167 Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Small-Vessel Vasculitides

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Definition

The antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides (AAV) comprise a group of disorders characterized by necrotizing vasculitis with a paucity of immune deposits associated with antibodies against cytoplasmic constituents of neutrophils, particularly proteinase 3 (PR3) and myeloperoxidase (MPO). In this group, three major clinical entities are present: *Wegener's granulomatosis* (*WG*), *Churg–Strauss syndrome* (*CSS*), and *microscopic polyangiitis* (*MPA*). It should be emphasized that most but not all patients show a positive ANCA by serology.

Wegener's Grantulomatosis

Wegener's granulomatosis (WG) is a necrotizing vasculitis affecting small to medium-sized vessels. The disease is characterized by granulomatous inflammation involving respiratory tracts, including sinuses, nasal passages, pharynx, and lungs, and pauci-immune necrotizing crescentic glomerulonephritis, and in most patients the presence of ANCA.

Epidemiology

WG is rare in childhood. This has resulted in descriptions in the pediatric population that have been based on smaller numbers of patients, most often in the form of case reports, case series, and literature reviews. The two largest single-center pediatric series to date have reported on a combined total of only 40 patients. In a recent report of 60 patients, the mean age of diagnosis was 11.7 years.

Etiology and Pathogenesis

The etiology of WG remains unknown. Both genetic and environmental factors seem to be involved. Familial occurrence is extremely rare. Use of cocaine and exposure to silica have been indicated as environmental factors. As carriage of *Staphylococcus aureus* is strongly associated with PR3–ANCA positive Wegener's granulomatosis, the bacterium might be involved in the PR3-specific autoimmune response. However, it has not been possible yet to produce the disease associated with PR3 ANCA in animals.

Pathology

The characteristic pathologic finding is granulomatous involvement in arteries. Kidney biopsy is indicated in children with kidney involvement. Characteristic finding is pauci-immune necrotizing crescentic glomerulonephritis (◉ *Fig. 167.1*). Granuloma formation is rarely observed in kidney tissue unlike to the lung or sinus biopsy.

Clinical Manifestations

Clinical manifestations are nonspecific and virtually any organ can be involved. However, presenting and diagnostic symptoms are usually confined to the respiratory tract and the kidneys. The classical triad of the disease is paranasal sinus involvement, pulmonary infiltration, and kidney involvement (◉ *Table 167.1*). Constitutional symptoms, including fever, malaise, and weight loss, are common at presentation. In different pediatric series, upper respiratory tract involvement (sinusitis, epistaxis, otitis media, etc.) has been reported in 84–100% of the patients, while lower respiratory tract involvement in 80–87%. Since subglottic stenosis is common in the pediatric practice, the presence of upper airway involvement (subglottic, tracheal, and endobronchial stenosis) has been added as a criterion to the revised classification criteria in childhood WG.

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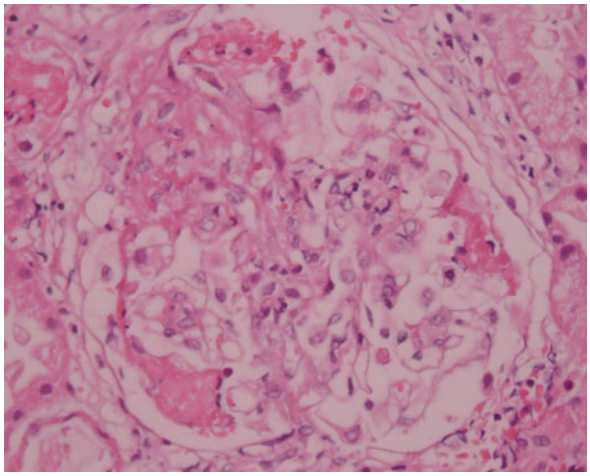

Figure 167.1
Necrotizing crescentic glomerulonephritis in a child with ANCA-associated vasculitis

Renal involvement, which is characterized by necrotizing pauci-immune glomerulonephritis in biopsy, is frequently seen and often causes renal failure requiring dialysis. Skin lesions including purpura and panniculitis/nodules may be seen in one third of the patients. Conjunctivitis, scleritis, and proptosis have also been reported as frequent symptoms at onset or during the course of the disease. Arthritis/arthralgia, hypertension, gastrointestinal involvement venous thrombotic events and CNS involvement occur less frequently. The disease may also present in a limited form.

Diagnosis and Laboratory Findings

Many of the "classic" features of the disease may be lacking early in the course. Although diagnostic criteria do not exist, for diagnosis the child should have (1) small-vessel vasculitis; (2) granulomatous inflammation of the airways; (3) nodules, infiltrations on chest radiographs; and (4) renal involvement. According to recently proposed classification criteria, three out of six criteria should be present for WG (*Table 167.1*).

There is usually mild anemia and thrombocytosis. Marked elevation of acute phase reactants are usually present. Urinalysis may show microscopic hematuria, proteinuria, and casts in case of renal involvement. Renal impairment may be present.

ANCA is highly associated with WG (*Table 167.1*). ANCA may be either cytoplasmic (c-ANCA), which is related to proteinase 3 (PR3) or more rarely related to myeloperoxidase (MPO). Sensitivities of PR3-ANCA and MPO-ANCA for WG are 70–80% and 10%, respectively. A few patients with WG are ANCA-negative.

Table 167.1
EULAR/PRINTO/PRES (Ankara, 2008) classification criteria for Wegener's granulomatosis (From Ozen et al. (2010))

Three of the following six should be present:
1. Abnormal urinalysis[a]
2. Granulomatous inflammation on biopsy
3. Nasal and/or sinus and/or oral inflammation
4. Subglottic, tracheal, or endobronchial stenosis
5. Abnormal chest X-ray or computed tomography
6. Any ANCA positivity

[a] If kidney biopsy is performed, it characteristically shows necrotizing pauci-immune glomerulonephritis

Radiologic Findings

Chest radiographs or CT are abnormal in up to two thirds of the patients and include nodules, cavitation and infiltrates, and pleural effusions. Sinus radiographs will reflect the sinusal involvement.

Treatment

Since there are few data relating to treatment of children with WG evidence-based treatment, recommendations come from studies performed in adult population.

Localized disease defined by the European Vasculitis Study (EUVAS) group refers to patients with symptoms restricted to the upper and/or lower airways, without constitutional symptoms or systemic vasculitis. In this group, Methotrexate may be used to induce remission.

EUVAS approaches the treatment of (systemic) WG and MPA in a similar fashion, and thus the treatment of these two diseases will be reviewed together. Conventional treatment is to induce remission with cyclophosphamide and corticosteroids in these two ANCA-associated vasculitides, WG, or MPA. Patients should be started with oral prednisone plus pulse intravenous cyclophosphamide or oral cyclophosphamide to induce remission. In this study of adults, prednisone was tapered to 10 mg by 6 months. Cyclophosphamide doses should be adjusted to age, renal function (level of evidence 1b; recommendation A).

In the CYCAZAREM study, azathioprine has proven to be effective for maintenance therapy after 3–6 months of remission induction therapy with prednisolone and oral cyclophosphamide. Leflunomide, methotrexate, and

mycophenolate mofetil may be alternative therapies to maintain remission.

In severe renal vasculitis and immediately life-threatening disease, plasma exchange should be started to improve renal prognosis (level of evidence 1b; recommendation A). In refractory disease, there are no randomized trials providing evidence for the best therapy. Rituximab has been proven to be effective in recent trials of ANCA-associated vasculitides in adults.

Prognosis

The use of immunosuppressives has resulted in much lower mortality rates than those published in early studies of WG. Lack of ear, nose, and throat involvement has also been shown to be a significant indicator of increased risk of mortality. Treatment may result in significant morbidity and mortality.

Churg–Strauss Syndrome (Allergic Granulomatosis)

Churg–Strauss syndrome (CSS) is a disease characterized by pulmonary and systemic small-vessel necrotizing vasculitis, vascular and/or extravascular granulomas, eosinophilia and tissue infiltration by eosinophils, occurring in individuals with asthma, and often allergic rhinitis or sinusal polyposis. Asthma and severe eosinophilia in combination with vasculitic organ manifestations are key features of this unique disease.

Epidemiology

Reports of CSS occurring in children are limited and generally consist of single case reports. In a recent systematic review, where 33 children with CSS have been included, mean age at onset has been found as 12 years with a male-to-female ratio of 0.74.

Etiology and Pathogenesis

Etiology and pathogenesis remain unknown. Inhaled allergens, infections, drugs have been implicated as triggers. A possible contribution of leukotriene receptor antagonists to the development of CSS has been suggested.

The pathogenic role of anti-MPO autoantibodies is now well established both in vitro and in vivo. However, the mechanisms leading to vasculitis in CSS are yet to be elucidated, particularly in ANCA-negative patients.

Pathology

Histological signs of CSS include eosinophilia, vasculitis, or granuloma. Small-vessel vasculitis is found in most of the patients, extravascular eosinophils are histologically evident in 80% of the patients, while granulomas are seen in 45% of them.

Clinical Manifestations

History of asthma has been reported in 91% of the patients while sinusitis in 77% at the time of clinical presentation. Pulmonary infiltrates are also a common finding (85%), whereas pleural effusions are rarely seen (12%). Other organs such as the skin (66%), peripheral nerves (39%), and the gastrointestinal tract (40%) are also involved. Renal and musculoskeletal symptoms occur rarely. Cardiac involvement is frequently seen and is characterized by granulomatous pericardial disease (27%) and eosinophilic cardiomyopathy (42%). Severe mitral valve regurgitation has also been reported. Other organs are rarely affected.

Diagnosis

According to the American College of Rheumatology criteria for classification of the CSS, a patient is considered to have CSS in the presence of at least four of the following criteria with a sensitivity of 85% and a specificity of 99.7%: (1) asthma, (2) eosinophilia, (3) history of allergy, (4) mono/polyneuropathy, (5) pulmonary infiltrates, (6) paranasal sinus abnormality, (7) extravascular eosinophils in biopsy.

Laboratory Findings and Pathology

The most striking laboratory features are significant eosinophilia ($\geq$10% of the peripheral leukocytes) and elevation of serum IgE level. Acute phase reactants are increased in active disease. ANCA positivity is not a consistent finding however the usual association is with MPO-ANCA.

Chest X-Ray may reveal diffuse pulmonary infiltrates with impaired pulmonary function tests.

Treatment and Prognosis

Strict and aggressive therapy is indicated in patients with CSS. Most children respond well to initial steroid therapy. However, those patients with vital organ involvement immunosuppressive agents such as cyclophosphamide, azathioprine, or metotrexate are often needed.

Mortality is significantly higher (19%) in children than adults (5%). This is partly explained by the more severe cardiac involvement, which has major impact on mortality.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is defined as non-granulomatous small-vessel vasculitis with few or no immune deposits affecting small vessels. Necrotizing glomerulonephritis is very common and necrotizing arteries of medium-sized arteries may also be present. Pulmonary capillaritis without upper respiratory tract involvement often accompanies to glomerulonephritis. It can mimic classical PAN histologically, as both diseases produce necrotizing arteritis. The key distinction between them is in the involved vessel size since MPA is predominantly small-vessel vasculitis, while PAN is confined to mid-sized arteries. In addition, MPA is often associated with a high titer of MPO-ANCA.

Epidemiology

Microscopic polyangiitis is rare in children. The annual prevalence of MPA has been reported as 25.1 per million adults in France. In two pediatric series, the mean age at diagnosis was 12 years.

Etiology, Pathogenesis and Genetic Background

Infections may have an initiating role, although a specific antigen has not been indicated. MPO-ANCA has been implicated in the pathogenesis. There are several in vitro data supporting the observation that ANCA are capable of endothelial damage. In two elegant animal models, anti-MPO antibodies in mice and in rats induced necrotizing and crescentic glomerulonephritis with widespread vasculitis in the lung and other organ systems.

Genetic factors may be operative in the pathogenesis. MPO levels are influenced by two single nucleotide polymorphisms in the gene, MPO463 and MPO129. The MPO 463 polymorphism has been associated with an increased risk of development of MPO-ANCA associated disease.

Clinical Manifestations

The constitutional features of MPA are similar to those of classical PAN. However, the predominant feature is progressive (often rapidly) glomerulonephritis with or without pulmonary involvement. It is one of the leading causes of pulmonary-renal disease in children. Renal disease manifests as nephritis and renal functions may be acutely impaired. Myalgia, skin lesions, joint disease, gastrointestinal symptoms, and central and peripheral nervous system involvement have all been defined in MPA. In some series, end stage renal disease has been reported as high as 40%.

Diagnosis and Laboratory Findings

Diagnosis depends on characteristic renal biopsy findings in the presence of typical clinical manifestations and a positive p-ANCA staining with high MPO-ANCA level by ELISA. Classical PAN, Henoch Schonlein purpura, Wegener's granulomatosis, Churg–Strauss syndrome, and systemic lupus erythematosus should be considered in differential diagnosis.

Leukocytosis, thrombocytosis, and elevation of erythrocyte sedimentation rate and C-reactive protein level are consistently present. Urinalysis shows proteinuria and hematuria. Renal functions may be impaired.

MPO-ANCA is important in diagnosis and follow-up of the disease. In childhood, those patients with necrotizing glomerulonephritis and pulmonary involvement seem to have the highest MPO-ANCA levels.

Treatment and Prognosis

Guidelines for treatment of Wegener's Granulomatosis (WG) are applicable for MPA as well.

Five-year survival rates vary between 45% and 74% in different adult series. Renal involvement is a significant factor in predicting poor prognosis, either in the form of proteinuria (>1 g/day) or raised creatinine levels. Overall relapses seem to be less frequent as compared to WG.

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