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Perspective

Antineutrophil cytoplasmic antibodies-associated glomerulonephritis: From bench to bedside

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Abstract

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of autoimmune disorders that predominantly affects small vessels. The onset of the disease is closely associated with ANCA. Renal involvement, also known as ANCA-associated glomerulonephritis (AGN), is one of the most common manifestations of AAV. In this mini-review, we describe the clinical and pathological features of AGN. We then focused on recent studies on the mechanism of acute kidney lesions, including fibrinoid necrosis and crescent formation. Following the basic aspects of kidney injury in AGN, we demonstrated the clinical importance of kidney injury in determining the outcome of patients with AGN. The prognostic value of the 2010 Histopathological Classification of AGN and validating studies were summarized. Finally, treatment and novel therapeutic strategies were introduced addressing the importance of optimizing management of this patient population.

Keywords: Antineutrophil cytoplasmic antibodies; Renal involvement; Prognosis; Treatment

Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a group of autoimmune disorders that include microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and their localized forms.[1] AAV predominantly affects small vessels. The onset of the disease is closely associated with ANCA, which is specific for myeloperoxidase-ANCA (MPO-ANCA) or proteinase 3-ANCA (PR3-ANCA).[1] The pathogenesis of ANCA is well demonstrated through *in vivo* and *in vitro* studies but the mechanism of ANCA development largely remains unclear. Possible factors that could cause ANCA and the associated vasculitis include infection, neoplasms, and drugs including propylthiouracil, methimazole, and many others which could interact with macrophages/monocytes as well as T, B cells.[2–4] AAV is characterized by necrotizing inflammation of the small vessel. Mortality may reach 90% if patients with AAV are left untreated. Despite adequate immunosuppressive therapy, the prognosis of patients with AAV remains poor.[5] In

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previous studies, we found that the 5-year survival rate of AAV was about 70%, and infection was a common cause of the death.[6] In a recent meta-analysis, AAV patients were found to have higher mortality than the general population.[7] Currently, immunosuppressants are the standard treatment of AAV, but long-term of immunosuppressive therapy could cause many adverse effects, including increased rates of infections, malignancies and cardiovascular diseases.[8] Therefore, the side-effects of immunosuppressant could be associated with increased mortality in AAV patients.

Renal involvement, also known as ANCA associated glomerulonephritis (AGN), is one of the most common manifestations of AAV that could occur in more than half of the patients, and dialysis-dependency at disease onset is high.[9,10] As studies point out that renal involvement is an important factor affecting the prognosis of patients with AAV, we focus on kidney damage in AAV in this review to further understand the disease and improve its prognosis.

AGN—clinical and pathological presentations

The clinical presentations of renal involvement in AAV include hematuria, proteinuria or rapidly progressive glomerulonephritis depending on the severity of vasculitic kidney damage.[11] Hematuria, either microscopic or gross hematuria, is present in almost all the AGN patients and is closely associated with severity of the disease. Apart from the glomerular lesions, the severity of renal involvement in AAV could vary according to different serology of ANCA. In our previous study and other literature,[12,13] patients with PR3-ANCAs presented with minor renal involvement in comparison with those positive to MPO-ANCAs. Patients with PR3-ANCAs could present with less proteinuria or lower serum creatinine levels. Contrary to the presentation of renal involvement, patients with PR3-ANCA positivity have a higher prevalence of extra-renal organ manifestations than do those with MPO-ANCA positivity.[14] Moreover, the difference might be due to etiology of the disease and the pathogenesis of PR3/MPO ANCA.

The hallmark lesion in patients with AGN is the so-called pauci-immune necrotizing crescentic glomerulonephritis which often presents as necrotizing or crescentic glomerulonephritis without deposition of immunoglobulins. The pauci-immune condition is defined as less than 2 + immunofluorescence staining for immunoglobin (Ig) G, IgA, IgM, C3, and C1q. Apart from the pauci-immune glomerulonephritis, immune complex deposition could also be found in the kidneys of some patients with AAV.[15–17] Though it is not clear whether immune complex deposition in AAV could be due to the overlapped syndrome (AAV superimposed on immune complex-mediated glomerular lesions), it is clear that patients with immune complex might present with a higher level of proteinuria than do those without.[15]

Pathological features of AGN—fibrinoid necrosis and crescent formation

In the acute phase of AAV, fibrinoid necrosis and neutrophilic infiltration could be present in the kidney. These could present in glomeruli as segmental necrosis and crescent formation which are the characteristics of AGN. With the progression of the disease, the acute lesions would then evolve into chronic sclerotic lesions with leukocyte infiltration. In this process, leukocytes and macrophages play important roles.

Macrophages are myeloid immune cells that are positioned throughout the body tissues and have been demonstrated to be derived from circulating monocytes. Tissue macrophages can also be replenished by bone marrow-derived monocytes.[18,19] Upon activation, macrophage could generate classically activated (M1) macrophages, which could promote tissue injury and alternatively activated (M2) macrophages, which could promote tissue repair.[18] Because of the bipolar mode of macrophage in maintaining homeostatic functions, macrophages have received much attention. In the study by Zhao et al,[20] $CD68^+$ and $CD163^+$ macrophages were found to be predominated at sites of fibrinoid necrosis in AAV patients, exceeding the quantity of neutrophils and T cells. Furthermore, normal-appearing glomeruli had significantly more $CD68^+$ and $CD163^+$ macrophages than controls. The authors thus hypothesized that M2 macrophages might be precursor steps in the evolution of fibrinoid necrosis and subsequent crescents formation. In the study by O'Reilly et al,[21] urinary soluble CD163 (sCD163) which was the biomarker of macrophage activation, was closely associated with active vasculitis. Furthermore, Rousselle et al[22] found monocytes could promote crescent formation in a mice model of AAV. Those studies thus suggest macrophage/monocyte would be related to vasculitic kidney damage.

In literature,[23,24] complement deposition was found to be associated with cellular crescents which suggested it might also play a role in crescent formation and kidney damage in AAV. During the development of segmental fibrinoid necrosis, interstitial monocytes and $CD3^+$ T cells infiltrated and then contributed to further kidney damage. In the animal models of AAV, T cells were reported to be involved in the

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