most other populations GPA is the more common form.

Pathogenesis

Vasculitis is defined by the presence of immune-mediated blood vessel wall inflammation and the underlying pathogenic mechanisms vary in each condition. However, the commonly held paradigm of autoimmune disease pathogenesis may be applicable in vasculitis — that is, an interplay of environmental factors in genetically predisposed individuals leads to the development of an aberrant immune response that can target or injure normal tissue and organs.

The target of the aberrant immune response is well defined in some forms of vasculitis, such as AAV and anti-GBM disease. Target autoantigens have not been identified in LVV, although it is likely that loss of arterial wall immune tolerance is critical to disease onset.

Diagnostic approach to patients with suspected vasculitis

The assessment of patients with suspected vasculitis aims to confirm the diagnosis and define the severity and extent of disease, as this often determines the choice and intensity of treatment. It is also important to consider secondary causes and to exclude disease mimics. In patients with a confirmed diagnosis of vasculitis, several assessment tools can be used to monitor disease activity and related damage (e.g. Birmingham Vasculitis Activity Score, Vasculitis Damage Index). However, these are infrequently used outside of a research setting.

The recent Diagnostic and Classification Criteria for Vasculitis (DCVAS)[3] study developed classification criteria for several vasculitides, which are designed to identify homogeneous groups of patients with vasculitis for clinical research studies and will perform poorly if used as diagnostic criteria in patients in whom non-vasculitis diagnoses (e.g. infection, other inflammatory diseases) have not been excluded. Continuing work from the DCVAS group may develop diagnostic criteria for routine clinical use in the future.

Clinical assessment

Non-specific constitutional symptoms (e.g. lethargy, anorexia, weight loss, low-grade fever, arthralgia) are common features and can predate the onset of more specific clinical features and organ-specific manifestations by many weeks or months.

Patients demonstrate symptoms and signs related to the tissue or organ ischaemia or inflammation determined by the site of the affected vessels. Common clinical patterns are described in Table 1.

Key clinical and laboratory features in the common systemic vasculitides

		Disease	Brief description	Key clinical and laboratory features
Large vessel		GCA	Granulomatous arteritis of the aorta/branches, often temporal artery	Age >50 years, headache, jaw claudication, visual disturbance, aortic insufficiency
		TA	Granulomatous arteritis of the aorta/branches	Age <50 years, limb claudication, weak/absent pulses, discordant blood pressure in limbs, vascular bruits
Medium vessel		Polyarteritis nodosa	Medium vessel arteritis without glomerulonephritis	Hypertension, livedo reticularis, abdominal and testicular pain, myalgias, neuropathy, ANCA negative, may be HBV associated
		Kawasaki disease	Medium/small vessel arteritis with mucocutaneous lymph node syndrome	Age <5 years, fever, lymphadenopathy, conjunctivitis, rash, coronary arteritis/aneurysm
Small vessel	ANCA-associated	Granulomatosis with polyangiitis	Necrotizing granulomatous inflammation of the respiratory tract, vasculitis of small to medium vessels	Sinusitis, epistaxis, lung nodules/cavities, pauci-immune GN, PR3-ANCA positive
		Microscopic polyangiitis	Necrotizing vasculitis of small vessels, no granulomatous inflammation	Pauci-immune GN, pulmonary haemorrhage, neuropathy, MPO-ANCA positive
		Eosinophilic granulomatosis with polyangiitis	Eosinophil-rich granulomatous inflammation of the respiratory tract, vasculitis of small to medium vessels	Asthma, sinusitis, neuropathy, myocarditis, eosinophilia, MPO-ANCA positive in 40%
	Immune-complex	Anti-GBM disease	Vasculitis of glomerular/pulmonary capillaries with anti-GBM antibodies	RPGN, lung haemorrhage, anti-GBM positive, ANCA positive in 30%
		Cryoglobulinaemic vasculitis	SVV with cryoglobulin deposits	Palpable purpura, nephrotic/nephritic syndrome, neuropathy, serum cryoglobulins, low C4, can be HCV associated
		IgA vasculitis	SVV with IgA deposits	Can occur at any age, but more common in those <20 years old. Palpable purpura, GN, arthritis, abdominal pain, raised serum IgA

GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; MPO, myeloperoxidase; PR3, proteinase 3; RPGN, rapidly progressive glomerulonephritis.

Table 1

In LVV these can include limb claudication, angina and neurological deficits. It is critical that cranial involvement in GCA is detected promptly, given the risk of irreversible visual loss if left untreated; symptoms include temporal headache or tenderness, jaw claudication and visual disturbances such as amaurosis fugax and diplopia.

Examination of patients with suspected LVV should include assessment of blood pressure and arterial pulsation in all extremities, auscultation for vascular bruits and ophthalmology assessment (GCA). Carotidynia may indicate the presence of carotid artery inflammation. Cardiac examination may reveal aortic valve insufficiency as a complication of aortitis in several forms of LVV. Rarely, patients present with life-threatening vascular events such as dissection or vessel rupture.

It is important to recognize that in some forms of SVV almost any organ system can be affected, so comprehensive assessment (including neurological, ophthalmic and full cutaneous examination) is mandatory. As many forms of SVV cause glomerulonephritis, assessment of urinary abnormalities by dipstick testing and quantification of proteinuria should always be performed.

Laboratory findings

An acute phase response is common in all vasculitides, including elevated serum C-reactive protein and erythrocyte sedimentation rate. Leucocytosis, thrombocytosis, normochromic normocytic anaemia and polyclonal hypergammaglobulinaemia can also be present. A range of additional serological and immunological tests are required in the work-up of vasculitis, both to aid

diagnosis and to exclude secondary causes and mimics, depending on clinical context (Table 2). Some forms of SVV have reliable serological diagnostic indicators (e.g. ANCA, anti-GBM disease). Circulating ANCA have >90% sensitivity and specificity for GPA/MPA, although ANCA-negative cases are well recognized (and ANCA may occasionally be detected in other inflammatory and infectious diseases). At present, there are no specific circulating biomarkers for the large or medium vessel vasculitides.

Imaging

A variety of non-invasive imaging techniques are now used in the diagnosis and assessment of patients with suspected LVV (Table 3); however, the optimum modality and the use of imaging for monitoring disease activity and response to treatment remains somewhat controversial.[4] In GCA, imaging with ultrasonography or magnetic resonance imaging (MRI) has been found to have similar diagnostic value to temporal artery biopsy (TAB). Imaging in SVV is usually determined by the pattern of suspected organ involvement (Figure 2).

Biopsy

Before the uptake of advanced non-invasive imaging techniques, TAB was regarded as an essential gold standard for the diagnosis of GCA, particularly in individuals with symptoms of cranial arteritis. In acute disease, focal granulomatous pan-arteritis typically with multinucleate giant cells may be observed. These lesions can be scattered irregularly ('skip lesions') in affected vessels, so adequate sampling (segments >1 cm) is required to avoid false-negative results. Given the arterial distribution of vessel involvement in extra-cranial GCA and in TA, targeted tissue sampling is often not possible.

In SVV, targeted biopsy of organs with suspected involvement may confirm the diagnosis (Figure 3). Renal biopsy has a high diagnostic yield when urinary abnormalities and/or kidney impairments are present and typically reveals proliferative or necrotizing glomerulonephritis. Immunostaining of the biopsy can assist with disease classification (immune-complex SVV versus AAV, which is typically pauci-immune). Other tissue biopsies (e.g. lung, skin, sinus) in SVV have lower positive diagnostic yield but can be useful to exclude other pathology (e.g. malignancy) and vasculitis mimics.

Differential diagnoses, secondary causes and vasculitis mimics

It is essential to consider secondary causes of vasculitis, such as drugs and infections. Importantly, some infections can also mimic features of vasculitis, and certain infections can also induce ANCA, leading to misdiagnosis. Important infectious mimics to consider include bacterial endocarditis, tuberculosis (TB), HIV-associated vasculopathy, coronavirus disease (COVID-19)-associated pernio lesions and Kawasaki-like disease, and mycotic aneurysms. Potential non-infectious mimics are summarized in Table 4.

Management

The mainstays of medical treatment for vasculitis are corticosteroids and immunosuppressive drugs, which are used to suppress immune-mediated vascular injury. The choice of drugs and treatment regimens varies in each form of vasculitis. Key treatment principles include the following.

Rapid initiation of treatment

This is needed to prevent irreversible vascular or tissue injury, such as visual loss in GCA or irreversible kidney damage in AAV.

Laboratory investigations in the assessment of suspected vasculitis

Laboratory	Test	Uses
Urine	Urine microscopy	Detect erythrocyturia, red blood cell casts suggest acute GN in SVV
	Urinary protein	Quantify protein loss indicative of GN in SVV, often subnephrotic
	Urine culture	Exclude infectious causes of urinary abnormalities
Immunology	ANCA	Identify AAV
	Anti-GBM antibodies	Identify anti-GBM disease
	ANA/Anti-dsDNA	Identify SLE
	Complement C3/C4	Low C4 compatible with cryoglobulinaemia
	Cryoglobulins, rheumatoid factor	Detect cryoglobulinaemia, may show rheumatoid factor activity
	Immunoglobulins	Raised serum IgA in IgA vasculitis, detect hypogammaglobulinaemia before immunosuppression
Microbiology and infection	HIV/hepatitis serology	Screen for virus-associated vasculitis, required before immunosuppression and prophylaxis. HBV and HCV are associated with PAN and cryoglobulinaemic vasculitis respectively.
	Blood cultures	Detect bloodstream infections mimicking vasculitis such as infective endocarditis.
	Parasitology/*Aspergillus* serology	Investigate eosinophilia in suspected EGPA
	TB screening	Detect TB infection, screen at-risk patients before immunosuppression
	Syphilis serology	Identify syphilis-associated aortitis

dsDNA, double-stranded DNA; EGPA, eosinophilic granulomatosis with polyangiitis; GN, glomerulonephritis; HIV, human immunodeficiency virus; RPGN, rapidly progressive glomerulonephritis; TB, tuberculosis.

Table 2

Imaging modalities employed in large and medium vessel vasculitis

Modality	Uses	Advantages	Disadvantages
Doppler ultrasound	Assess vessel wall/lumen, useful for smaller and superficial vessels	Inexpensive, no radiation, repeatable	Operator dependent, unsuitable for non-superficial vessels
MRI/MRA	Assess aorta and major branches	No radiation, repeatable	Poor small vessel resolution, expensive
CTA	Assess aorta and major branches	Differentiate vascular structures	Radiation, iodinated contrast
FDG-PET	Whole-body assessment, early vessel inflammation	Most sensitive for early inflammation	Not specific, no information on vessel wall structure or lumen patency, expensive
Conventional angiography	Luminal assessment, microaneurysms in medium vessels	Excellent resolution, potential for intervention	No vessel wall assessment, iodinated contrast, requires arterial access

CTA, computed tomography angiography; FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; MRA, magnetic resonance angiography.

Table 3

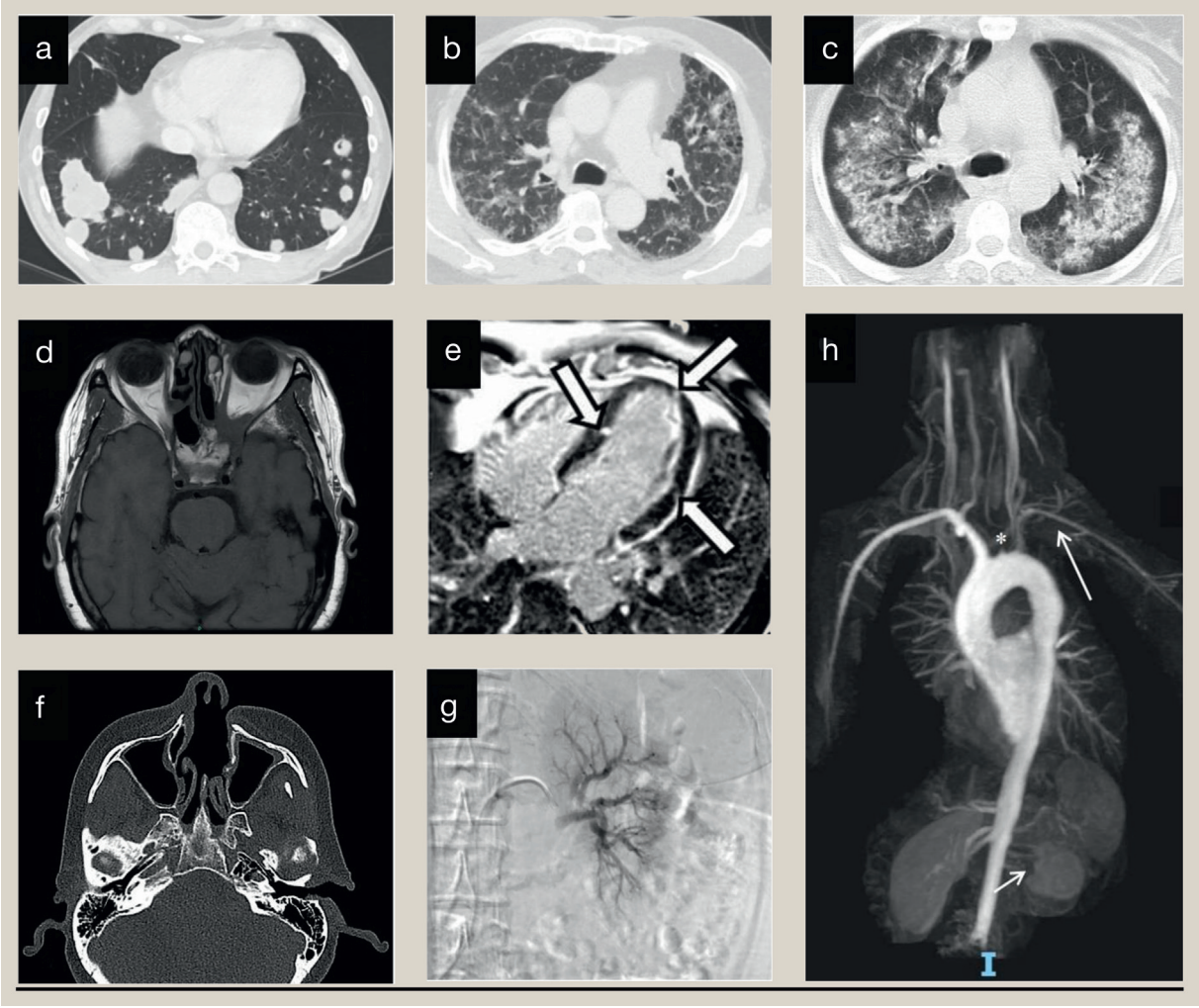

Figure 2 Imaging in systemic vasculitis. (**a**–**c**) Pulmonary computed tomography (CT) findings in ANCA-associated vasculitis: (**a**) multifocal pulmonary nodules with cavitation in GPA; (**b**) interstitial lung disease, with a non-specific interstitial pneumonia pattern and honeycombing, in MPA; and (**c**) diffuse bilateral ground-glass opacification, with peripheral sparing, indicative of lung haemorrhage in MPA. (**d**) MRI showing left orbital apex inflammation in GPA. (**e**) Gadolinium-enhanced cardiac MRI in eosinophilic granulomatosis with polyangiitis showing multiple small subendocardial areas of enhancement (white arrows) indicative of myocarditis. (**f**) Sinus CT showing a large septal perforation and erosion of the turbinates in GPA. (**g**) Intra-arterial renal angiography in polyarteritis nodosa, demonstrating multiple arterial microaneurysms, with a predilection for vessel branching points. (**h**) Magnetic resonance angiogram in TA, showing occlusion of the left common carotid artery (star) and narrowing of the left subclavian artery (long arrow). There is proximal stenosis affecting the left renal artery resulting in a small ischaemic left kidney (short arrow).

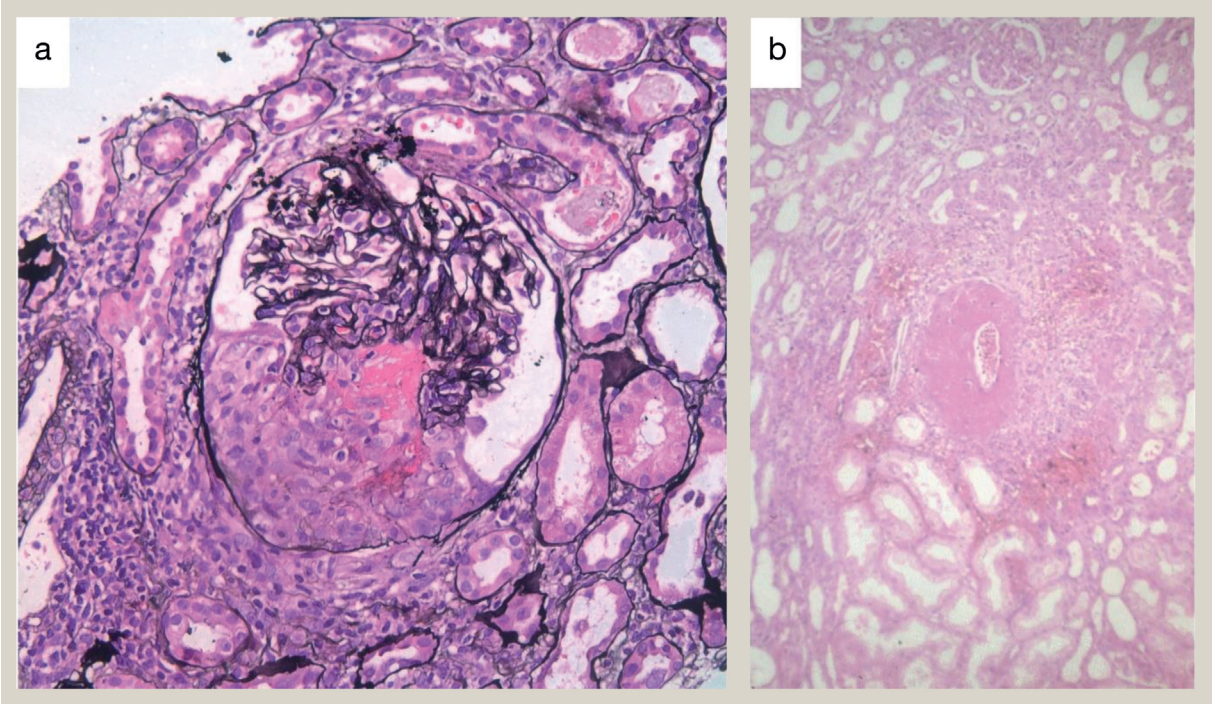

Figure 3 Renal pathology in systemic vasculitis. (**a**) Kidney in GPA showing focal glomerular necrosis and proliferating cells in the Bowman's space (i.e. crescentic glomerulonephritis). (**b**) Kidney in polyarteritis nodosa showing circumferential necrotizing arteritis and perivascular inflammation in an arcuate artery.

Non-infectious vasculitis mimics

Large and medium vessel vasculitis mimics	Small vessel vasculitis mimics
• Atherosclerosis including chronic peri-aortitis	• Cholesterol embolization
• IgG4-related disease	• Calciphylaxis
• Fibromuscular dysplasia	• Thrombotic and hypercoagulable states, including thrombotic microangiopathies
• Post-radiation therapy	• Malignancy
• Congenital conditions (e.g. coarctation)	
• Inherited connective tissue diseases	
• Malignancy	

Table 4

When vasculitis is suspected, it may be necessary to commence treatment (e.g. corticosteroids) before obtaining diagnostic tests, although these should be arranged as soon as possible.

Remission induction

The goal of initial treatment is to induce remission. This usually requires high-dose corticosteroids and/or immunosuppressive agents. High-dose corticosteroids should be reduced promptly in a tapering regimen that adequately suppresses disease activity. Immunosuppressive drugs commonly used in the treatment of vasculitis include disease-modifying antirheumatic drugs (e.g. methotrexate, mycophenolate mofetil, azathioprine), biologic therapies (e.g. rituximab, anti-tumour necrosis factor therapy) or cytotoxic agents (e.g. cyclophosphamide). Plasma exchange can have a role in severe presentations of some forms of vasculitis.

Remission maintenance

This aims to maintain control of disease activity and prevent disease relapses, often with tapering doses of corticosteroids and other immunosuppressive drugs. The choice and duration of maintenance treatment is determined by the type of vasculitis, its risk of relapse and the patient's characteristics.

Preventing and managing treatment-related complications

Patients require monitoring for treatment-related adverse effects. The increased risk of infection can warrant prophylactic antimicrobial therapy, and the uptake of vaccinations should be encouraged. Vaccine responses are attenuated after treatment with immunosuppressive therapies and so, where possible, vaccinations should be given before immunosuppression. Corticosteroids have numerous well-recognized adverse effects, such as peptic ulcer disease, metabolic disorders and osteoporosis, and these can require prophylaxis or treatment (e.g. proton pump inhibitors, bisphosphonates). In patients of child-bearing potential fertility preservation and contraception should be discussed. Some vasulitides reduce fertility through systemic inflammation or by directly by affecting reproductive organs. More commonly, drugs such as cyclophosphamide can cause infertility due to direct gonadal toxicity. Approaches to fertility preservation include the use of GnRH analogues, oocyte cryopreservation or ovarian tissue storage for women, and semen storage for men. Several immunosuppressants (e.g. mycophenolate mofetil, methotrexate, cyclophosphamide) are teratogenic,

and this should be discussed with patients when planning treatment.

Management of disease-related complications and co-morbidities

After the vasculitis is controlled with immunosuppressants, additional non-immunosuppressive treatments can be required to treat the complications of vasculitis, such as chronic kidney disease (e.g. renin–angiotensin blockade, sodium glucose co-transporter 2 (SGLT2) inhibition) or chronic interstitial lung disease (e.g. anti-fibrotic therapies such as nintedanib). Patients with vasculitis have an elevated risk of cardiovascular disease and may benefit from treatment of risk factors such as hypertension and dyslipidaemia.

Percutaneous and surgical interventions

These can be required for the treatment of aneurysmal and steno-occlusive disease in LVV. Interventions should be performed after a period of immunosuppressive treatment when vessel wall inflammation is quiescent.

Prognosis and follow-up

Without treatment, vasculitis is associated with significant morbidity and mortality. Before the introduction of immunosuppressive therapy, survival in AAV was <10% within 1 year of diagnosis. Outcomes have improved dramatically with advances in treatment, and most vasculitides are now managed successfully as chronic relapsing–remitting diseases. However, the prognosis is highly dependent on the underlying diagnosis, and the adverse effects of therapy, including infection, malignancy and cardiovascular disease, contribute significantly to the morbidity of the illness.

Patients require careful and regular monitoring to detect and manage relapses, disease complications, treatment adverse effects and co-morbidities. Their care should be led by physicians with expertise in vasculitis and often requires the involvement of multiple specialists. A recent UK-based study confirmed that patients with vasculitis who are managed in specialist centres with access to dedicated multidisciplinary care and nursing support benefit from improved clinical outcomes and experience of care.[5]

Information for patients

Patients should be given a clear verbal explanation of the nature of the disease, treatment options, adverse effects of treatment and short-term and long-term prognoses. They should be given support though access to specialist nursing support and appropriate education. Reliable internet sources of information and patient support groups include:

- Vasculitis UK: http://www.vasculitis.org.uk/
- Vasculitis Foundation: https://www.vasculitisfoundation.org/
- Vasculitis Clinical Research Consortium: https://www.rarediseasesnetwork.org/cms/vcrc ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 72-year-old woman presented with a 2-month history of rash, arthralgia, nasal congestion, epistaxis and progressive dyspnoea. She had no significant medical history.

Investigations

- Haemoglobin 103 g/litre (120–160)
- White blood cell count 13.4 × 10^9/litre (4.0–11.0)
- Neutrophil count 8.6 × 10^9/litre (2.5–7.0)
- Lymphocyte count 2.9 × 10^9/litre (1.0–4.5)
- Eosinophil count 0.9 × 10^9/litre (<0.4)
- Platelets 561 × 10^9/litre (150–400)
- Creatinine 496 micromol/litre (60–110)
- C-reactive protein 52 mg/litre (<5)
- Adjusted calcium 2.3 mmol/litre (2.2–2.6)
- anti-neutrophil cytoplasm antibody (ANCA) immunofluorescence showed a perinuclear ANCA pattern with 2+ intensity
- MPO-ANCA ELISA assay 56 IU/litre (<3)
- Chest X-ray showed multiple bilateral cavitating nodules

Which is the most likely diagnosis?

A. Eosinophilic granulomatosis with polyangiitis
B. Granulomatosis with polyangiitis
C. Microscopic polyangiitis
D. Renal limited vasculitis
E. Sarcoidosis

Question 2

A 32-year-old woman presented with a 6-month history of lethargy, weight loss and headache. In the previous month, she reported she had had a dull ache in her left arm. On clinical examination, there was tenderness of the left carotid artery and absent pulsation in the left radial and brachial artery.

What is the preferred imaging modality?

A. Colour Doppler ultrasonography
B. Contrast-enhanced CT angiography
C. Contrast-enhanced MR angiography
D. Intra-arterial angiography
E. ^{18}F-fluorodeoxyglucose positron emission tomography CT

Question 3

A 53-year-old man presented with rash, abdominal pain and diarrhoea. He reported weight loss, generalized arthralgia and a low-grade fever for the preceding 4 weeks.
On clinical examination, his blood pressure was 192/112 mmHg and there was weakness of right wrist extension with numbness on the dorsum of the right hand. Urinalysis was positive for blood (3+) and negative for protein, leucocytes and nitrites.

Investigations

- Erythrocyte sedimentation rate 69 mm/hour (<20)
- C-reactive protein 45 mg/litre (<5)
- Creatinine 145 micromol/litre (60–110).
- Antinuclear antibodies (ANA), anti-neutrophil cytoplasm antibodies (ANCA) and rheumatoid factor were negative

Which test will provide the most diagnostic information?

A. Colonoscopy
B. Mesenteric angiography
C. Nerve conduction studies
D. Renal biopsy
E. Skin biopsy