Small vessel vasculitides

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Abstract

There are two major groups of small vessel vasculitides: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) and immune complex vasculitides. AAVs are the most common small vessel vasculitides and have benefited the most from recent advances with large randomized controlled trials. Rituximab now plays an important role in both induction and maintenance treatment of this relapsing–remitting condition. More recent developments include the introduction of avacopan as a steroid-sparing agent and indications for plasma exchange in AAVs. Immune complex vasculitides are associated with immune complex deposition in the vasculature. They include antiglomerular basement membrane disease, which is rare and usually presents with pulmonary–renal syndrome, IgA vasculitis, the most common systemic vasculitis in children, and vasculitides secondary to systemic immune complex diseases.

Keywords Antiglomerular basement membrane disease; antineutrophil cytoplasmic antibodies; cryoglobulinaemic vasculitis; eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); granulomatosis with polyangiitis (Wegener granulomatosis); Henoch–Schönlein purpura; IgA vasculitis; microscopic polyangiitis; MRCP; vasculitis

Key points

- Rapid diagnosis and treatment are important to prevent organ damage in patients with systemic vasculitis
- There have been significant developments in the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in recent years, including the introduction of avacopan and the development of separate guidelines for the treatment of eosinophilic granulomatosis with polyangiitis
- Relapses are common in ANCA-associated vasculitis, and treatment duration must be tailored to the individual
- IgA vasculitis (Henoch–Schönlein purpura) is the most common cause of systemic vasculitis in children and does not usually require immunosuppressive treatment
- Cryoglobulinaemia and infectious causes of small vessel vasculitis must be considered when associated with low complement concentrations

Introduction

The 2012 Chapel Hill Consensus Conference classifies vasculitis depending on size of the vessel affected. Small vessel vasculitides are divided into antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) and immune complex vasculitides and are causes of rapidly progressive glomerulonephritis (RPGN).

AAVs, the most common small vessel vasculitides, are strongly associated with ANCA; they are pauci-immune, with limited microscopic evidence of immune complex deposition. In comparison, immune complex vasculitides are associated with immune complex deposition in the vasculature; these include antiglomerular basement membrane (GBM) disease, immunoglobulin (Ig) A vasculitis (Henoch–Schönlein purpura) and vasculitides secondary to systemic immune complex diseases such as systemic lupus erythematosus (SLE), dysproteinaemias, cryoglobulinaemias and chronic infections.

This article describes recent advances in understanding the pathogenesis of these conditions and reviews common presentations. Recent clinical trials and disease management are considered.

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Investigations in small vessel vasculitides

There are no diagnostic criteria for small vessel vasculitides. A combination of clinical assessment and serological testing is needed, and tissue biopsy should be considered for diagnosis.

Routine laboratory investigations: common abnormalities include leucocytosis, thrombocytosis (>400,000/mm^3), normochromic, normocytic anaemia and elevation of inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein. Complement concentrations are typically normal in AAVs and IgA vasculitis; however, C4 is low in cryoglobulinaemias, C3 is often low in anti-GBM disease and can be associated with disease severity, and both C3 and C4 can be low in SLE.

Urinalysis: an active urinary sediment with red blood cells and casts indicates glomerular disease. Proteinuria is often present, although usually not in the nephrotic range. Active renal disease can be present even if creatinine and urea results are normal; therefore, in the context of suspected vasculitis with microscopic haematuria and proteinuria, the threshold for renal biopsy should be low.

ANCAs: these antibodies are a very useful marker for the diagnosis of AAV but are not diagnostic. Systemic granulomatosis with polyangiitis (GPA) is associated with proteinase 3 (PR3)-ANCA (75%); however, in limited GPA, ANCA is negative in

40% of patients. Myeloperoxidase (MPO)-ANCA is usually associated with microscopic polyangiitis (MPA) (60%), although PR3-ANCA can also occur (Table 1). Only 30–40% of patients with eosinophilic GPA (EGPA) are ANCA positive, mainly MPO-ANCA. Positive ANCA serology can also occur in clinical contexts such as subacute bacterial endocarditis, other infections, medications (including propylthiouracil, carbimazole, hydralazine and minocycline), illicit substances (such as cocaine and levamisole), and inflammatory bowel disease.

Anti-GBM antibodies: these are highly sensitive and specific for anti-GBM disease.

Other autoantibodies: antineutrophil antibodies, anti-double-stranded DNA and anti-extractable nuclear antigen antibodies are commonly requested to rule out other autoimmune disease such as SLE.

Cryoglobulins: cryoglobulins can be isolated when a warm blood sample is delivered to the laboratories. Tests to rule out a plasma cell dyscrasia are usually also sent, including for immunoglobulins and serum free light chains and serum protein electrophoresis.

Chest radiography: pulmonary haemorrhage is most commonly seen in AAV and anti-GBM disease (Figure 1) associated with low haemoglobin, low arterial partial pressure of oxygen (PO_2) and raised corrected transfer factor. It also occurs rarely in other vasculitides. In GPA, chest radiography commonly shows pulmonary nodules that often cavitate. Other radiographic features

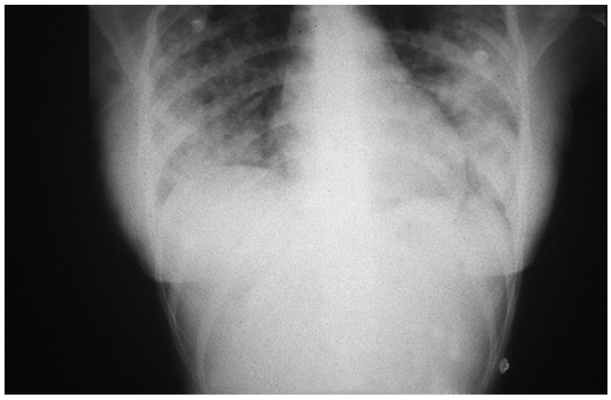

Figure 1 Portable chest radiograph of a man with acute pulmonary haemorrhage, showing bilateral interstitial shadowing.

Differential diagnosis of pulmonary–renal syndrome

Disease	Vasculitis	Granulomas	ANCA status	Features
GPA	Present	Present	PR3-ANCA (75%)	Nose and sinuses, lungs, kidneys (70%), joints, eyes
MPA	Present	Absent	MPO-ANCA (60%)	Kidneys (>90%) – RGPN (65%)
EGPA	Present	Present	Only 30% ANCA positive (90–100% MPO-ANCA)	Lungs, upper airways, peripheral nerves, heart, skin, kidneys (25%)
Anti-GBM disease	Present	Absent	Sometimes positive (10–38%)	Linear IgG deposition on the GBM Anti-GBM antibody positive (rare cases of negative circulating anti-GBM antibody) Acute renal failure and pulmonary haemorrhage
SLE	Present	Absent	Seldom positive	Antinuclear factor and anti-dsDNA positive Low C3 and C4
IgA vasculitis	Present	Absent	Negative	Lung involvement uncommon IgA deposition in vessel walls and mesangium
Behçet's disease	Present	Absent	Negative	Diagnosed on clinical criteria Associated with recurrent oral and genital ulceration, eye lesions (including uveitis) and skin lesions; renal involvement usually mild. Lung involvement is less common
Infection	Rarely present	Absent	Negative but can be positive and associated with immune complex glomerulonephritis	Pneumonia can be associated with acute tubular necrosis or interstitial nephritis (rarely) Subacute bacterial endocarditis is rarely associated with ANCA-negative pauci-immune glomerulonephritis Post-streptococcal glomerulonephritis Blood cultures, atypical serology and anti-streptolysin O titre should be undertaken

dsDNA, double-stranded DNA.

Table 1

include reticulonodular shadowing, pneumonic changes, collapse and pleural involvement with effusions. Individuals with MPA can have evidence of fibrosis and interstitial lung disease, this occurs in 15% of cases.

Renal biopsy: biopsy remains the gold standard for diagnosing small vessel vasculitides and is recommended for establishing a new diagnosis and relapse in AAV.

Other tissue biopsies: nasopharyngeal or transbronchial biopsy often shows non-specific inflammation in GPA. Skin biopsy can be useful in IgA vasculitis.

Ruling out chronic infections: tests for HIV, hepatitis B and hepatitis C screening, blood cultures, and echocardiography with or without further imaging should be performed as appropriate.

ANCA-associated vasculitis

AAVs are categorized into three groups based on patterns of clinical involvement: GPA (formerly known as Wegener granulomatosis), MPA and EGPA (formerly known as Churg–Strauss syndrome). EGPA is probably best considered as a distinct disease and will be discussed separately from GPA and MPA. Treatment involves induction of remission followed by maintenance treatment. Duration of treatment must balance relapse risk with managing drug toxicity.

Epidemiology

The global prevalence of AAV is estimated to be 198 cases per million people. In the UK, the estimated prevalence is 135 cases per million people. The incidence and prevalence of AAV are both increasing because of improvements in disease recognition through ANCA testing, alongside advances in treatment. AAV occurs at any age, including childhood, but is most common in older adults (peak age of onset 65–74 years). It affects male and female patients equally.

Aetiology and pathogenesis

The aetiology of AAV is complex and includes a combination of genetic factors and environmental triggers.

While AAVs are not inherited diseases, genome-wide association studies have shown associations between PR3-ANCA, α_1-antitrypsin, PR3 itself and human leukocyte antigen (HLA)-DP, while polymorphisms in *HLA-DQ* are associated with MPO-AAV.

AAV can be caused by exposure to drugs, including levamisole-contaminated cocaine, propylthiouracil, minocycline, penicillamine, hydralazine and immune check point inhibitors (especially PD-1 inhibitors). There are case reports of anti-tumour necrosis factor (TNF)-α monoclonal antibodies very rarely causing AAV. Patients with drug-induced AAV can have atypical patterns of ANCA positivity; there should be a low threshold for suspecting drug-induced AAV in younger patients with symptoms of upper respiratory tract-limited vasculitis who are ANCA positive. Infectious agents have been implicated as initiators of vasculitis; nasal carriage of *Staphylococcus aureus* has been associated with relapse in GPA. Environmental exposure to smoking and silica has been associated with an increased risk of AAV.

Research in animal models and using patient samples *in vitro* suggests that ANCA are not only a useful diagnostic test but are key to the pathogenesis of AAV. PR3 and MPO are normally intracellular components. Excessive presentation of PR3 or MPO autoantigens to the immune system and loss of tolerance leads to ANCA production. ANCA then binds to either PR3 or MPO on cytokine-primed monocytes and neutrophils, causing excessive activation and adhesion to endothelial cells; damage is then caused along with activation of the alternate complement system. Blockade of complement C5a and its receptor has been shown to ameliorate the disease. Production of autoantibodies necessitates the involvement of B cells, which are also key to pathogenesis.[1]

Pathology

AAV is characterized by inflammation and necrosis of capillaries, arterioles and venules, but can also affect larger vessels. In the kidney, the process leads to focal segmental necrotizing glomerulonephritis with crescent formation, but with little or no immunoglobulin deposition. There is often associated interstitial inflammation. In the lung, the findings are usually of capillaritis, often associated with lung haemorrhage. Granulomas (focal aggregates of macrophages and T cells) occur in GPA, but not in MPA; in the upper airways this granulomatous reaction can present as ulceration.

Clinical features

The clinical manifestations of AAV largely depend on the vascular bed affected, but the lungs and kidneys are the most commonly involved organs. The differential diagnosis of this syndrome is wide (Table 1). Systemic non-specific symptoms such as malaise, flu-like symptoms, fatigue and weight loss are common in AAV, and can pre-date other symptoms. The main characteristics and differences between GPA and MPA are summarized in Table 1.

Specific organ involvement

Pulmonary involvement occurs at some stage in 85% of patients with GPA. They can present with asymptomatic pulmonary infiltrates or with symptoms such as cough, haemoptysis, pleuritis or dyspnoea.

Renal disease can range from an active urinary sediment (containing red cells and casts) with normal renal function, to RPGN with severe damage, common in both GPA and MPA. 'Renal limited vasculitis', with characteristic features of pauci-immune necrotizing glomerulonephritis, can occur, more commonly with MPO-ANCA.

Upper respiratory tract disease is primarily seen in GPA and presents as sinusitis, epistaxis, otitis media, hoarseness and stridor. Retro-orbital masses with proptosis are often associated with extensive sinus disease. Complications of granulomatous inflammation can cause mucosal ulceration and nasal septal perforation with a saddle nose. Subglottic stenosis, which can become scarred and irreversible, occurs in up to 16% of adults and 48% of children.

Other organs can also be involved. Ocular involvement is common, presenting with conjunctivitis, scleritis or uveitis. Optic nerve vasculitis and retinal artery thrombosis are rare but important complications. Loss of sight has been reported in 8%

of patients. Non-erosive arthritis occurs in up to 28% of patients. Skin disease, seen in up to 50% of patients, can manifest as palpable purpura, ulcers and subcutaneous nodules. Involvement of the nervous system (mononeuritis multiplex, peripheral neuropathy), gastrointestinal tract (haemorrhagic ulceration, bowel perforation) and heart (coronary arteritis) can also occur; these are severe manifestations and require prompt treatment to avoid irreversible organ damage.

Management

AAV must be recognized and treatment initiated early. A prolonged time to remission increases the risk of death and damage. The treatment of AAV is divided into two phases: induction of remission and maintenance of remission. Relapses are common, necessitating long-term treatment and follow-up.[2]

Induction of remission: has changed significantly in recent years informed by clinical trials. Previously, standard induction for organ- or life-threatening disease was achieved with high-dose corticosteroids plus pulsed cyclophosphamide. Randomized controlled trials (RCTs) have subsequently established B cell depletion with the anti-CD20 monoclonal antibody rituximab, in combination with corticosteroids, as non-inferior to cyclophosphamide-based regimens when used as induction treatment and possibly superior in relapsing disease. Rituximab is advantageous in that it is not known to promote malignancy or reduce fertility.

Increasingly, clinical trials are showing that lower doses of corticosteroids are associated with less toxicity but no loss of efficacy. The PEXIVAS and LoVAS trials demonstrated that lower cumulative corticosteroid doses were non-inferior to standard treatment but associated with lower rates of severe infections. Intravenous methylprednisolone is frequently used, although its use is not evidence based and it is likely to contribute to glucocorticoid toxicity.

More recently, the ADVOCATE trial has shown that the C5a receptor inhibitor avacopan plus either cyclophosphamide or rituximab without the use of corticosteroids may be better at maintaining remission at 12 months than corticosteroid regimens. However, in this study the prednisolone was stopped at 6 months, while avacopan was continued. Post-hoc analysis also revealed that avacopan may lead to a greater improvement in estimated glomerular filtration rate (eGFR) than corticosteroids when the baseline eGFR is 15–20 ml/minute/1.73 m^2 (the trial excluded patients with an eGFR <15 ml/minute/1.73 m^2). Avacopan is now licensed for use under expert supervision in the UK.

A recent meta-analysis of plasma exchange (PEX) has suggested that, while PEX has no effect on mortality or pulmonary haemorrhage, it reduces the risk of developing end-stage kidney disease (ESKD) in individuals with more severe renal involvement within 12 months; however, it also increases the risk of infection. Thus, there may be a role for PEX when used judiciously, balancing the risks and potential benefits. Current Kidney Disease Improving Global Outcomes (KDIGO) guidance is to consider PEX when serum creatinine is >300 micromol/litre. PEX should also be offered to all patients with an overlap syndrome of AAV and anti-GBM disease.[3]

Maintenance of remission: regimens are started once remission has been achieved, which usually occurs by 3–6 months. If corticosteroids have been used, tapering should continue as per the PEXIVAS low-dose steroid trial schedule.

Rituximab is fast becoming the mainstay of maintenance treatment. Two RCTs (MAINRITSAN, RITAZAREM) have shown superiority of rituximab maintenance treatment at a fixed interval dosing compared with azathioprine.

Where rituximab is not tolerated or is contraindicated, azathioprine and methotrexate are equally effective. Methotrexate should not be used if the eGFR is <60 ml/minute/1.73 m^2. Mycophenolate mofetil should be reserved for patients intolerant of azathioprine, rituximab and methotrexate.

The duration of maintenance therapy is unclear but should be at least 18 months and usually not more than 4 years. A recent pooled analysis of the three MAINRITSAN trials confirmed that a minimum of 18 months' treatment gives the best outcome, while 4 years' therapy is preferable in individuals treated with azathioprine.

Relapse: this is common, especially with PR3-ANCA disease; 50% of patients relapse within 5 years of diagnosis. Relapse can occur at any time, and patients should be reviewed regularly (3-monthly) to detect early signs of disease recurrence and drug toxicity. Relapse occurs more commonly in individuals who are PR3-ANCA positive, have cardiovascular organ involvement or have a lower serum creatinine at presentation. Indicators of relapse include:

- recurrence of symptoms (which can differ from the original presentation)
- rising inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) in the absence of infection
- recurrence of or rising ANCA titre
- reappearance of haematuria and/or granular casts in the urine
- increased serum creatinine
- Increasing levels of proteinuria.

After a major relapse, induction therapy as described above should be restarted, preferably with rituximab as the RAVE trial showed this to be more effective. Repeated pulses of cyclophosphamide should be avoided because of the risk of malignancy associated with higher cumulative doses (>25 g). A minor relapse may be managed by increasing the corticosteroid dosage. Escalation of therapy should not be based solely on a rising ANCA titre, but this may prompt more frequent review.

Prognosis

Survival is currently 80% at 5 years, with infection the most common cause of death. Poor prognostic indicators include greater age, pulmonary haemorrhage and severe renal disease. ESKD occurs in 20–25% of patients. Consensus opinion suggests that patients who develop ESKD can be considered for transplantation but should not be listed until 1 year after disease remission. Continued ANCA positivity is not a contraindication to transplantation.

Eosinophilic granulomatosis with polyangiitis

EGPA is a rare multisystem disease classified among both hypereosinophilic disorders and AAV. It is the rarest of the AAVs, with an incidence of 1–3 per million people. It is typically

diagnosed at a younger age than other AAVs and peaks around middle age.

Vessel inflammation alongside blood and tissue eosinophilia are the hallmarks of the disease and the main cause of organ damage. It is increasingly recognized that there are two distinct disease phenotypes according to ANCA status: the ANCA-negative subset with predominantly eosinophil-driven disease manifestations, and the ANCA-positive subset with predominantly vasculitic manifestations. Only 30–40% of patients with EGPA have ANCA, most commonly MPO-ANCA.

Although the pathogenic role of MPO-ANCA has not been as clearly demonstrated in EGPA, it is presumed that the mechanism is similar to that in MPA.

Clinical features of EGPA classically evolve through an allergic phase characterized by asthma (>90%) and rhinosinusitis, an eosinophilic phase with blood and tissue eosinophilia, and a vasculitic phase with organ involvement secondary to small vessel vasculitis. However, these phases can overlap and may not be clearly defined. Asthma is often more severe in the weeks preceding the development of the vasculitis and it can be very difficult to differentiate from hypereosinophilic syndrome, especially if ANCA is negative.

EGPA is usually associated with blood eosinophilia ($>1.5 \times 10^9$/litre) and elevated IgE concentrations. Eosinophilic disease features include lung infiltrates, myocardiopathy and gastrointestinal manifestations. Cardiac involvement can also manifest as coronary artery vasculitis and myocardial infarction; it is more common in ANCA-negative patients and carries a poor prognosis. Gastrointestinal involvement can present in various ways with pain, diarrhoea and ascites. Vasculitic features of EGPA include a purpuric rash, neuropathy and RPGN; a rash and mononeuritis multiplex are common presenting features. Renal involvement is present in about 25% of patients and is a bad prognostic factor. Although clinical features typical of vasculitis, such as glomerulonephritis or neuropathy, are observed more frequently in ANCA-positive EGPA, they are also observed in ANCA-negative EGPA.

Treatment guidelines specific for EGPA are now available, informed by three recent RCTs (Figure 2).[4] Management is guided by the Five Factor Score (FFS), which comprises:

- renal dysfunction (serum creatinine >140 micromol/litre)
- proteinuria >1 g/day
- cardiomyopathy
- gastrointestinal involvement
- central nervous system (CNS) involvement.

An FFS score ≥1 is considered to represent severe disease that requires aggressive treatment. However, the recent European Alliance of Associations for Rheumatology (EULAR, formerly the European League Against Rheumatism) guidelines highlight important manifestations of EGPA that require aggressive treatment but are not included in the FFS score and should be considered in treatment decisions; these include the presence of peripheral neuropathy, alveolar haemorrhage or ocular involvement.

Induction of EGPA is achieved with high-dose corticosteroids as the mainstay of treatment. If the FFS score is ≥1, or there are additional manifestations as listed above, cyclophosphamide or rituximab should be used in conjunction with corticosteroids.

Maintenance of remission is achieved with continuing corticosteroids but relapse rates are high in EGPA. However, trials using anti-IL5 monoclonal antibodies have suggested benefit. The MIRRA RCT showed that 50% of EGPA patients given mepolizumab 300 mg subcutaneously every 4 weeks in addition to the standard of care achieved remission compared with only 19% given standard care alone. Mepolizumab also allowed for a reduction of the prednisolone dose required to maintain remission. In those with severe disease (FFS ≥1), corticosteroids plus rituximab ± mepolizumab should then be used. More recently, benralizumab, an anti-IL5α receptor antibody, was shown to be non-inferior to mepolizumab to induce remission in refractory or relapsing EGPA, providing another treatment avenue.

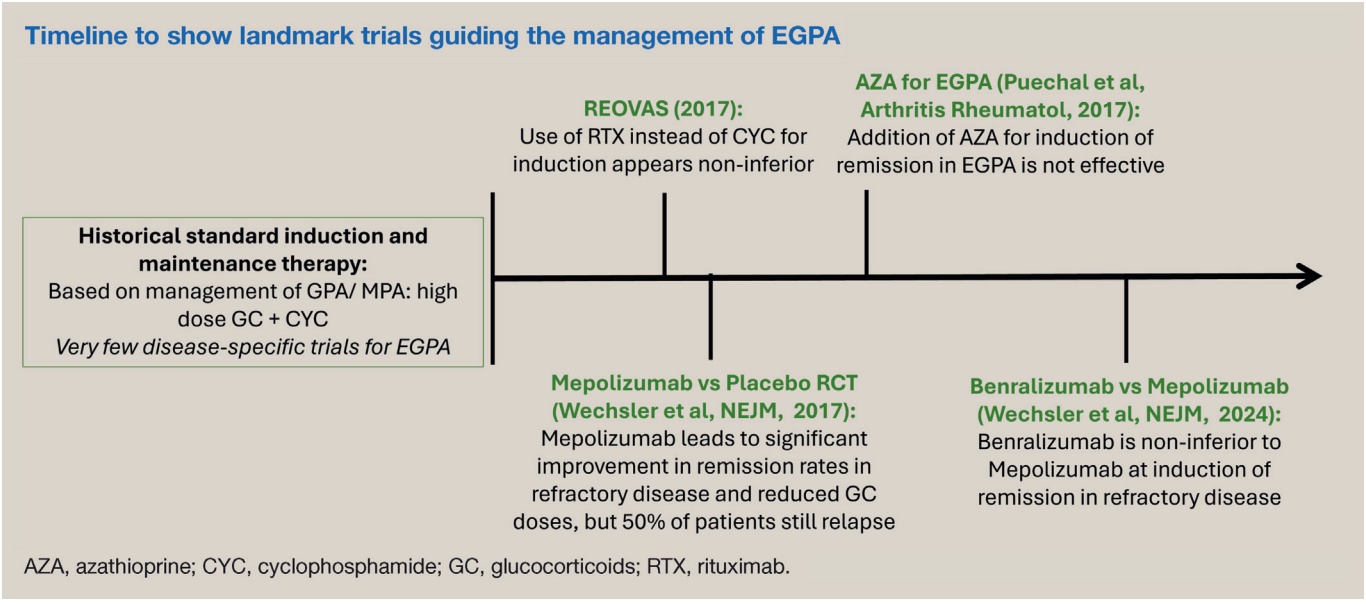

Figure 2

Azathioprine and methotrexate are also used for maintenance of remission but there is little evidence of benefit.

There are currently no reliable biomarkers of disease severity in EGPA and patients can relapse even with low eosinophil counts. Hence, regular clinical assessment to identify signs of relapse is critical.

Immune complex-associated vasculitides

Anti-GBM disease (Goodpasture syndrome)

Anti-GBM disease is a rare autoimmune condition (incidence approximately 1 per million per year). A bimodal age distribution peaks in the third and sixth to seventh decades. A unique feature of anti-GBM disease is that it tends to cause a single isolated period of illness and does not commonly cause relapses. The focus is to therefore treat the disease rapidly to prevent irreversible damage.

Environmental factors that lead to exposure of alveolar capillaries to the immune system may be important in its aetiology; these include smoking, cocaine inhalation, infections (such as influenza and SARS-CoV-2 (COVID-19)), and exposure to organic solvents, metal dust and hydrocarbons. Alemtuzumab, a lymphocyte-depleting agent used to treat multiple sclerosis, has been associated with triggering disease. There is evidence that HLA-DRB1 and HLA-DR15 confer an increased risk of the development of anti-GBM disease.

The autoantigen is the non-collagenous domain of the $\alpha 3$ chain of type IV collagen, which is found in the basement membrane of the lung and kidney. It is hypothesized that these antigens become exposed to the immune system by damage to the basement membrane (whether by toxins, mechanical damage (lithotripsy) or AAV), leading to loss of tolerance in susceptible individuals.

Clinical manifestations involve approximately 60–80% of patients developing rapidly progressive renal dysfunction associated with haematuria and non-nephrotic-range proteinuria; 50% present with pulmonary haemorrhage; 20–40% present with renal disease only; and 10% present with isolated lung involvement. Approximately 15% of patients present with haematoproteinuria with normal kidney function that can rapidly deteriorate (creatinine concentration can double within a few days).

Kidney biopsies show crescentic glomerulonephritis with linear deposition of IgG on the GBM, and anti-GBM antibodies are detectable in the serum. Crescents are most often uniform in age unlike other causes of RPGN. A significant proportion (10–38%) of patients with anti-GBM disease also test positive for ANCA (usually MPO-ANCA); these patients are more likely to relapse with a similar frequency to that of patients with MPA, unlike single-positive anti-GBM, which rarely relapses. Patients requiring dialysis at presentation have a poor renal prognosis (8% renal survival at 1 year in one series). However, rapid treatment can lead to good outcomes in individuals who are not dialysis dependent.

Treatment of anti-GBM disease aims to remove the pathogenic autoantibodies from the circulation, reduce inflammation and stop further production of autoantibodies. Treatment is based largely on historical comparisons and results obtained in studies of other forms of vasculitis and glomerulonephritis.

Rapid removal of autoantibodies is usually achieved with daily plasmapheresis over a 2–3-week period until the autoantibody concentrations are below the normal range or just detectable. High-dose corticosteroids together with cyclophosphamide are given to prevent the formation of further autoantibodies. Cyclophosphamide can usually be discontinued by 3–6 months without maintenance therapy, with a slow taper of corticosteroids over 6–9 months. However, 'double-positive' patients with MPO-ANCA as well as anti-GBM antibodies are usually given longer term maintenance immunosuppression similar to AAV, as their ANCA disease can relapse.

Some small case series are using rituximab to treat anti-GBM disease. Emerging trials are investigating the use of the endopeptidase imlifidase, which is currently used in renal transplant recipients, to destroy the pathological IgG autoantibodies. Phase II results were encouraging and a Phase III trial is in process.

Renal transplantation can be considered in patients who have undetectable anti-GBM antibodies for >6 months as the risk of recurrence in the transplant is low (<3%). However, if a transplant is performed while anti-GBM antibodies are detectable, the risk of recurrence is 50%. Individuals with Alport syndrome have a 5–10% risk of developing anti-GBM antibodies after transplantation but this less frequently leads to clinical disease. If it is going to cause glomerulonephritis in this population, it normally occurs shortly after transplantation.

IgA vasculitis (Henoch–Schönlein purpura)

IgA vasculitis is a systemic vasculitis characterized by IgA-1-dominant immune deposits affecting small vessels. The aetiology is still under investigation, and both genetic and environmental factors appear to play a role. Twin studies suggest that IgA vasculitis and IgA nephropathy have a shared pathophysiology, but in IgA nephropathy, IgA-1 dominant immune deposits are limited to the kidney. Individuals with IgA vasculitis are generally excluded from most trials investigating IgA nephropathy.

Epidemiology: IgA vasculitis is the most common systemic vasculitis of childhood, with an incidence of 27/100,000 patient–years, compared with 2/100,000 patient–years in adults. It displays a variable and often relapsing course. Patients are at risk of developing chronic kidney disease and hypertension in the longer term without signs of active disease, the course of the renal lesion often being worse in older patients. In contrast, IgA nephropathy is more common in adulthood and follows a chronic, progressive course rather than a relapsing and remitting course.

Pathology: the multi-hit model is the most current understanding of pathogenesis in IgA vasculitis. The model suggests that galactose-deficient IgA-1 originates from the mucosal lymphoid tissue in the gut. Triggers such as infection and genetic susceptibility lead to the formation of anti-Gd-IgA1 autoantibodies, which can form immune complexes. These immune complexes deposit in the vessel walls of the kidneys, skin and other locations, which activates complement and leads to the damage seen in IgA vasculitis. This is in contrast to IgA nephropathy, where the IgA deposits are limited to the kidney.

Clinical features: the features are:

- a rash, usually affecting the buttocks and lower limbs (100% of patients; Figure 3)
- arthralgia (75%)
- gastrointestinal involvement, with abdominal pain and bloody diarrhoea (30–40%)
- glomerulonephritis (50%), often more severe with increasing age
- involvement of other organs, including the CNS (seizures) and lung (pulmonary haemorrhage).

There are no internationally agreed criteria for the diagnosis of IgAV in adults, so the diagnosis is based on clinical symptoms and confirmed by tissue biopsy. Skin biopsy reveals leucocytoclastic vasculitis with IgA deposition in the blood vessels or dermo-epidermal junction. Renal histology can vary from mild mesangial proliferation to focal segmental necrotizing glomerulonephritis but always shows IgA deposition in the mesangium. Renal biopsy should be performed in individuals with proteinuria and haematuria, because the severity of renal involvement (particularly the number of crescents) is an important determinant of prognosis.

Treatment: extra-renal disease is usually self-limiting and treatment should be supportive. Corticosteroids should not be used to prevent the development of nephritis in children.

KDIGO advises that, in patients with IgAV with renal involvement who are not at high risk of progressive chronic kidney disease, or who do not have RPGN, the focus should be on providing best supportive care with renin–angiotensin–aldosterone axis inhibition and sodium glucose co-transporter-2 (SGLT2) inhibitors, which have prognostic benefit. If a patient has a high risk of progression of chronic kidney disease, a detailed discussion with the person about the benefits and risks of immunosuppression should be undertaken and glucocorticoids can be offered. Patients with IgA vasculitis and RPGN should be treated according to guidelines for AAV but the evidence base for this is weak. The presence of crescents alone without a rise in creatinine does not constitute RPGN.

Emerging therapies are based on recent insights into IgA nephropathy pathogenesis, although patients with IgA vasculitis were excluded from these studies. The complement system has been implicated in mediating the inflammation associated with immune complex deposition, and various complement pathway inhibitors are under investigation.

Nefecon is an encapsulated form of budesonide that delivers the corticosteroid directly to the Peyer's patches in the terminal ileum, where most of the pathogenic IgA is believed to be produced. The NeflgArd phase III clinical trial in IgA nephropathy demonstrated an almost 30% decrease in urine protein:creatinine ratio and preserved kidney function over 12 months. It has been approved in the USA and UK for the treatment of IgA nephropathy.

Finally, there has been a systematic review of the use of rituximab in IgA vasculitis specifically. The review concluded that there is significant evidence that rituximab is safe and beneficial for inducing remission and establishing maintenance in patients refractory to corticosteroids and non-biological immunosuppressive medications.

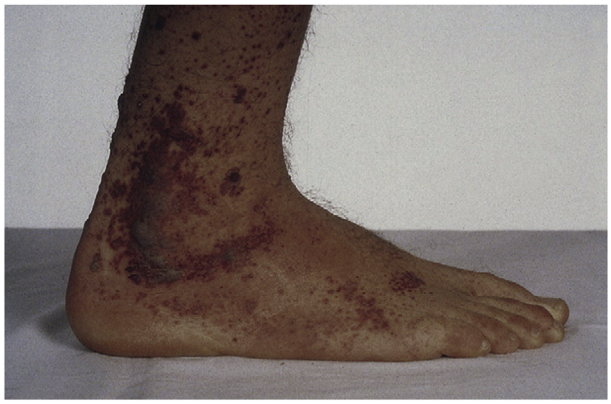

Figure 3 This purpuric rash has coalesced to form necrotic patches. The differential diagnosis includes primary small vessel vasculitis and IgA vasculitis. The rash associated with IgA vasculitis usually involves the buttocks and extensor aspects of the lower limbs. It usually resolves within 1 month, but fresh crops often appear.

Secondary immune complex-associated vasculitides

A number of systemic immune complex disorders can be associated with vasculitis, including autoimmune rheumatic diseases, dysproteinaemias, infections and malignancies (Table 2). It is particularly important to consider infections such as hepatitis B or C (often associated with cryoglobulins), HIV and chronic bacterial infections such as subacute bacterial endocarditis in the differential diagnosis of vasculitis. This is because treatment of underlying infection is an important part of management, particularly when complement concentrations are low.

Cryoglobulinaemic vasculitis

Cryoglobulins are immunoglobulins that reversibly precipitate at temperatures $<37\,^{\circ}C$ and dissolve on rewarming. Cryoglobulinaemic vasculitis is a systemic vasculitis affecting small and medium-sized vessels, caused by immune complexes of these cryoprecipitating immunoglobulins. The prevalence of cryoglobulinaemic vasculitis is now reported to be 1 in 100,000 individuals.[5]

Cryoglobulinemias are classified into three subtypes according to the composition of the cryoglobulin (Table 3). Monoclonal cryoglobulins (type 1) are associated with plasma cell dyscrasias

The differential diagnosis of immune complex vasculitis is wide and investigations should be targeted to rule out a secondary cause

Diseases associated with immune complex vasculitis

- Primary vasculitides — anti-GBM disease, IgA vasculitis
- Autoimmune rheumatic disorders — rheumatoid arthritis, SLE, dermatomyositis
- Infections — hepatitis B and C (often from cryoglobulins), HIV, streptococci, subacute bacterial endocarditis
- Dysproteinaemia — cryoglobulinaemia, Waldenström macroglobulinaemia
- Others — inflammatory bowel disease, neoplasia, α_1-antitrypsin deficiency

Table 2

Brouet classification of cryoglobulins

	Components of cryoglobulin	Prevalence (%)	Associated with
Type 1	Monoclonal immunoglobulin	5–25	Plasma cell dyscrasias
Type 2	Polyclonal IgG complexed with monoclonal IgM RF	40–60	Hepatitis C, HIV
Type 3	Polyclonal immunoglobulins	40–50	Connective tissue disease

Table 3

(e.g. Waldenström macroglobulinaemia, multiple myeloma) and tend to present with symptoms of hyperviscosity and thrombosis (i.e. digital ischaemia rather than vasculitis); they are not considered further here.

Mixed cryoglobulins containing >1 immunoglobulin component (types 2 and 3) are present in around 75% of cryoglobulinaemias; they are more commonly associated with vasculitis. In type 2 disease, the cryoglobulins are composed of a mix of monoclonal IgM with rheumatoid factor activity (RF) and polyclonal IgG. Type 3 is characterized by polyclonal IgM with RF activity and polyclonal IgG. Mixed cryoglobulins are commonly associated with chronic viral infections, especially hepatitis C (Table 3), but also B cell lymphomas and autoimmune connective tissue diseases (e.g. SLE, Sjögren syndrome). However, approximately 10% are idiopathic.

Clinical manifestations of cryoglobulinaemic vasculitis include a triad of weakness, purpura and arthralgia, seen in 80% of patients early in the course of the disease. Palpable purpura of the lower extremities caused by cutaneous vasculitis is seen in up to 90% of patients; Raynaud phenomenon has been described. Arthralgia is usually symmetrical, involves mainly the larger joints and can worsen in cold temperatures. Sensory or sensorimotor polyneuropathy presents with painful paraesthesia of the lower limbs or a mononeuritis multiplex. Glomerulonephritis presenting with proteinuria, haematuria and renal dysfunction is seen in around 20–35% of individuals at diagnosis. Other organ involvement includes the cardiac system, liver and CNS; patients can also present with fever, fatigue and sicca symptoms.

Investigation shows low complement C4 concentrations from activation of the classical complement pathway by the immune complexes. The C3 complement concentration is typically normal or near normal, and the RF concentration is increased. Cryoglobulins can be precipitated from plasma when a warm blood sample is delivered to the laboratory, however, the cryocrit level does not correlate with disease activity. Renal biopsy in cryoglobulinaemic vasculitis typically shows membranoproliferative glomerulonephritis with immune complex deposition. Skin biopsy shows leucocytoclastic vasculitis.

Treatment of cryoglobulinaemia depends on the underlying disorder. With plasma cell dyscrasias and lymphomas, disease-specific chemotherapy is indicated. Patients with hepatitis C-associated mixed cryoglobulinaemia with major organ involvement, such as RPGN or nephrotic syndrome, neurological or cardiac involvement, should be given combined therapy with immunosuppression and antiviral therapy; this has been shown to control organ damage more rapidly than antiviral treatment alone. Rituximab with corticosteroids has been shown to be an effective treatment for mixed cryoglobulinaemia and is well tolerated. Additional PEX can be necessary for rapidly progressive disease.

Although most patients achieve partial or complete remission, mortality is high; 75% of patients survive 10 years, infection is the leading cause of death, and relapses are common. ◆

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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 70-year old woman presented with a purpuric rash and joint pains. She had a past medical history of type 2 diabetes mellitus (latest glycated haemoglobin (HbA_{1c}) 92 mmol/mol (20–42)).

Investigations

- Creatinine 301 micromol/litre (60–110)
- C-reactive protein 34, mg/litre (<10)
- p-ANCA positive on immunofluorescence, confirmed to be MPO-ANCA with a titre >200 U/ml.

What treatment should be considered for induction of remission in this patient?

A. Corticosteroids + avacopan + rituximab + plasma exchange
B. Corticosteroids + rituximab
C. Methotrexate + rituximab + plasma exchange
D. Avacopan only
E. Corticosteroids + avacopan + rituximab + methotrexate

Question 2

A 40-year-old man presented with a 4-week history of increasing breathlessness, nasal congestion and abdominal pain. He had a history of asthma.
On clinical examination, he had a purpuric rash over his legs.

Investigations

- Haemoglobin 135 g/litre (130–180)
- White cell count 13 × 10^9/litre (4.0–11.0)
- Eosinophil count 3.0 × 10^9/litre (0.04–0.40)
- Creatinine 350 micromol/litre (60–110)
- Antineutrophil cytoplasmic antibodies were negative

What is likely to be the most appropriate management?

A. High-dose glucocorticoids
B. Mepolizumab + cyclophosphamide
C. High-dose glucocorticoids + rituximab
D. Plasma exchange
E. Methotrexate and mycophenolate mofetil (MMF)

Question 3

A 25-year-old woman presented with a purpuric rash on her legs and buttocks. She had also noticed some blood in her urine over the previous 2 days. She was normally fit and well and had recovered from an upper respiratory tract infection 2 weeks before. Urine dipstick testing showed blood ++, with negative results for protein, nitrites and leucocytes.

Investigations

- Haemoglobin 135 g/litre (115–165)
- White cell count 9.0 × 10^9/litre (4.0–11.0)
- Eosinophils 0.1 × 10^9/litre (0.04–0.40)
- Creatinine 75 micromol/litre (60–110)
- Antinuclear antibodies (ANAs) were negative
- Antineutrophil cytoplasmic antibodies were negative
- HIV, hepatitis B and hepatitis C serology was negative
- Myeloma screen was negative

What is the most likely diagnosis?

A. IgA vasculitis
B. Cryoglobulinaemic vasculitis
C. Eosinophilic granulomatosis with polyangiitis
D. Granulomatosis with polyangiitis
E. Microscopic polyangiitis