ANCA-associated vasculitis and anti-GBM disease: the experience in China

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Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and anti-glomerular basement membrane (GBM) disease, the typical autoimmune diseases causing necrotizing crescentic glomerulonephritis (CrGN), have been largely reported in Caucasian patients. However, since the establishment of standard assays in China to screen for serum ANCA and anti-GBM autoantibodies over 10 years ago, Chinese patients with the two diseases were increasingly identified and studied. This editorial comment focuses on the updated information of Chinese patients with the two diseases.

ANCA-associated vasculitis and pauci-immune crescentic glomerulonephritis

The annual incidence of AAV in Europe is 10–20 per million per year [1]; the incidence in China is not available yet. In our referral diagnostic centre in Peking University First Hospital, over 200 new patients with AAV are diagnosed annually; this indicates that AAV is not rare in Chinese [2].

Chinese patients with ANCA-associated vasculitis

Clinical characteristics of Chinese patients with AAV

Regarding the disease spectrum, there is a striking preponderance of microscopic polyangiitis (MPA), constituting...
about 80% of the patients with AAV [2]. This is similar to Japanese patients with AAV [3]. In AAV patients older than 65 years, the proportion of MPA is even higher [4], in contrast to many Caucasian populations, especially in northern Europe at high latitude where Wegener's granulomatosis (WG) is much more common [1]. Myeloperoxidase (MPO), rather than proteinase-3 (PR3), is the major target ANCA antigen in Chinese patients [2,4]. Even in patients with a clinical picture of WG, about 60% of them have ANCA directed to MPO [5]. The reason for the high prevalence of MPO-ANCA in Chinese patients with AAV, even in the disease classically associated with PR3-ANCA, is not clear yet. It has been suggested that different genetic backgrounds and environmental factors might be the contributors [6]. Accordingly, the involvement of the ear, nose and throat seems less common than that from some reports in Caucasians [2,4,7]. The influence of high prevalence of MPA and MPO-ANCA on the clinical picture is reflected by the higher prevalence of renal involvement and severe renal damage [8].

Although individuals of all ages can be affected, with a slightly female predominance [2], over 40% of our patients are older people (≥65 years old at diagnosis) [4]. In comparison with younger patients (<65 years old at diagnosis), older patients have more pulmonary involvement and worse patient and renal survivals. Furthermore, older patients have a higher risk of secondary pulmonary infection after initiation of immunosuppressive therapy, especially in those with pulmonary interstitial fibrosis. In fact, pulmonary infections together with older age and renal function at presentation are independent predictors of mortality [4].

**Monitoring relapses of AAV in remission**

Chinese patients with AAV also experience relapses despite long-term immunosuppressive therapy. Persistent positive ANCA during remission might be associated with relapses [9]. Even after patients progress to end-stage renal disease (ESRD), life-threatening relapses such as severe pulmonary haemorrhage, though not common, may still occur [10]. We found that 70% of the relapses in patients with AAV affected the same organ as during the onset of the disease, which might facilitate early recognition of relapse [11]. Circulating neutrophil gelatinase-associated lipocalin, a marker of neutrophil degranulation, might be a useful biomarker for assessing disease activity and relapse of AAV [12].

**Complement activation via alternative pathway is involved in human AAV**

An animal study by Xiao et al. suggested that complement activation via the alternative pathway is necessary in the murine anti-MPO antibody-induced mouse pauci-immune necrotizing Glomerulonephritis [13]. We found glomerular C3c deposition in about one-third of the patients with AAV in direct immunofluorescence of renal biopsy [14]. Our further study found that, in renal specimens of patients with MPO-ANCA-associated vasculitis, membrane attack complex (MAC), C3d, factor B and factor P could be detected, while mannose-binding lectin and C4d could not be detected. C3d and factor B co-localized with MAC, and factor P co-localized with C3d. These results suggested that activation of the complement system via the alternative pathway is involved in the development of human AAV [15].

**Propylthiouracil-induced AAV**

Propylthiouracil (PTU), the most commonly used anti-thyroid drug in Asia, is one of the most common medications to induce AAV in Chinese. Our early screening found that over 20% of patients taking PTU, with a mean duration of 29.4 months, have positive serum ANCA. This proportion is higher than that from Europe [16], which might be due to the dosage and duration of taking PTU as well as different genetic backgrounds [6]. However, only about one-fourth of the patients with PTU-induced ANCA have clinical vasculitis [17]. The different clinical phenotypes of patients with PTU-induced ANCA, with and without clinical vasculitis, provide a unique opportunity to investigate the role of ANCA in the development of clinically evident vasculitis.

Our studies suggested that the longer duration of using PTU, occurrence of MPO-ANCA, increasing titres and avidity of MPO-ANCA and occurrence of serum anti-endothelial cell antibodies are closely associated with the development of clinical vasculitis [17]. PTU-induced ANCA usually recognize multiple antigens, which may be used to differentiate it from primary AAV [17,18]. PTU-induced MPO-ANCA has higher titres but lower avidity and recognized restricted epitope(s) on MPO [17]. PTU-induced MPO-ANCA may remain positive for a long time. However, after cessation of PTU and induction therapy, the long-term outcome of patients is much better than primary AAV. Once remission is achieved, maintenance therapy might not be necessary [18,19].

**ANCA-negative pauci-immune glomerulonephritis**

Pauci-immune CrGN is one of the most common causes of rapidly progressive glomerulonephritis. In the majority of patients with pauci-immune CrGN, the renal disorder is regarded as part of AAV. The vast majority of patients with pauci-immune CrGN have serum ANCA. However, some patients with pauci-immune CrGN lack ANCA and this subgroup of patients had not been fully investigated. Our recent study compared the clinical and histopathological characteristics of patients with ANCA-negative pauci-immune CrGN with their ANCA-positive counterparts. It was found that ANCA-negative patients have higher levels of proteinuria, poorer renal outcomes and less constitutional and extra-renal symptoms than ANCA-positive patients. ANCA-negative pauci-immune CrGN might represent a distinct disease entity independent of ANCA-positive pauci-immune CrGN [20].

The pathogenesis of ANCA-negative pauci-immune CrGN is not clear yet, but neutrophils [21] and complement activation [22] might play a major role.

**Anti-GBM disease**

Anti-GBM disease is characterized by linear deposition of immunoglobulin G (IgG) along GBM. When it is accom-
panied by pulmonary haemorrhage, it is also called Goodpasture's syndrome. The disease is caused by circulating autoantibodies against the non-collagenous domain of the α3 chain of Type IV collagen (α3(IV) NC1) with two well-defined cryptic epitopes EA and EB [23].

Anti-GBM disease is rare, with an incidence of 0.5 to 1 case per million per year in Caucasians and less common in blacks [24]. In China, although the incidence is not available, over 30 anti-GBM-positive sera from new patients were screened annually in our referral diagnostic centre, indicating that this disease is not rare in the Chinese. Our recent study found that the DRB1*1501 allele was significantly associated with anti-GBM disease (36/ 88 vs 64/400, P = 1.597 × 10^{-7}) with the allele frequency of 0.77. Therefore, the HLA-DRB1*1501 allele is the genetic marker for susceptibility to the disease in Chinese, the same as in Caucasians and Japanese [25].

Clinical and histopathological features of anti-GBM disease in Chinese

Chinese patients with anti-GBM disease have two peaks in age. The first peak is in the second and third decades of life with a striking male preponderance and a higher frequency of pulmonary haemorrhage. The second peak is in the sixth and seventh decades of life with a slight male predominance [26]. The older patients have milder renal damage and less pulmonary involvement, but similar renal survival and worse patient survival, compared with younger patients [unpublished data].

About 30% of our patients are ‘double positive’ for anti-GBM antibodies and ANCA. The renal prognosis of double-positive patients is similar to that of patients with anti-GBM antibodies alone and much worse than that of patients with AAV [27]. Thus, intensive plasma exchange and immunosuppressive therapy for anti-GBM disease is crucial in the early stage and maintenance therapy is necessary for vasculitis in remission. Our further study demonstrated that anti-GBM antibodies in ‘double-positive’ patients have a broader spectrum of target antigens and lower levels of autoantibodies against α3(IV) NC1, compared with those without ANCA [28].

Although the typical linear deposition of IgG is observed in the majority of patients, exceptional cases are frequently identified, some with concurrent immune complex-mediated glomerulonephritis such as membranous nephropathy, immunoglobulin A (IgA) nephropathy, membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis and lupus nephritis. The nephritis may reveal the cryptic epitopes and thus induce an anti-GBM autoimmune response [29].

Patient survival rate is 72.7% at 1 year and renal survival rates are 35.8% at 2 months and 25.0% at 1 year, similar to the reports from Hong Kong, Japan and Caucasian populations. The combination therapy including plasmapheresis, corticosteroids and cyclophosphamide has an overall beneficial effect on patient and renal outcome, especially in patients with pulmonary haemorrhage or severe renal damage at presentation [unpublished data]. Poorer prognosis occurs in patients with serum creatinine over 600 μmol/L, oliguria or anuria at presentation, crescent involving over 85% of glomeruli and renal involvement before pulmonary haemorrhage [26].

Evolution of human anti-GBM antibodies in the development and progression of the disease

The aetiology of anti-GBM disease is unknown. Recently, we purified natural autoantibodies against GBM from normal human sera [30]. These natural autoantibodies also recognize α3(IV)NC1, EA and EB, but with lower titre, lower avidity and restricted to the IgG2 and IgG4 subclasses [30,31]. We speculated that the changing immune characteristics of anti-GBM antibodies may be associated with the development and progression of the disease. In fact, our serial studies demonstrated that the level and avidity of anti-GBM antibodies are closely associated with disease severity [26,32]. During disease progression, the restricted IgG subclass of IgG4 in patients with normal renal function [33] is widely spread to the four IgG subclasses in patients with severe renal damage [34] and inter- and intra-molecular epitope spreading occurred during disease progression [35].

Summary

AAV and anti-GBM disease are not rare in the Chinese. They are the two major causes of CrGN in Chinese similar to Caucasian reports. Clinical phenotype-based studies may reveal the pathogenic mechanism of the autoantibodies, which may provide useful information to improve the clinical management of these patients in the near future.

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