

Burning vessels

A review of vasculitis for primary care

MAIANH NGUYEN MB BS

ROGER GARSIA MB BS, PhD, FRACP, FRCPA

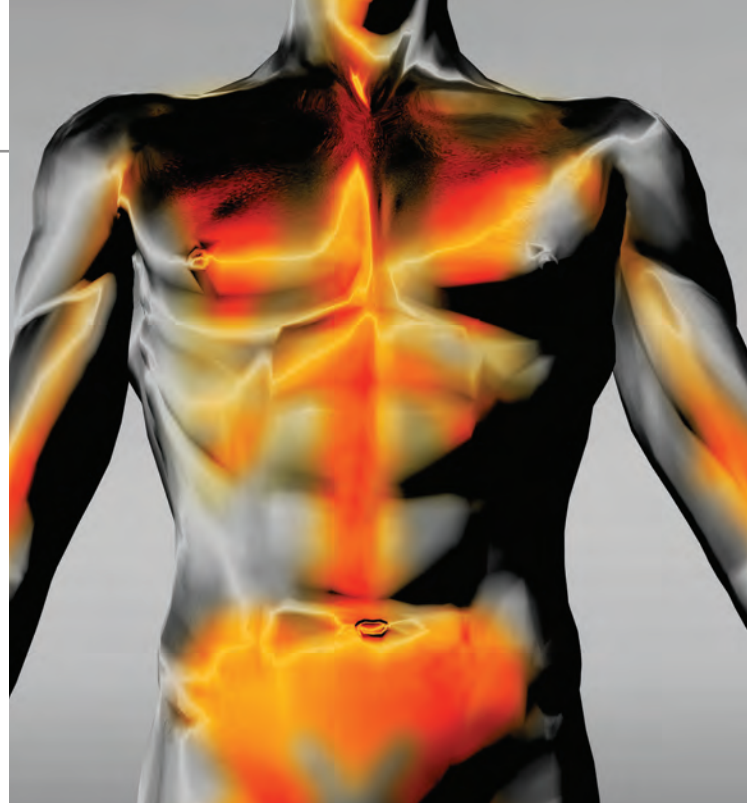
The manifestations of vasculitis are protean and may mimic common diseases such as sinusitis and respiratory infections. Pathogenesis involves immune dysregulation, and treatment usually centres on intensive immunosuppression.

KEY POINTS

- The manifestations of vasculitis depend on the size of the blood vessels affected by inflammation.
- Vasculitis leads to morbidity and mortality if not promptly and effectively treated.
- Symptoms are often nonspecific and may include fever, weight loss, fatigue, headache and rash.
- Features that should raise immediate suspicion for underlying vasculitis include asymmetric polyneuropathy, new-onset proteinuria or glomerular haematuria, headache combined with visual loss or palpable purpura.
- Urgent treatment is required for patients who present with deteriorating vision, haemoptysis or signs of rapidly progressive glomerulonephritis.
- Treatment depends on the extent of organ involvement but often involves intensive immunosuppression based on glucocorticoids.
- Rituximab may be used in organ-threatening disease at treatment outset.

MedicineToday 2015; 16(3): 26-39

Dr Nguyen is an Immunology Fellow at Royal Prince Alfred Hospital, and Clinical Associate Lecturer at The University of Sydney, Sydney. Associate Professor Garsia is a Consultant Immunologist, Chairman of the Division of Medicine and Director of HIV Clinical Services at Royal Prince Alfred Hospital, and Clinical Associate Professor of Medicine at The University of Sydney, Sydney, NSW.



Vasculitis (plural: vasculitides) is a broad term that encompasses a variety of pathological processes leading to inflammation and fibrinoid necrosis of blood vessels. Clinical diagnosis is difficult because of the wide spectrum of symptoms and signs (see the case history in Box 1). Histological examination is definitive but is subject to sampling error, potentially leading to equivocal or false-negative results. Generous tissue volumes are therefore required to improve the reliability of biopsy findings.

Although there are classification and nomenclature systems for vasculitis, these are not always useful if patients do not fulfil specific disease criteria.¹ Vessel calibre is a useful basis for classification (Box 2), but large vessel vasculitides may involve small vessels and vice versa. To add to the difficulty, vasculitis may be systemic or organ specific, self-limiting or relapsing–remitting, and primary or secondary. Vessel damage leads to wall thickening, luminal narrowing, aneurysm formation and vessel occlusion, causing haemorrhage or end-organ ischaemia.

This review will focus on small vessel vasculitides, with a brief discussion of other primary vasculitides. Secondary vasculitides caused by infection, malignancy, drug hypersensitivity, cryoglobulinaemia or connective tissue autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus, will not be covered.

Pathophysiology

Understanding of the pathophysiology of vasculitis is incomplete. The vasculitides are variably associated with immune complex deposition, antineutrophil cytoplasmic antibodies (ANCA), T lymphocyte responses and granuloma formation. Although vasculitis is considered a form of immune dysregulation, the inciting antigens and initiating events are often unknown.

1. AN ILLUSTRATIVE CASE HISTORY

An 80-year-old woman presented with a one month history of dry cough and increasing breathlessness, associated with frontal headache, lethargy, fever and night sweats. Results of initial investigations included patchy consolidation seen on chest x-ray (Figure 1), an elevated C-reactive protein level (70 mg/L), white cell count of $11 \times 10^9/L$, haemoglobin level of 120 g/L and creatinine level of 50 $\mu\text{mol/L}$.

The patient was commenced on oral and then intravenous antibiotics without substantial improvement. A CT scan of the chest and sinuses showed bilateral pulmonary air space consolidation, cavitation in the right lower lobe, multiple lung field nodules and blockage of the ethmoid sinus.

Antineutrophil cytoplasmic antibody (ANCA) testing gave positive results, with a classic cytoplasmic pattern (C-ANCA) on indirect immunofluorescence and a markedly elevated anti-proteinase-3 (PR-3) level of 85 units/L measured on immunoassay (typical normal range, 0 to 5 units/L).



Figure 1. Chest x-ray showing consolidation in the right upper and middle lobes and patchy consolidation in the left lower lobe.

Urinalysis revealed dysmorphic red cells but because of the patient's age and general frailty, a renal biopsy was not performed.

The constellation of clinical features and results were consistent with granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis). The patient underwent induction immunosuppression with intravenous, then oral, glucocorticoids and several cycles of dose-reduced cyclophosphamide. Trimethoprim-sulfamethoxazole was prescribed for *Pneumocystis* prophylaxis and for potential benefit in GPA.

After six months of induction therapy, maintenance therapy using azathioprine was introduced, with subsequent tapering of prednisolone. A lumbar vertebral fracture due to osteoporosis was a late complication of treatment; the patient required rehabilitation and zoledronate treatment. She recovered from GPA with preserved lung and renal function and remains in remission two years later.

However, it is becoming more apparent that neutrophils are involved in the pathogenesis of vasculitis. ANCAs are antibodies directed against enzymes found in neutrophil and monocyte granules, including myeloperoxidase (MPO) and proteinase-3 (PR-3). These antibodies are detected in a high proportion of patients with small vessel vasculitides (also referred to as ANCA-associated vasculitides). These include:

- granulomatosis with polyangiitis (GPA; formerly known as Wegener's granulomatosis)
- microscopic polyangiitis (MPA)
- eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome).

ANCAs are typed according to the location of neutrophil staining by indirect immunofluorescence; C-ANCAs bind in the cytoplasm, whereas P-ANCAs are so called because they are detected in the perinuclear region owing to fixation artefact (Figures 2a and b). Almost all C-ANCAs are directed against PR-3 whereas 40 to 70% of P-ANCAs are directed against MPO. As an alternative to indirect immunofluorescence, a range of quantitative immunoassay techniques, including enzyme-linked immunoassays (ELISA), are available to measure ANCAs, and rising ANCA levels can predict disease flares or relapses.

ANCAs are pathogenic and can occasionally cause disease in newborn human infants by placental transfer. The mechanism of ANCA-associated vascular damage appears to be through neutrophil-mediated release of granules and cytokines. Upon

activation, neutrophils extrude their intracellular contents in the form of webs or neutrophil extracellular traps (also known as NETs) made of unwound chromatin and granule contents, in an attempt to trap and destroy pathogens.² The immune system's exposure to these intracellular antigens appears important in the development of autoantibodies to MPO and PR-3.

2. CLASSIFICATION OF VASCULITIS BASED ON SIZE OF VESSEL PRIMARILY INVOLVED

Small vessels

- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Granulomatosis with polyangiitis (Wegener's granulomatosis)
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Cryoglobulinaemic vasculitis
- Cutaneous leucocytoclastic vasculitis
- Hypersensitivity vasculitis
- Antiglomerular basement membrane disease (Goodpasture's disease)

Medium arteries

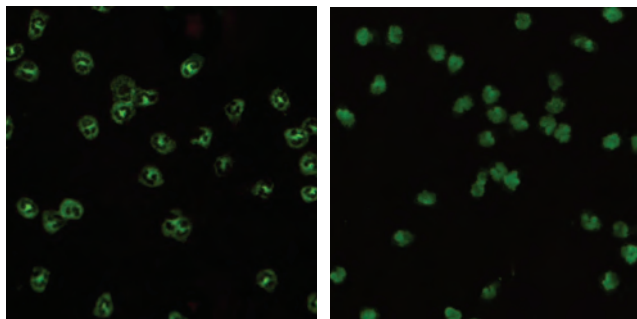
- Kawasaki disease
- Polyarteritis nodosa
- Buerger's disease (thromboangiitis obliterans)

Large arteries

- Giant cell arteritis (cranial arteritis or temporal arteritis)
- Takayasu's arteritis

Variable vessel size

- Behçet's disease
- Cogan's syndrome



Figures 2a and b. Immunofluorescence staining of neutrophils by different classes of antineutrophil cytoplasmic antibodies (ANCAs). a (left). Cytoplasmic (C-ANCA) pattern, largely corresponding to PR-3 antibodies. b (right). Perinuclear (P-ANCA) pattern.

Images courtesy of Dr Jessie Lee, Immunology, Royal Prince Alfred Hospital, Sydney, NSW.

Propylthiouracil, an antithyroid drug, is associated with the development of anti-MPO antibodies in 30% of patients and less frequently with clinical ANCA-associated vasculitis. Propylthiouracil appears to inhibit NET breakdown, which exposes the immune system to intracellular antigens for longer, potentiating the risk of autoantibody development. A mouse model showed that injection of immunogenic, propylthiouracil-induced NETs resulted in an MPO (P-ANCA) vasculitis, capillaritis, pulmonary haemorrhage and glomerulonephritis.³

Autoimmune disease often has a genetic component, and a recent study confirmed a link between certain HLA-DP and HLA-DQ histocompatibility types and PR-3 and MPO ANCA vasculitis, respectively. This finding is yet to be incorporated into diagnostic algorithms.

3. ORGAN-SPECIFIC PRESENTING SYMPTOMS OF VASCULITIS

Central and peripheral nervous systems

- Headache
- Confusion
- Blindness or amaurosis fugax
- Mononeuritis multiplex
- Numbness and tingling
- Stroke or transient ischaemic attack

Cardiovascular system

- Chest pain suggesting myocarditis or myocardial ischaemia
- Hypertension
- Blood pressure difference between limbs
- Limb claudication or limb pain on exertion, relieved with rest

- Jaw claudication or pain while chewing

Respiratory system

- Cough
- Shortness of breath
- Pneumonia mimics
- Haemoptysis

Gastrointestinal system

- Abdominal pain, particularly after meals

Renal system

- Haematuria
- Proteinuria

Skin

- Nodules
- Palpable purpura or leucocytoclastic vasculitis
- Ulcers

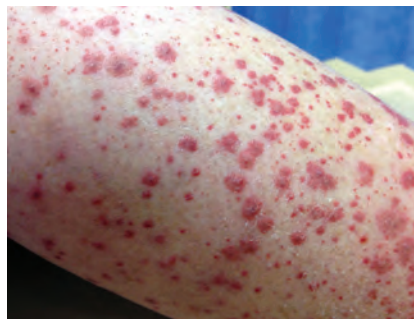


Figure 3. Palpable purpura in a patient with Henoch-Schönlein purpura.

Clinical presentation and classification

Diagnosis is challenging because of the varied ways that patients present. Constitutional symptoms (fever, weight loss, fatigue and rash) and nonspecific symptoms (arthralgia, myalgia) are common. Symptoms localised to organ systems are listed in Box 3. Certain features should prompt consideration of vasculitis, including:

- palpable purpura (Figure 3)
- haemoptysis
- rapidly progressive glomerulonephritis
- mononeuritis multiplex.

Large vessel vasculitis

Takayasu's arteritis, which is rare, and giant cell arteritis, which is more common, both principally affect large vessels. The aorta is particularly affected, but other vessels that are subject to stenosis include temporal, occipital, ophthalmic, vertebral, subclavian and axillary arteries, and internal and external carotid arteries (usually near the origin). Patients are at risk of blindness, subclavian steal syndrome, aneurysm formation and dissection.

Giant cell arteritis

Giant cell arteritis, also known as temporal arteritis or cranial arteritis, usually affects elderly people, with a peak incidence between 70 and 80 years of age. The annual incidence rate of giant cell arteritis in patients aged over 50 years is 15 to 30 cases per 100,000, with most cases affecting women. Half may initially present with features of polymyalgia rheumatica, including ache and stiffness in the neck and limb girdles.

Although giant cell arteritis was originally thought to be self-limited, it tends to persist as a chronic vasculitis. Clinical manifestations include headache, jaw claudication, scalp tenderness or failing vision. Ischaemic optic neuropathy presents as painless loss of vision and is a medical emergency. Other visual symptoms can include diplopia or visual field defects. These require urgent specialist review and timely commencement of immunosuppression to preserve residual vision and prevent contralateral vision loss. Giant cell arteritis rarely affects the skin, kidneys or lungs.



Figure 4. Magnetic resonance angiography in a patient with Takayasu's arteritis, showing occlusion of the left common carotid (C) and subclavian arteries, with reduced calibre of the left vertebral artery (V). An axillo-axillary bypass graft is in situ (arrow).

Takayasu's arteritis

In contrast to giant cell arteritis, Takayasu's arteritis disproportionately affects Asian women under the age of 50 years and has an incidence of 2.6 cases per million persons. Patients with Takayasu's arteritis may present with claudication or asymmetric blood pressure readings in the limbs. Diligent examination may reveal a subclavian bruit and reduced or absent pulses, with cerebral and limb circulation sustained by collaterals.

Investigation of large vessel vasculitis

Confirmation of giant cell arteritis requires the finding of granulomatous vasculitis on histology, but a suggestive history, clinical examination, laboratory tests and imaging help to reinforce the diagnosis. Examination of a temporal artery biopsy specimen of at least 2 cm is confirmatory in 85 to 95% of cases, but a negative biopsy result does not preclude the diagnosis, and histological confirmation should not delay the initiation of treatment in patients at risk of vision loss. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are often elevated but can be normal in 4% of patients with confirmed giant cell arteritis. Anaemia is another common finding.

In Takayasu's arteritis and giant cell arteritis, magnetic resonance angiography (MRA, Figure 4) or CT can assess the extent of large vessel involvement and assist diagnosis in patients whose biopsy results are not diagnostic. Contrast enhancement of vessel walls may occur because of inflammation, and wall thickening, or even occlusion, may be visualised on imaging. Occasionally, patients are referred for further investigation after initial radiology, performed for nonspecific symptoms such as fever and weight loss, shows features of vasculitis.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) detects metabolically active cells and can identify sites of intense vascular inflammation (Figure 5). However, as the appearance can be similar to inflammatory atherosclerosis, the modality is not sufficiently sensitive or specific to recommend its routine use in the investigation of large vessel vasculitis.

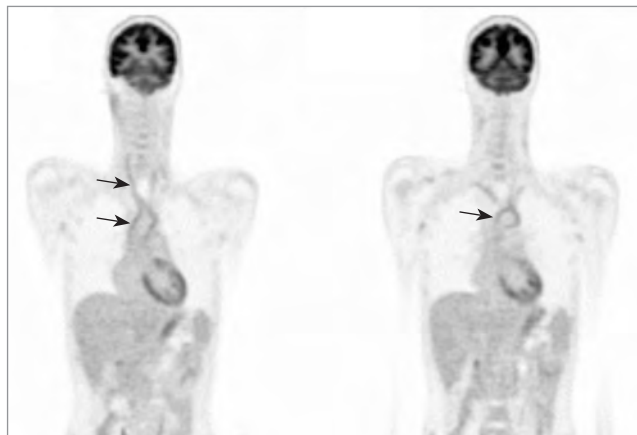


Figure 5. Fluorodeoxyglucose-positron emission tomography in a patient with Takayasu's arteritis showing enhancement of large vessel walls (arrows).

Treatment of large vessel vasculitis

Treatment of giant cell arteritis uses oral glucocorticoid monotherapy as the norm, with minimal data on corticosteroid-sparing agents such as methotrexate or azathioprine. Prednisolone is commenced at induction doses of 1 mg/kg per day; a gradual reduction can commence when symptoms resolve and laboratory values normalise. Intravenous methylprednisolone pulses may be required in patients whose vision is severely threatened.

The treatment of Takayasu's arteritis depends on disease severity. Patients are medically managed with glucocorticoids and additional agents such as methotrexate, azathioprine and mycophenolate; cyclophosphamide is used in severe cases. Strict blood pressure control is the other key management component, with some patients requiring antihypertensives. In certain patients with longstanding disease, surgical intervention with vascular grafts and bypass surgery may be required to relieve stenoses and occlusions.

Medium vessel vasculitis

Medium-sized vessels, such as those supplying the intra-abdominal organs and intestine, may also be targets for vasculitic inflammation.

Polyarteritis nodosa

Polyarteritis nodosa is a necrotising arteritis that affects medium-sized vessels. It is not associated with ANCA or glomerulonephritis but can be associated with immune complex deposition. Some of these immune complexes contain hepatitis B or other microbial antigens. Polyarteritis nodosa affects three times as many men as women and occurs generally between the ages of 40 and 50 years. Patients may present with abdominal pain after meals (termed mesenteric angina) and commonly have asymmetric peripheral polyneuropathy.

Kawasaki disease

Kawasaki disease is a medium vessel vasculitis that generally affects children under 5 years of age and leads to coronary artery aneurysms in 20 to 25% of patients. Annual incidence rates per 100,000 in the UK, USA and Japan are 8, 17 and 134, respectively, with a seasonal peak during winter and spring. The basis for ethnic and geographic variation is unknown. Aneurysms greater than 8 mm in diameter are at the highest risk of aneurysm thrombosis, coronary artery stenosis and subsequent myocardial infarction. Kawasaki disease is associated with mucocutaneous lymphadenopathy syndrome, and children can present with fever, palmar and plantar erythema, periungual desquamation, strawberry tongue, conjunctivitis, mucositis, rash and enlarged cervical lymph nodes.

In Kawasaki disease, combination treatment using prednisolone and intravenous immunoglobulin (IVIG) reduces the risk of coronary artery abnormalities when compared with corticosteroid use alone, and leads to quicker resolution of fever and normalisation of CRP level. Accordingly, Kawasaki disease is an approved indication for high-dose IVIG supply from the National Blood Authority of Australia. Aspirin treatment is also standard of care in affected children.

Primary angiitis of the central nervous system

Another medium vessel vasculitis is primary angiitis of the central nervous system, a rare disorder with an insidious onset. Patients may present with headaches, encephalopathy, dementia or stroke-like symptoms. Definitive diagnosis requires brain biopsy, although angiography may be suggestive; without treatment, the disease is usually fatal.

Small vessel vasculitis

ANCA-associated polyangiitis

GPA, MPA and EGPA are vasculitides that affect small intraparenchymal vessels such as arterioles, capillaries and venules (Box 2). These vasculitides characteristically lack immune complex deposition, and classification relies on ANCA status. ANCA-associated small vessel vasculitis is more common in adults aged between 50 and 60 years and affects both sexes equally.

EGPA presents with asthma, lung involvement and peripheral blood eosinophilia. It is a differential diagnosis in patients with poorly controlled asthma despite moderate-dose inhaled glucocorticoids. Patients with EGPA who are ANCA positive are more likely to have peripheral neuropathy, glomerulonephritis and purpura, whereas those who are ANCA negative are more likely to have heart involvement and lung infiltrates. Renal disease occurs in 50% of patients with EGPA.

Patients with GPA and MPA are generally positive for PR-3 and MPO ANCA, respectively, and tend to have both lung and kidney involvement. GPA is characterised by a necrotising granulomatous vasculitis of the upper and lower respiratory tract, and patients may present with sinus pain, nasal discharge, nasal

mucosal ulceration and haemoptysis. MPA has similar manifestations to GPA but does not cause granulomas.

Treatment of GPA, MPA and EGPA is discussed below.

Henoch–Schönlein purpura

Henoch–Schönlein purpura (also known as IgA vasculitis) is a small vessel vasculitis that manifests clinically with palpable purpura (predominantly seen on the extremities and buttocks, see Figure 3), abdominal pain, arthralgia, gastrointestinal complications and glomerulonephritis. Direct immunofluorescence testing of tissue specimens demonstrates IgA deposition in arteriolar walls and renal glomeruli. Henoch–Schönlein purpura occurs predominantly in children but can affect adults. The annual incidence rate in children is 14 per 100,000, peaking in winter. Renal disease in Henoch–Schönlein purpura mostly resolves but may progress in 10 to 20% of older children and adults. Overall, the prognosis is excellent and care is mainly supportive.

Investigations for suspected vasculitis

In patients suspected to have vasculitis, a prompt and definitive diagnosis before initiation of treatment often requires hospital admission for in-depth investigation. Recommended investigations include the following.

Blood tests

- ESR (often greater than 50 mm/h in patients with giant cell arteritis) and CRP level
- ANCA titre by indirect immunofluorescence
- MPO and PR-3 levels by immunoassays
- Eosinophil count (characteristically up to $9 \times 10^9/L$ in EGPA; correlates with disease activity)
- Investigations for associated conditions, such as hepatitis B and C
- Investigations to exclude similar clinical syndromes, such as antglomerular basement membrane syndrome.

Urinalysis

- Dipstick analysis, followed by formal urinalysis for proteinuria and dysmorphic, glomerular red cells.

Imaging

- Chest x-ray can show abnormalities such as nodules, cavities or fixed infiltrates.
- CT or MRA can visualise large vessel disease.
- Conventional angiography with injection of contrast is required to image smaller vessels, particularly intracerebral vessels.

Histopathology

- Diagnosis should be based on histological examination of tissue if possible.

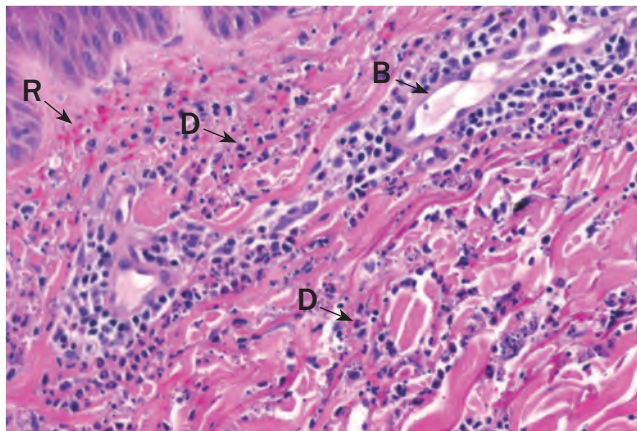


Figure 6. Skin biopsy specimen consistent with leucocytoclastic vasculitis, showing a blood vessel (B) surrounded by an inflammatory infiltrate (neutrophils and mixed inflammation), extravasated red blood cells (R) and neutrophilic nuclear dust, also known as leucocytoclasia (D).

Image courtesy of Dr Renn Montgomery, Department of Anatomical Pathology, Liverpool Hospital, Sydney, NSW.

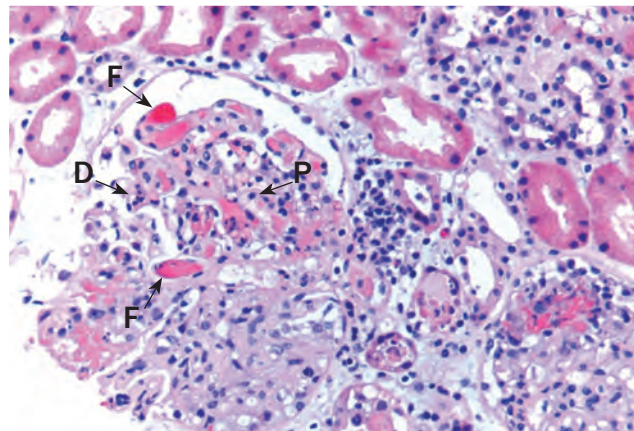


Figure 7. Renal biopsy specimen showing thrombotic microangiopathy with evidence of fibrin thrombi in capillaries (F), nuclear debris (D) and polymorphs (P).

Image courtesy of Dr Renn Montgomery, Department of Anatomical Pathology, Liverpool Hospital, Sydney, NSW.

- An inflammatory infiltrate, including T cells, macrophages and neutrophils, is seen around vessels (Figure 6) with fibrinoid necrosis of the vessel walls.
- Skin biopsy specimens should be sent both fresh in normal saline and fixed in formalin for immunofluorescence and histopathology, respectively.
- Renal biopsy specimens may show focal segmental glomerulonephritis or, in exceptional cases, thrombotic microangiopathy (Figure 7).

Additional tests

- Respiratory function tests are valuable when there is lung involvement, and bronchoalveolar lavage may be helpful.
- Echocardiography, electrocardiography and cardiac MRI are useful to determine the degree of involvement, to look for complications of vasculitis and to exclude mimics such as endocarditis.
- Blood cultures can exclude some infections, which may present with similar symptoms to vasculitis.
- FDG-PET may highlight sites of involvement but can also reveal alternative causes for the presentation, including malignancy.
- Nerve conduction studies can reveal damage to peripheral nerves from ischaemia.

Assessing severity

The two main scoring systems used for vasculitis are the Five-Factor Score and the Birmingham Vasculitis Activity Score (mainly used for research). The Five-Factor Score, revised in 2011, includes the following criteria, which are associated with

a higher five-year mortality rate:⁴

- age over 65 years
- presence of cardiac involvement
- presence of renal insufficiency (peak serum creatinine level greater than 150 $\mu\text{mol/L}$)
- presence of gastrointestinal involvement
- absence of ear, nose and throat involvement.

The five-year mortality rates for patients with zero, one and two or more of these criteria are 9%, 21% and 40%, respectively.

Specialist referral

Specialist management is recommended for patients suspected to have any of these vasculitides, and urgent referrals are necessary for patients with life- or organ-threatening involvement. The specialty chosen depends on the main organ affected; however, management often requires multidisciplinary input because of the multisystem nature of the disease. Specialties involved in the care of a patient with vasculitis may include immunology, rheumatology, neurology, nephrology and respiratory medicine. Dermatological presentations are also common.

Treatment of ANCA-associated vasculitis

Although the following discussion focuses on treatment of ANCA-associated vasculitis, treatment options may be applicable to other vasculitides, depending on disease severity.

The treatment strategy for ANCA-associated vasculitis aims to control disease and minimise treatment toxicity by:

- inducing remission using intensive immunosuppression
- then introducing tapering maintenance therapy for a minimum of 18 months.

4. INDUCTION THERAPY	5. MAINTENANCE THERAPY	6. COMPLICATIONS OF TREATMENT
<p>Early or limited disease</p> <ul style="list-style-type: none"> • Glucocorticoids alone • Methotrexate alone • Trimethoprim–sulfamethoxazole alone (rarely used) <p>Generalised disease</p> <ul style="list-style-type: none"> • Rituximab or cyclophosphamide in combination with glucocorticoids <p>Generalised disease with rapidly progressive glomerulonephritis or alveolar haemorrhage</p> <ul style="list-style-type: none"> • Rituximab or cyclophosphamide in combination with glucocorticoids • Consideration of plasmapheresis <p>Relapse</p> <ul style="list-style-type: none"> • Rituximab and glucocorticoids 	<p>Localised disease</p> <ul style="list-style-type: none"> • Low-dose glucocorticoids alone • Methotrexate alone • Trimethoprim–sulfamethoxazole alone (rarely used) <p>Generalised disease</p> <ul style="list-style-type: none"> • Azathioprine or methotrexate in combination with low-dose glucocorticoid • Mycophenolate in combination with low-dose glucocorticoids as second-line treatment <p>Alternative agents</p> <ul style="list-style-type: none"> • Repeated doses of rituximab • Four-weekly intravenous immunoglobulin 	<p>Azathioprine and methotrexate: liver dysfunction, delayed hypersensitivity reaction, myelosuppression</p> <p>Cyclophosphamide (usually managed by hospital specialists): leucopenia, renal impairment, infertility, hair loss, mouth ulcers, bladder cancer, haemorrhagic cystitis</p> <p>Mycophenolate: myelosuppression, gastrointestinal side effects including vomiting and diarrhoea</p> <p>Trimethoprim–sulfamethoxazole: rash, nausea, interstitial nephritis, hepatotoxicity</p> <p>Corticosteroids: osteoporosis, hyperglycaemia, hypertension, weight gain, mood disturbance, adrenal suppression or crisis, avascular necrosis</p>

Despite improvements in treatment, recurrence is common, and further induction therapy may be necessary.

Screening before immunosuppression

Because of the potential for latent infections to reactivate during immunosuppression, patients should be screened for HIV infection, hepatitis B and C and, if from endemic areas, tuberculosis and *Strongyloides* infestation. Screening for sexually transmitted diseases including syphilis may be appropriate in some patients.

Although reactivation of hepatitis B in patients who have previously cleared the virus is infrequent, prophylaxis with lamivudine or entecavir is still recommended during immunosuppression and for three months following treatment. In patients who are at high risk of reactivation, hepatitis B viral load monitoring is also recommended.

In patients with hepatitis C, RNA polymerase inhibitors such as sofosbuvir, and protease inhibitors are potentially curative. In the future, their use may become the standard of care in patients with hepatitis C who require immunosuppression.

Patients with latent tuberculosis may require single-agent isoniazid prophylaxis when treated with potent immunosuppression.

Induction therapy

The choice of induction agent depends on the likelihood of irreversible organ damage. Common regimens may include methylprednisolone, cyclophosphamide, rituximab and high-dose IVIG, with consideration given to plasmapheresis (Box 4).⁵

Rituximab is a monoclonal antibody that binds to the cluster of differentiation 20 (CD20), a marker found on B cells, which leads to temporary B cell depletion. Randomised controlled trials

comparing rituximab and cyclophosphamide have shown comparable efficacy in inducing remission in organ-threatening systemic vasculitis.⁶ However, both rituximab and cyclophosphamide can potentially result in the serious complication of irreversible progressive multifocal leukoencephalopathy, a rare terminal process that affects cerebral white matter due to reactivation of polyoma John Cunningham (JC) virus. JC virus infection is common and harmless in immunocompetent people but can become life-threatening in those who are immunocompromised. Informed consent prior to immunosuppression requires an appreciation of both the risks associated with treatment and the risks to vital organs without adequate treatment.

Rituximab is a preferred option in young women wishing to retain fertility, as cyclophosphamide and other alkylating agents can lead to premature menopause. Cyclophosphamide can also be associated with haematological suppression and late malignancy, principally bladder cancer, and the idiosyncratic complication of haemorrhagic cystitis, which can be delayed in onset.

A study of remission rates after cyclophosphamide therapy found that pulsed intravenous cyclophosphamide given every three to four weeks was not inferior to daily oral cyclophosphamide.⁷ There were no significant differences between the two regimens in mortality, renal function, end-stage renal disease or adverse events. Although pulsed cyclophosphamide is associated with a higher relapse rate, it is generally preferred in clinical practice because of the lower cumulative dose compared with daily oral dosing.

Mycophenolate, which does not have genotoxic effects on chromosomes but is teratogenic, is an alternative induction agent

if cyclophosphamide toxicity or rituximab-induced immunosuppression are considered unacceptable.

During the induction period, when immunosuppression is deepest, trimethoprim–sulfamethoxazole is used to prevent *Pneumocystis jirovecii* pneumonia. Trimethoprim–sulfamethoxazole has also been used alone as an induction agent in patients with limited, local upper airways disease, but relapse rates are high.

In ANCA-associated vasculitis, patients presenting with renal failure (serum creatinine level > 500 µmol/L) had a reduced risk of progression to end-stage renal disease when plasmapheresis was used in conjunction with cyclophosphamide.⁸ However, overall survival and severe adverse events were similar when compared with combination methylprednisolone and cyclophosphamide.

IVIg is a useful option in patients who are unable to tolerate other agents or have complications such as recurrent infections.

Maintenance therapy

After induction of remission, 18 to 24 months of maintenance therapy is required to reduce the rate of relapse (Box 5). Azathioprine is not inferior to daily oral cyclophosphamide in maintaining remission and is the preferred option, at a dose of 2mg/kg per day only for those with normal thiopurine methyltransferase levels. Patients with low thiopurine methyltransferase levels would require much lower doses of azathioprine in consultation with haematological expert monitoring. Methotrexate has similar efficacy to azathioprine and is an alternative.

The French Vasculitis Group recently found rituximab 500 mg (given as a loading dose at weeks 0 and 2, then at six-monthly intervals) to be more efficacious in maintaining remission than daily azathioprine.⁹ However, its routine use is not currently recommended because of a lack of reliable guidelines and long-term safety data for repeat rituximab dosing.

Long-term, low-dose glucocorticoids may alter disease activity and reduce relapse rates but are associated with increased morbidity due to corticosteroid-related complications. Their use is therefore minimised if possible.

Mycophenolate is associated with higher relapse rates than azathioprine and is generally used only when other options are not appropriate. Trimethoprim–sulfamethoxazole is superior to placebo in preventing relapse in patients with limited upper airway involvement but is ineffective if other organs are involved.

Treatment in pregnancy

Many immunosuppressive agents are either teratogenic or can cause abortions. Female patients are advised to use reliable contraceptive measures during the course of immunosuppression, and pregnant patients are treated in close consultation with obstetricians.

Natural history and risk factors for relapse

The natural history of vasculitis can follow several different paths, including:

- a relapsing–remitting course (ANCA-associated vasculitis)
- spontaneous resolution with complications (Kawasaki disease) or
- acute episodes that are self-limited and generally do not have long-term sequelae (Henoch–Schönlein purpura).

Relapse is common in ANCA-associated vasculitides, even with adequate induction and maintenance therapy. Relapse often occurs during glucocorticoid taper or after cessation of maintenance therapy. Relapse rates are higher in patients with GPA and MPA, those who are PR-3 antibody positive, and those with inadequate induction or early withdrawal of immunosuppression. A persistently elevated or rising anti-MPO or anti-PR-3 level may predict relapse, but relapses can also occur without warning.

Monitoring by GPs

GPs should be aware of the potential complications of vasculitis treatments (Box 6). They should also be aware of the complications common to all forms of immunosuppression, such as increased risk of skin cancer, infection and cardiovascular disease from chronic inflammation.

Patients taking long courses of corticosteroids are at risk of adrenal crisis during dose reduction or accidental omission and should have a corticosteroid action plan for situations including acute infection or surgery. Monitoring for corticosteroid-induced osteoporosis requires serial bone mineral density scans. Calcium and vitamin D supplementation are routine in the setting of corticosteroid therapy.

Prophylaxis against multiple pathogens may be needed during immunosuppression; trimethoprim–sulfamethoxazole is routinely used for primary prophylaxis against *Pneumocystis*, and patients with shingles may require secondary prophylaxis against herpes zoster. Febrile neutropenia in an immunosuppressed patient is a medical emergency that requires hospital admission for intravenous antibiotics.

Other precautions for patients who are immunosuppressed include avoiding drug interactions with immunosuppressants and, importantly, avoiding live vaccines. Cancer screening, such as skin checks and regular Pap smears, are useful for detecting early premalignant change.

Recurrence of symptoms, particularly those associated with a patient's original presentation, suggests a vasculitis flare and requires prompt liaison with the treating specialist.

Conclusion

The vasculitides are an important and heterogeneous group of conditions. Patients can present with protean symptoms and signs. GPs should be particularly alert for patients with an atypical disease course, such as asthma, sinusitis or lower respiratory tract

infection that does not respond to empirical measures, as undiagnosed vasculitis may mimic these conditions. Symptoms and signs such as palpable purpura, mononeuropathy, haemoptysis, abnormal dipstick urinalysis results, visual deterioration or monocular blindness should immediately prompt GPs to seek urgent specialist referral for further investigation and early treatment of vasculitis.

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ACKNOWLEDGEMENTS: We thank Dr Renn Montgomery, Liverpool Hospital, Sydney, NSW, and Dr Jessie Lee, Royal Prince Alfred Hospital, Sydney, NSW, for the histopathology and immunofluorescence images, respectively.

COMPETING INTERESTS: None.

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