

# Anti-Glomerular Basement Membrane Glomerulonephritis and Vasculitis: The Existence of Two Different Pathogenetic Mechanisms for the Formation of Crescentic Glomerulonephritis with or without Vasculitis and the Association with Antineutrophil Cytoplasmic Antibody

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## Editorial

Anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) is typically characterized by the presence of circumferential crescent, as well as linear IgG deposition along the glomerular basement membrane (GBM). This disease is frequently associated with pulmonary hemorrhage, which is referred to as Goodpasture syndrome. We can detect anti-GBM antibody (Ab) in the serum, which reacts with the GBM of renal specimens obtained from normal subjects.

When an immunofluorescence (IF) study is performed on the kidney of patients with this disease, IgG deposition is occasionally demonstrated on Bowman's capsule as well and C3 is also found along the GBM at a lower frequency and intensity. However, no deposition of immunoglobulins or complements on the peritubular capillaries (PTCs) and arterioles / arteries were observed in the interstitium. In addition, although some reports have shown IgG deposition along the basement membrane of the distal tubulus, we have not experienced this phenomenon in our cases to date [1].

On the other hand, when a renal biopsy is performed at the early phase of the disease, we cannot identify apparent acute tubulointerstitial nephritis, which is manifested by the infiltration of acute inflammatory cells, except for the surrounding areas of damaged glomeruli [2]. According to the definition of 2012 revised International Chapel Hill Consensus Conference Nomenclature of vasculitides, anti-GBM disease is included as vasculitis. This vasculitis occurs only in the glomerular and alveolar capillaries [3]. Therefore, I investigated the presence of lesions which are not included in the glomerular and alveolar capillaries.

Excluding the glomerular capillary loops and alveolar capillaries, only several cases of apparent arteritis, capillaritis or venulitis in the kidney and / or other organs have been reported [4]. In our institution, we experienced two cases which were associated with vasculitis out of total 12 biopsy cases of anti-GBM GN. One case showed arteriolitis near the glomerulus and the other case revealed peritubular capillaritis (PTCitis) [5]. The former case was characterized with fibrinoid degeneration in the arterial wall and the latter manifested with the loss of CD31 and type IV collagen staining on the PTCs as well as the infiltration of acute inflammatory cells around the PTCs. The staining loss of CD31 and type IV collagen on the PTCs indicates damage in these capillaries and the occurrence of PTCitis. Some cases belonging to this type of PTCitis was presumed to be due to the immune complex deposition of a neutrophil cytoplasmic antigen and its antibody, and this finding was confirmed in an investigative study cases related to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [6]. When we consider the existence of two different types of anti-GBM GN (crescentic GN without vasculitis vs. crescentic GN with vasculitis), two different pathogenetic mechanisms could exist. Namely, one type is caused only by anti-GBM Ab, whereas the other type is related to both anti-GBM Ab and ANCA. Indeed, 25-30% of anti-GBM GN patients

were recently documented to have ANCA in their sera [7,8]. The most common ANCAs are anti-myeloperoxidase (MPO) Ab or anti-proteinase 3 (PR3) Ab, however, 7 additional ANCAs are known to exist and play roles in the pathogenesis of various diseases [9]. Therefore, we studied the existence of ANCAs in the two above-mentioned cases. The two cases were negative for both MPO- and PR3-ANCAs. However, ANCA positivity was noted by an IF study on the neutrophils in the case with PTCitis, but no conclusive positivity of other ANCA subsets by an ELISA (ANCA panel kit, WIESLAB, Euro Diagnostica) was obtained at that time. On the other hand, regarding the case with arteriolitis, due to the fact that all of the patient's serum had been used up, we thus could not perform either the IF study or the subset ELISA tests for ANCAs at that time.

The existence of vasculitis in anti-GBM GN has not been satisfactorily studied. However, the frequent demonstration of ANCAs in the patients' sera suggests the co-existence of vasculitis, including PTCitis, in their renal specimens. Indeed, we occasionally encounter cases with GI bleeding and purpura in the legs, which are presumed to be due to vasculitis, in addition to kidney and/or lung manifestations. Furthermore, lung tissues obtained in the cases of pulmonary hemorrhage are described to not demonstrate any IgG deposition in the tissues. This finding also implies the association of ANCAs in the lung tissues. In conclusion, the association between vasculitis and anti-GBM GN should be elucidated.

## Addendum

Based upon my experience, I concluded that the anti-GBM Ab titers are generally high in cases with anti-GBM GN without ANCA, whereas their titers in ANCA-associated vasculitis cases tend to be low. (Anti-GBM GN without ANCA: n=4, titer 789-106 EU, mean 315 EU versus Anti-GBM GN with ANCA: n=7, titer 700-16 EU, mean 249 EU.)

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