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Perspective

Antineutrophil cytoplasmic antibodies-associated glomerulonephritis: From bench to bedside

Yong-Xi Chen, Xiao-Nong Chen*

Department of Nephrology, Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200025, China

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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 described 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 and 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]

* Corresponding author.
E-mail address: cxn10419@rjh.com.cn (X.-N. Chen).

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In 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

development of glomerular crescent.[25] As there is some argument about the study because the glomerular lesions in an animal model were different from those in the human specimen, the mechanism of the crescent and fibrinoid necrosis formation is not clearly understood yet.

Renal histology in AGN—a key factor for predicting renal outcome

Large groups of studies have demonstrated the prognostic value of renal biopsy because specific renal pathological lesions are associated with renal outcome.[26] Furthermore, renal biopsy specimens provide evidence to predict renal outcome as well as kidney function at disease onset.[27,28] Given this background, a histopathologic classification was proposed to study the correlation between renal injury patterns and patients' prognosis.[26] The classification consists of four categories—focal (≥50% of normal glomeruli), sclerotic (≥50% of globally sclerosed glomeruli), crescentic (≥50% of glomeruli with cellular crescents) and mixed (<50% normal, <50% crescentic, <50% globally sclerotic glomeruli) classes depending on the percentage of globally sclerotic or crescentic glomeruli in the renal specimens. Since the proposal of the 2010 classification, many studies have been published to validate the application of 2010 classification in different populations, but the results were controversial. Therefore, combining the results by carrying out a meta-analysis might be useful to further validate the clinical application of the 2010 classification to predict the outcome of AAV patients.

We thus performed a meta-analysis[13] combining data from 17 studies from Asia, Europe, North America, South America and Australia. In all, 1601 patients including 61 pediatric patients and 1540 adults were enrolled in our study. Our meta-analysis results showed that renal outcome was the best in focal class while worst in sclerotic class. However, renal outcome was not significantly different between mixed and crescentic classes. As the only meta-analysis in the literature discussing the application of 2010 histopathological classification in AAV patients,[29] our study thus provides evidence that showed the prognostic value of proportion of normal and sclerotic glomeruli in determining the renal outcome of AAV patients. As sclerotic lesions usually represent chronic glomerular injuries in the kidney, sclerotic class is associated with worse renal outcome. It is known that crescent is one of the characteristics of AAV patients. Crescent usually represents active vasculitis lesion in AAV patients. However, our meta-analysis did not find significant difference regarding renal outcome between crescentic class and mixed class. Considering the percentage of normal and crescentic glomeruli in renal biopsy specimens constitutes the major differences between focal and crescentic class, our results thus pointed out that prognostic value of crescent might not be as useful as normal or sclerotic glomeruli. One possible explanation for this result is the different treatment responses of patients with active vasculitis to standard treatment. Though there is some argument supporting the combining of these two classes[29,30] and some studies already did so while validating the 2010 classification,[29,31] we suggested stratifying patients with those histopathological classes in large study cohort would be useful.

Tubulointerstitial injury is an important factor that affects renal outcome in patients with glomerulonephritis. However, tubulointerstitial parameters were not included in the 2010 classification due to avoidance of statistical complexity. The absence of tubulointerstitial injury in the classification does not mean it is not important because in our study, in which 186 AAV patients were diagnosed in our center,[13] we found the focal class had the mildest and the sclerotic class the most severe tubulointerstitial injury. Therefore, tubulointerstitial injury might affect renal outcome, but further studies taking into account tubulointerstitial lesion as well as glomerular lesions might be necessary.

It has been seven years since the initial proposal of 2010 histopathological classification in AAV. Though certain limitation exists in its application in clinical practice, our meta-analysis confirmed its prognostic value to predict renal outcome in those patients. Further studies aiming to modify the classification and provide the realistic prognosis of the patients with AAV might be necessary. We encourage more studies using the 2010 classification to assess different treatment responses to provide optimistic management of this disorder and tailored treatment accordingly.

Treatment of AGN

AGN treatment was mostly the same as AAV treatment. Briefly, treatment can be divided into two phases—induction of remission and maintenance therapy. Induction therapy commonly comprises high-dose glucocorticoids in combination with cyclophosphamide or methotrexate. However, if the patient experiences life-threatening organ involvement like pulmonary hemorrhage, plasma exchange or high-dosage methylprednisolone would be

beneficial.[32] Plasma exchange has been shown to have a therapeutic effect in patients with AAV who have severe renal impairment (serum creatinine >6 mg/dl or requiring dialysis), and those with alveolar hemorrhage.[33] Maintenance therapy usually requires long-term immunosuppressant for at least 18−24 months after successfully finishing induction therapy,[8] and recent studies showed prolonged remission maintenance therapy would provide some evidence for reducing relapses.[34,35] Azathioprine or methotrexate and low-dose glucocorticoids are currently the standard treatment of maintenance therapy. Other immunosuppressants such as leflunomide or mycophenolate mofetil prove useful in a small group of patients and are suggested as the second-line treatment of the disease.

Biological therapies are new approaches to treat patients with AGN. Rituximab, an anti-CD20 monoclonal antibody is one of the new alternative methods to treat patients with renal diseases. By depleting circulating and tissue-resident CD20 cells, rituximab has been increasingly used off-label in various autoimmune diseases including AGN and various studies have published showing the efficacy of rituximab in treating patients with the disease. Specks et al[36] demonstrated in their study that a single course of rituximab was as effective as conventional immunosuppressants for remission induction therapy. Furthermore, many other studies reported a high rate of improvement by rituximab in treating patients with GPA and EGPA.[37,38] Moreover, rituximab was shown to be superior to traditional immunosuppressant—azathioprine for remission therapy.[39] However, the results of rituximab treatment were not unanimous. The RAVE study marked a watershed in the therapy of rituximab because the study showed the rituximab was not superior to cyclophosphamide in patients with severe AAV but might be superior in relapsing diseases.[40] As a novel therapeutic strategy in AGN, rituximab was also associated with many side effects including hypogammaglobulinemia, infusion reactions, hepatitis B reactivation, *Pneumocystis jirovecii* pneumonia and others.[41] More studies are necessary to investigate the therapeutic effects and safety of rituximab in treating patients with the disease.

Apart from rituximab, Avacopan—a C5a receptor inhibitor was found to be effective in treating patients with AAV.[42] Other agents like tumor necrosis factor (TNF) blockade (infliximab) and soluble TNF receptor antagonist (etanercept) are still being studied to investigate their efficacy or safety in AAV patients.

Conclusion

It has been more than 20 years since we first discovered ANCA and then proved its pathogenesis. Tremendous advances have been made in understanding the nature of AAV. Though lots of work has been done to investigate the mechanism of the disease, and improve therapeutic strategy and disease management, much remains unclear in this field, and the prognosis of the disease is unsatisfactory. Further work is required to optimize better prognosis and disease management.

"*The road ahead afar, and I will search long and far.*" On the road of optimized management of AAV, we are heading in the right direction.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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