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Pathology and Pathogenesis of ANCA-associated Glomerulonephritis

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The histopathologic hallmarks of acute glomerulonephritis (GN) caused by antineutrophil cytoplasmic autoantibodies (ANCA) are fibrinoid necrosis and crescent formation. The immunopathologic hallmark of ANCA GN is a paucity (low level) of immune deposits by immunofluorescence microscopy. This distinguishes ANCA GN from immune complex GN, C3 glomerulopathy, and anti-GBM GN. ANCA GN has little or no immunoglobulin or complement deposited in glomeruli because a major component of the activation of neutrophils and monocytes that results in GN and vasculitis occurs in the circulation prior to localization within glomerular capillaries and other vessels. Different pathogenic mechanisms in different forms of GN caused differences in the frequency and severity of crescent formation. Anti-GBM GN is the most destructive and has the highest frequency and severity of crescent formation. ANCA GN is second in severity but on average has fewer crescents than anti-GBM GN. GN caused by coexisting ANCA and anti-GBM has severity that is more like anti-GBM GN. In glomeruli with acute ANCA mediated inflammation, the acute lesions typically have fibrinoid necrosis, breaks in glomerular basement membranes and cellular crescent formation. Glomerular fibrinoid necrosis is caused by release of plasma containing coagulation factors at sites of capillary rupture resulting in fibrin formation. Within several weeks, glomerular fibrinoid necrosis is transformed into areas of sclerosis, and cellular crescents are transformed into fibrocellular and then fibrous crescents. Usually, and the same biopsy specimen, different glomeruli have different degrees of severity and different activity and chronicity because new lesions continue to develop until remission occurs. Multiple different ANCA GN pathological classification systems have been proposed to help predict response to therapy and renal survival. The Berden classification system and modifications of this system have been widely evaluated with variable results. This approach categorizes ANCA GN based on the % normal glomeruli, % glomeruli with cellular or fibrocellular crescents, and % glomeruli with globally sclerotic glomeruli. In the original study in 2010 (KI 2010,21:1628) the focal class (≥50% normal glomeruli) had the best prognosis, the sclerotic class (≥50% global sclerosis) had the worst prognosis, the crescentic class (≥50% cellular or fibrocellular crescents) and the mixed class (≥50% abnormal glomeruli with no predominance of crescents or global sclerosis) had intermediate outcome, with crescentic class have a better outcome than

mixed class. Some validation studies have confirmed the original correlations, including a study from Korea (Kidney Res Clin Pract. 2021;40:77-88). Multiple other validation studies have shown variable outcomes for the crescentic and mixed groups, or no difference (e.g. CJASN 2020;15:1103-1111). This variability may be related to differences in the overall activity versus chronicity in the mixed and crescentic group among different cohorts. ANCA disease segmental necrotizing vasculitis can affect kidney vessels in addition to glomerular capillaries, including medullary vasa recta (medullary angiitis) and small to medium arteries. ANCA disease can be renal limited or have small vessel vasculitis in any other organ in the body, sometimes accompanied by granulomatous inflammation. Microscopic polyangiitis (MAP) has systemic vasculitis but no granulomatosis, granulomatosis with polyangiitis (GPA) has systemic vasculitis with granulomatosis, and eosinophilic granulomatosis with polyangiitis (EGPA) has blood eosinophilia and asthma. EGPA has the lowest frequency of ANCA positivity unless there is evidence for vasculitis or glomerulonephritis. In Europe and North America, GPA has a predominance of ANCA specific for proteinase 3 (PR3-ANCA) whereas MPA has a more equal distribution of PR3-ANCA and ANCA specific for myeloperoxidase (MPO-ANCA). In Asia all clinicopathologic variants of ANCA disease have predominantly MPO-ANCA. Some patients with ANCA have pathologic findings consistent with concurrent immune complex GN or anti-GBM GN. Immune complex GN with ANCA positivity and glomerular fibrinoid necrosis and crescents have more aggressive disease than the same pattern of immune complex GN without ANCA. Patients with concurrent ANCA and anti-GBM have glomerulonephritis that, at onset, is more severe and more like anti-GBM GN than ANCA GN. Anti-GBM disease without ANCA rarely has disease relapse after the initial acute injury remits, whereas patients with anti-GBM and ANCA are at risk for recurrences of ANCA disease after anti-GBM disease resolves (Kidney International 2017;92, 693–702).

The pathogenesis of ANCA disease involves complex interactions of the adaptive and innate immune systems, with influences from genetic and environmental factors (Figure 1). The pathogenesis of ANCA is initiated by the genesis of pathogenic autoantibodies that is facilitated by impairment of regulatory T cells and B cells. Genome wide association studies have identified different HLA loci associated with PR3-ANCA versus MPO–ANCA, which is expected because different HLA molecules present different antigens to the immune system. Epigenetic regulation of expression of ANCA target antigens in neutrophils may have a role in ANCA disease. Once a pathogenic level of ANCA is present in the circulation, in vitro and in vivo animal model studies indicate that neutrophils and monocytes can be activated by ANCA if there is a synergistic pro-inflammatory stimulus (for example a concurrent viral infection). Engagement of Fcγ receptors is important for neutrophil activation. Once activated, neutrophils up regulate receptors that facilitate adherence and penetration of vascular endothelium, and release factors that activate the alternative complement pathway, which attracts more neutrophils and crimes neutrophils for activation by ANCA. A mouse model of MPO ANCA GN induced by IV injection of anti-MPO

IgG (e.g. JCI 2002;110:955-963) has been used in multiple studies to elucidate the pathogenesis of MPO-ANCA GN. No animal model of PR 3-ANCA is available. The MPO–ANCA GN model has demonstrated that anti-MPO IgG alone because his disease, anti-MPO-T cells alone does not cause disease, neutrophils and alternative complement pathway are required, genetic factors influence disease severity, and disease severity and phenotypes are modulated by Fcγ receptors, cytokines, kinin system, and adhesion molecules and their ligands. A critical pathogenic event is engagement of C5a receptors (C5aR) by C5a. In the mouse model of MPO ANCA GN induced by IV injection of anti-MPO IgG, blockade of the C5a receptor prevents disease induction (JASN 2014;25:225-231). Based on this pre-clinical model, clinical trials have been performed demonstrating that a C5a receptor inhibitor Avacopan) is effective in replacing high-dose corticosteroids during induction of remission in ANCA glomerulonephritis (JASN 2017;28:2756-2767). This translation of animal model studies to clinical practice demonstrates that knowledge of pathogenic events is important for the discovery of novel treatment strategies.

Figure 1: ANCA Pathogenesis