Small vessel vasculitides

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Abstract

Following the 2012 Chapel Hill Consensus Conference, small vessel vasculitides have recently been recategorized into two major groups. The first comprises antineutrophil 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 antiglomerular 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 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 Antiglomerular basement membrane disease; antineutrophil cytoplasmic antibodies (ANCA); cryoglobulinaemic vasculitis; granulomatosis with polyangiitis (Wegener's granulomatosis); Henoch–Schönlein purpura; IgA vasculitis; microscopic polyangiitis; MRCP; therapy; vasculitis

Key points

- Rapid diagnosis and treatment is important to prevent organ damage in patients with systemic vasculitis
- Rituximab and cyclophosphamide, with high-dose corticosteroids, are equally effective as induction therapy in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
- ANCA is a useful marker for the diagnosis of granulomatosis with polyangiitis and microscopic polyangiitis but must be interpreted within the clinical context
- Relapses are common in ANCA-associated vasculitis, and treatment duration must be tailored to the individual, using azathioprine or rituximab in patients with renal disease. Methotrexate is a suitable alternative in those without renal dysfunction
- IgA vasculitis (Henoch–Schönlein purpura) is the most common cause of systemic vasculitis in children and most do not require immunosuppressive treatment
- Cryoglobulinaemia and infectious causes of small vessel vasculitis must be considered when associated with low complement concentrations

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)

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). These conditions are strongly associated with ANCA. Although uncommon, with an incidence of 20 per million population, prevalence now approaches 200 per million because of increases in longevity resulting from improvements in treatment. These diseases occur at any age, including childhood, but are most common in elderly individuals (peak 55–70 years), and occur equally in both sexes.

Management of AAV is challenging. Rapid diagnosis and treatment are essential to reduce the permanent scarring and death caused by vasculitis. Considerable delay in diagnosis can occur because of the multiple non-specific manifestations associated with disease. Untreated, these conditions are fatal, although use of immunosuppression has improved 5-year survival to 80%. With treatment, these conditions often follow a relapsing–remitting chronic course, with 50% of patients relapsing within 5 years of diagnosis.

Aetiology and pathogenesis

Although the precise cause of AAV is unknown, significant advances have been made in understanding disease pathogenesis.

AAVs are autoimmune diseases. B cells produce ANCA, and clinical benefit following the use of B cell-depleting agents, such as rituximab, has identified them as important in disease pathogenesis. Imbalances in T cell subsets, including a reduction in number and function of T regulatory cells, probably contribute to the loss of tolerance and triggering of autoimmunity.[1] Excessive antigen presentation of proteinase 3 (PR3) and myeloperoxidase (MPO) has been implicated in generation of ANCA autoantibody through their overexpression on the neutrophil surface and in neutrophil extracellular traps (NETs).

ANCAs are most commonly directed against PR3 or MPO, enzymes expressed on the surface of cytokine-primed neutrophils and monocytes.[1] Interestingly, MPO-ANCA from patients with active disease and ANCA from patients in remission bind to different MPO epitopes. A report of the development of AAV in a neonate following maternal transfer of MPO-ANCA adds weight to the *in vitro* evidence that ANCAs are pathogenic.[1] Animal

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models also support this view, as intravenous transfer of MPO-ANCA induces development of pauci-immune focal necrotizing crescentic glomerulonephritis in recipient mice, and vasculitis can be generated in susceptible rats immunized with human MPO.[1] There is no precise rodent homologue of human PR3, but transfer of PR3-ANCA has recently been shown to induce pauci-immune necrotizing glomerulonephritis when injected into mice after reconstitution with human bone marrow.

Endothelial cells are important in localizing inflammation. In response to cytokines, endothelial cells enhance the expression of adhesion molecules that allow interaction with circulating leucocytes, and release factors promoting thrombosis. ANCAs bind and activate neutrophils, which adhere to endothelial cells and transmigrate, releasing inflammatory factors (degranulating, generating a respiratory burst and production of NETs) in the wrong place, promoting endothelial damage.[1]

Recent studies have identified the importance of complement in disease. Generation of C5a via the alternative pathway appears to be an important part of the pathogenic process in AAV, and blockade of the C5a receptor in animal models ameliorates disease.[1] C5a is a potent neutrophil chemo-attractant and also enhances expression of activatory immunoglobulin (Ig) G receptors (Fc γ receptors) on neutrophils. A recent proof of concept trial using a small molecule C5a receptor inhibitor under development and not licensed, avacopan, has suggested potential benefit in patients with AAV as a steroid sparing agent.

AAVs are not inherited diseases. Genetic associations with disease have, however, been identified using genome-wide association studies. Distinct HLA associations have been demonstrated for anti-PR3 ANCA (and GPA) and anti-MPO ANCA (and MPA), suggesting that they are separate disease entities.[1] In addition, PR3-ANCA is associated with the gene encoding its target antigen PR3, and the gene encoding α_1-antitrypsin, the endogenous inhibitor of PR3, implicating the antigen in the pathogenesis of GPA.[1] 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. HLA associations have also been identified in patients with EGPA. Patients with the ANCA negative subtype of EGPA have been shown to have polymorphisms in the IL-10 promoter gene that leads to increased production of IL-10, although this has not been validated in an independent cohort. Patients with AAV are also more likely to carry polymorphisms in *CTLA4* and *PTPN22*, which are thought to be 'general' susceptibility factors associated with autoimmune disease.

AAV can be caused by exposure to drugs, including levamisole-contaminated cocaine, propylthiouracil, minocycline and penicillamine.[1] Patients with drug-induced AAV often have very high titres of ANCA targeting multiple antigens, including MPO and other non-classical antigens such as elastase. Infectious agents have also been implicated as initiators of vasculitis; nasal carriage of *Staphylococcus aureus* has been associated with relapse in GPA.[1] Autoantibodies to, a glycosylated membrane protein that traffics from the cell surface to lysosomes, that is critical for cellular homoeostasis and responses to stress and has homology to protein epitopes on *Escherichia coli* bacteria, have been found in some patients with AAV.[1] Silica exposure, which can result in granuloma formation, is associated with 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 predate other symptoms. The archetypal presentation of severe systemic vasculitis is with a 'pulmonary–renal syndrome' – the combination of rapidly progressive organ dysfunction in both 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; therefore involvement of the lung and kidney should always be ruled out in individuals presenting in this way. Upper respiratory tract symptoms include sinusitis, epistaxis, otitis media, hoarseness and stridor. Retro-orbital masses with proptosis occur and 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. Limited GPA has a high propensity for relapse and can cause significant damage over time. Some of these patients may go on to develop systemic symptoms.

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: this occurs at some stage in 85% of patients with GPA. They 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, whereas in MPA nodules are not normally seen, and the pulmonary disease tends to display a more fibrosing, restrictive lung disease pattern. Life-

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