L39. Fulminant anca vasculitis

Introduction

ANCA-associated vasculitis (AAV) is a systemic disease that may affect many different organs and present with various symptoms. According to the recently published Chapel Hill Consensus Conference Nomenclature of vasculitides [1], AAV includes three different types of small-vessels vasculitis: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA or former Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA or former Churg-Strauss vasculitis).

Besides slowly progressive and chronic presentations, some patients develop rapidly progressive and sometimes fulminant symptoms with severe pulmonary, renal, intestinal, cardiac or central nervous system (CNS) involvement. These life-threatening complications often require admission in the Intensive Care Unit. Early diagnosis of AAV is necessary in order to initiate as soon as possible the specific immunosuppressive treatment, which includes short-term life-saving procedure and control of the disease in order to limit the organ lesions and long-term consequences. Even though the extent of these fulminant forms is not fully defined, it is possible to describe renal, pulmonary, gastro-intestinal, cardiac and neurological clinical presentations.

Renal presentation: acute renal failure

Rapidly progressive glomerulonephritis (RPGN) is the most typical renal presentation of AAV. It combines rapid deterioration of renal function – which may lead to dialysis within a few days –, micro- or macro-hematuria and usually non-nephrotic glomerular proteinuria. Renal failure is not always easy to detect, especially when extra-renal symptoms are mild or absent. Specific clinical symptoms, such as oliguria, uremia or fluid overload appear only at the very last stages of the renal disease and this point explains why diagnosis of the kidney involvement in AAV is sometimes too late.

Although ANCA positivity during an episode of acute renal failure with RPGN features is sufficient to start urgent immunosuppressive treatment, the renal biopsy is recommended in order to confirm the renal vasculitis, exclude differential diagnosis and give the prognosis of renal failure. The classical glomerular lesion is crescentic necrotizing glomerulonephritis with extracapillary proliferation of epithelial cells. The lesions are frequently focal and segmental with a mixture of normal glomeruli, glomeruli with active necrosis and cellular crescents, and glomeruli which are already partially or globally sclerosed, with presence of fibrotic crescents. Immunofluorescence microscopy study of the renal biopsy demonstrates little or no staining for complement or immunoglobulins, defining the so-called pauci-immune pattern. Numerous clinicopathologic studies have shown that kidney pathology can predict renal...
outcome. Favorable outcome has been associated with a high percentage of normal glomeruli or with the presence of active cellular crescents, independently of baseline renal function. On the other hand, there is a strong relationship between the percentage of globally sclerosed glomeruli, and adverse renal outcome [2]. These findings have lead to a new histopathologic classification of ANCA-associated glomerulonephritis into four categories, focal, crescentic, mixed and sclerotic, which have distinct long-term prognosis [3]. Besides glomerular involvement, renal dysfunction is often related to a major interstitial inflammation of the renal tissue. When this tubulo-interstitial nephritis is mainly cellular, sometimes with formation of intrarenal granulomas, prognosis is usually good, with rapid clearance of the inflammatory cells after initiation of corticosteroids. Nevertheless, when these lesions are fibrotic, they may predict adverse renal outcome even better than the severity of the initial glomerular lesions [4].

**Diffuse alveolar haemorrhage**

Pulmonary disease is found in almost half of the patients with AAV [5]. Among the different presentations of lung involvement, alveolar haemorrhage is the most severe and potentially life-threatening. Diagnosis is suggested by the presence of cough, haemoptysis and progressive dyspnoea. Acute respiratory failure requiring supportive mechanical ventilation is not rare (> 20%) [6]. It is confirmed by fibroscopy and broncho-alveolar lavage, showing presence of siderophages and excluding differential diagnoses such as infectious complications that can also present with similar clinical features, particularly in immunosuppressed patients. Anaemia due to diffuse alveolar hemorrhage (DAH) is almost constant and sometimes profound. ANCA-associated DAH is secondary to necrotizing vasculitis of alveolar capillaries, but DAH can also be observed in other auto-immune disorders, such as Good-pasture syndrome, SLE, cryoglobulinemia, in congestive heart failure, or in several infectious diseases [7]. Most cases of AAV-related DAH have an excellent outcome [5], but mortality rises to 50% for cases with respiratory failure requiring ventilator support [8].

**Gastro-intestinal involvement**

Although these manifestations are less frequent (20–25% of all AAV patients), gastro-intestinal manifestations are responsible for a substantial proportion of the mortality in this disease. The spectrum of the clinical presentations is large, including gastro-intestinal bleeding, bowel perforation, pancreatitis or cholecystitis. The recently revised Five-Factor Score (FFS), that has been shown to be highly predictive of overall mortality in AAV, integrates severe gastro-intestinal vasculitis [5]. It is important to note that inflammatory bowel diseases (IBD) such as Crohn’s disease and ulcerative colitis are frequently associated with the presence of pANCA, but the specificity of these auto-antibodies is frequently atypical in this setting, recognising lactoferrin or cathepsin G, but also myeloperoxidase in some cases. Distinction between AAV and IBD is based on pathological findings, detection of other serological markers such as anti-saccharomyces cerevisiae antibodies (ASCA) or the presence of other symptoms of systemic vasculitis.

**Cardiac disease**

Heart involvement is particularly frequent in EGPA (30 to 40% of patients), and is now recognized as the main cause of death in this specific subgroup of AAV. In GPA or in MPA, specific cardiac disease is seen in less than 15% of patients, but this item has also been included in the FFS because it is statistically associated with poor outcome [5]. Heart failure is frequently acute, with left ventricular (LV) dysfunction revealed by pulmonary oedema and respiratory distress [9]. Other manifestations are pericardial effusion or myocardial infarction. Cardiac imaging – echocardiography and MRI – shows wall motion disturbances and decrease of the LV ejection fraction, due to infiltration of the heart tissue by inflammatory cells and subsequent parietal fibrosis of the cardiac wall.

**Neurological involvement**

Peripheral neuropathy can appear very rapidly during the initial stages of AAV. Its incidence is estimated around 8% among patients with MPA or GPA, but it is much more frequent – 40 to 50% – among patients with EGPA. Although it is not a life-threatening complication, vasculitic motor-involving or sensory neuropathy can be associated with important disability and significant morbidity, especially in EGPA. Nerve biopsies can show either necrotizing vasculitis or eosinophilic infiltration around the nerve fibers. Neuropathy is not associated with overall mortality but only 35% of patients have complete resolution of their symptoms despite immunosuppressive treatment [10]. Central nervous system can also be affected by AAV, but this complication is also reported in less than 10% of all patients [11]. Cerebral vasculitis is rare, but neurological complications may also be secondary to a contiguous invasion of granulomas which develop in extracranial sites, such as orbital pseudotumours or destructive sinuses, especially in patients with inflammatory GPA.

**Treatment of fulminant AAV**

Immunosuppressive therapy must be initiated as early as possible, in order to stop the progression of vasculitis and limit the chronic lesions which may develop, particularly in the kidney, after resolution of the inflammatory process. High-dose corticosteroids and cyclophosphamide are considered as the gold standard of care for severe flares of AAV. The therapeutic scheme comprises, for most authors, intravenous methylprednisolone (500 or 1000 mg) for three consecutive days, followed by oral prednisone given initially at 1 mg/kg per day. High-dose corticosteroids usually permit a rapid resolution
of the inflammatory cellular infiltration in the kidney or in the lungs, but the adjunction of an immunosuppressive drug such as cyclophosphamide – intravenous or oral – is mandatory to control the necrotizing vasculitis and allow tapering of steroids. Although rituximab is probably as effective as cyclophosphamide for induction of remission in MPA or GPA, the recently published studies [12] had excluded patients with severe kidney failure (serum creatinine > 4 mg/dl) or DAH requiring mechanical ventilation. Until future studies demonstrate that the use of rituximab can also be beneficial in this group of patients, cyclophosphamide must remain the immunosuppressive drug of choice for life-threatening AAV.

The use of plasma exchange has also been proposed, in addition to the immunosuppressive medication, in AAV patients with acute renal failure or severe DAH. The possible direct pathogenic role of ANCA supports the hypothesis that early removal of preformed circulating auto-antibodies can contribute to the control of the AAV, during the first days of immunosuppressive therapy. The MEPEX study has shown that addition of seven plasma exchanges within the two first weeks of treatment increases the rate of renal recovery, without affecting the short-term mortality [13]. Furthermore, although no controlled trial has been performed, some series suggest that plasma exchange may improve pulmonary outcome in severe DAH [14].

Conclusion

Severe and rapidly progressive, single or multi-organ failure can reveal or complicate AAV. Early detection of vasculitis during an acute kidney, lung, heart or gut dysfunction is not always easy, especially in critically ill patients entering the intensive care unit and requiring supportive mechanical ventilation, hemodialysis or treatment of congestive heart failure. Presence of general signs preceding the admission of the patient or identification of a pulmonary-renal syndrome, which remains the most frequent clinical presentation of fulminant vasculitis, must lead to detection of ANCA and urgent initiation of specific AAV treatment, with corticosteroids, cyclophosphamide and sometimes plasmapheresis.

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References


L41. Perspectives on the treatment of giant cell arteritis

Giant cell arteritis (GCA) is a vasculitic disease that predominantly affects the large – to medium-sized arteries. It occurs in people over the age of 50 and is the most common primary systemic vasculitis that affects humans. Since the 1950s,