Small vessel vasculitides

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Abstract

Small vessel vasculitides have recently been reclassified following the 2012 Chapel Hill Consensus Conference[1] into two major groups. The first comprises anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, which are pauci-immune, with minimal immune deposits in vessel walls. ANCA-associated vasculitides are the most common cause of rapidly progressive glomerulonephritis. The second group comprises immune complex vasculitides, associated with immune complex deposition in the vasculature, including anti-glomerular basement membrane disease, IgA vasculitis (Henoch—Schönlein purpura), and vasculitides secondary to systemic immune complex diseases such as systemic lupus erythematosus, dysproteinaemias, cryoglobulinaemias, and chronic infections. This article describes recent advances in the understanding of the pathogenesis of these conditions and reviews common presentations. Consideration is given to recent clinical trials in the management of ANCA-associated vasculitides.

Keywords Anti-glomerular basement membrane disease; anti-neutrophil cytoplasm antibodies (ANCA); cryoglobulinaemic vasculitis; granulomatosis with polyangiitis (Wegener's granulomatosis); Henoch—Schönlein purpura; IgA vasculitis; microscopic polyangiitis; therapy; vasculitis

What's new?

- B cell depletion with rituximab, an anti-CD20 monoclonal antibody, is as effective as pulsed cyclophosphamide in inducing remission in ANCA-positive vasculitis
- Azathioprine is more effective for remission maintenance in ANCA-associated vasculitis than mycophenolate mofetil
- Genome-wide association studies have demonstrated that granulomatosis with polyangiitis and microscopic polyangiitis have separate HLA associations and are genetically distinct diseases
- Generation of complement component C5a is an important part of the pathological process in ANCA-associated vasculitis
- Anti-myeloperoxidase ANCA from patients with active vasculitis binds to different epitopes than anti-MPO ANCA from patients in remission

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

ANCA-associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg—Strauss syndrome).[1] These conditions are strongly associated with anti-neutrophil cytoplasmic antibodies. Although uncommon, with an incidence of 20/million population, prevalence now approaches 200/million because of increases in longevity due to improvements in treatment. These diseases can occur at any age, including childhood, but are most common in elderly patients (peak age 55—70 years), and occur equally in both sexes. Management of AAV is challenging. Rapid diagnosis is essential to reduce the permanent scarring caused by vasculitis and death from pulmonary haemorrhage. Considerable delay in diagnosis can occur because of the multiple non-specific manifestations associated with disease. Untreated, these conditions are fatal, although the use of immunosuppression has improved 5-year survival to 80%. With treatment, these conditions often follow a relapsing-remitting chronic course.

Aetiology and pathogenesis

The aetiology of ANCA-associated vasculitis is unknown. However, significant advances have been made in understanding disease pathogenesis. There is a strong clinical association with ANCA, which are autoantibodies, most commonly directed against proteinase 3 (PR3) or myeloperoxidase (MPO), enzymes that are expressed on the surface of cytokine primed neutrophils and monocytes. Interestingly, MPO-ANCA from patients with active disease and ANCA from patients in remission bind to different MPO epitopes.[2] Neutrophils respond by generating a respiratory burst, degranulating, and secreting pro-inflammatory cytokines. Endothelial cells are important in localizing inflammation. In response to cytokines, endothelial cells enhance expression of adhesion molecules that allow interaction with circulating leukocytes, and release factors promoting thrombosis. ANCA-activated neutrophils adhere to endothelial cells and transmigrate, releasing inflammatory factors in the wrong place, thereby promoting endothelial damage. Generation of C5a via the alternative pathway appears to be an important part of the pathogenic process in AAV,[3] and is a potential therapeutic target. C5a is a potent neutrophil chemo-attractant and also enhances the expression of activatory IgG receptors (Fc gamma receptors) on neutrophils.

A report of the development of AAV in a neonate following maternal transfer of MPO-ANCA adds weight to the in vitro evidence that ANCA are pathogenic. Animal models also support this view, as intravenous transfer of MPO-ANCA induces the development of pauci-immune focal necrotizing crescentic glomerulonephritis in recipient mice,[4] and vasculitis was generated in susceptible rats immunized with human MPO.[4] There is no precise rodent homologue of human PR3, but recently the transfer of PR3-ANCA was shown to induce pauci-immune

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necrotizing glomerulonephritis when injected into mice after reconstitution with human bone marrow.[5]

Large numbers of monocytes and T cells are present in chronic vasculitic lesions. Antigen-specific T cells have been demonstrated in patients with AAV, and they remain activated despite disease remission, suggesting that T cells contribute to the relapsing–remitting nature of AAV. The number and function of regulatory T cells has been shown to be impaired in AAV,[6] and the number of regulatory B cells is also reduced.[7]

Genetic contributions to the pathogenesis of AAV have been investigated with a genome-wide association study.[8] Distinct HLA associations were demonstrated for anti-PR3 ANCA (and GPA) and anti-MPO ANCA (and MPA), indicating that they are separate disease entities. In addition, PR3-ANCA was associated with the gene encoding its target antigen PR3, and the gene encoding α1 anti-trypsin, the endogenous inhibitor of PR3, implicating the antigen in the pathogenesis of GPA. Neutrophil surface expression of PR3 is controlled by epigenetic mechanisms, and individuals expressing large amounts of PR3 on the neutrophil surface are more likely to develop disease.[9] Patients with AAV are also more likely to carry polymorphisms in CTLA4 and PTPN22 genes, which are thought to be 'general' susceptibility factors associated with autoimmune disease.

AAV can also be precipitated by exposure to drugs, including propylthiouracil, minocycline and penicillamine. Infectious agents have often been implicated as initiators of vasculitis and nasal carriage of *Staphylococcus aureus* has been associated with relapse in GPA. Auto-antibodies to LAMP-2, which has homology to protein epitopes on *Escherichia coli* bacteria, have also been found in some patient with vasculitis. Silica exposure, which can also result in granuloma formation, is associated with an increased risk of AAV.

Pathology

AAV is characterized by inflammation and necrosis of capillaries, arterioles and venules, but can also affect larger vessels. In the kidney, the process primarily affects the glomeruli, leading to focal segmental necrotizing glomerulonephritis with crescent formation but without immunoglobulin deposition; this is termed 'pauci-immune glomerulonephritis'. There is often associated interstitial inflammation. In the lung, the findings are usually of capillaritis, often associated with lung haemorrhage. Granulomatous lesions occur in GPA and EGPA, but not in MPA. In the lung, there are often large, ill-defined collections of inflammatory cells near affected vessels; these can present as cavitating nodules. In the upper airways, this granulomatous reaction can present as ulceration.

Clinical features

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 archetypal presentation of severe systemic vasculitis is with a 'pulmonary-renal syndrome' – the combination of rapidly progressive organ dysfunction in both the lung and kidney. The differential diagnosis of this syndrome is wide (Table 1), but should always have systemic vasculitis near the top.

Limited GPA – is diagnosed when vasculitis is limited to the upper airways, including the nose, sinuses, orbit, eyes, trachea and bronchi. However, 90% of GPA patients with systemic disease also have one or more of these symptoms and so involvement of the lung and kidney should always be ruled out in patients presenting in this way. Upper respiratory tract symptoms include sinusitis, epistaxis, otitis media, hoarseness and stridor. Retro-orbital masses with proptosis occur and are 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. Limited GPA has a high propensity for relapse and can cause significant damage over time.

Systemic GPA often presents with some of the same symptoms as limited disease with additional vital organ involvement, including pulmonary disease and/or renal involvement with glomerulonephritis. Presentation with a rapidly progressive life-threatening illness is not uncommon.

MPA is characterized by rapidly progressive glomerulonephritis and pulmonary disease. Although nasal and upper airway symptoms can occur, they are less frequent, and granulomatous tissue destruction is not seen.

Specific organ involvement in GPA and MPA

Pulmonary involvement occurs at some stage in 85% of patients with GPA. Patients can present with asymptomatic pulmonary infiltrates, or with one or more symptoms such as cough, haemoptysis, pleuritis or dyspnoea. Lung nodules with or without cavitation are commonly seen in GPA, while in MPA nodules are not normally seen and the pulmonary disease tends to display a more fibrosing, restrictive lung disease pattern. Life-threatening alveolar haemorrhage, presenting with acute breathlessness, hypoxaemia and haemoptysis, can occur in both conditions.

Renal disease can range from an active urinary sediment (containing red cells and casts) with normal renal function, to rapidly progressive glomerulonephritis with severe damage. 'Renal limited vasculitis', with characteristic features of pauci-immune necrotizing glomerulonephritis without other organ involvement, is part of the spectrum of MPA. Up to 77% of patients with GPA will develop glomerulonephritis at some point.

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

Clinical features of EGPA

EGPA is characterized by marked hypereosinophilia with tissue eosinophil infiltration, formation of granulomata and vasculitis. It is less common than either GPA or MPA; the estimated incidence is 2.4/million/year. Allergic rhinitis and/or asthma precede the development of vasculitis, and are often associated with non-specific symptoms. Asthma is often more severe in the weeks preceding vasculitis. A rash and mononeuritis multiplex are common presenting features. Pulmonary involvement