Crescentic Glomerulonephritis: New Aspects of Pathogenesis

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Summary: This review provides a summary of recent advances in the understanding of crescentic glomerulonephritis, focusing on antineutrophil cytoplasm antibody (ANCA)-associated vasculitis and anti–glomerular basement membrane (anti-GBM) antibody disease. In ANCA-associated vasculitis (AAV), four main conceptual advances are discussed as follows: (1) evidence for the pathogenicity of ANCA, (2) molecular mimicry and the role of infection in AAV, (3) evidence for aberrant T-cell responses and T-cell regulation in AAV, and (4) advances in understanding of genetic predisposition to AAV. In relation to anti-GBM disease we discuss the following: (1) the nature of the Goodpasture autoantigens, (2) T-cell responses and regulation in anti-GBM disease, and (3) human leukocyte antigen and non–human leukocyte antigen genetic associations.
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Glomerular crescents are a histopathologic marker of severe renal injury, characterized by disruption in the integrity of the glomerular capillary wall, leading to macrophage, T-cell, and plasma protein infiltration into Bowman space. Crescentic glomerulonephritis is the most aggressive form of glomerulonephritis and, if untreated, patients can progress to end-stage renal failure within weeks of presentation. Response to treatment is dependent on the proportion of cellular versus fibrous crescents. Crescentic glomerulonephritis can be caused by a variety of inflammatory and autoimmune disorders. The presence and distribution of glomerular immune deposits is used to classify the form of crescentic glomerulonephritis, and also has pathogenetic significance. There are three main groups: (1) pauci-immune (scanty or absent immune deposits), generally caused by antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV), (2) linear deposition of IgG on the capillary wall owing to anti–glomerular basement membrane (GBM) disease, and (3) immune complex glomerulonephritis with granular immune deposits (Fig. 1).

In this review, the first two categories, pauci-immune crescentic glomerulonephritis owing to AAV and anti-GBM disease are discussed. The third category, immune complex glomerulonephritis (most commonly caused by lupus nephritis, membranoproliferative nephritis, IgA nephropathy, Henoch-Schonlein purpura, postinfectious glomerulonephritis, or cryoglobulinemia) is discussed elsewhere in this issue.

ANCA-ASSOCIATED CRESCENTIC GLOMERULONEPHRITIS

Pauci-immune glomerulonephritis caused by AAV is the most common form of crescentic glomerulonephritis (80%), and usually is associated with the presence of ANCA in the serum, reactive to either proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA). PR3 and MPO are constituents of neutrophil granules and monocyte lysosomes. AAV are multisystem vasculitides that cause destructive inflammation of small arterioles, leading to several clinically and pathologically defined clinical entities: Granulomatosis with polyangiitis (Wegener's) (GPA), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and renal limited vasculitis. As a component of GPA, renal vasculitis is the most common severe manifestation, occurring in more than 50% at presentation, but in 70% to 85% during the course of the disease.[1] AAV causes considerable morbidity and mortality, with end-stage renal failure developing in more than 20% of patients at 5 years.[2] With treatment, 85% of patients will go into remission, but the diseases follow a relapsing-remitting course, with a 50% relapse rate within 5 years.[2]

MPO-ANCA is associated predominantly with MPA and CSS, whereas PR3-ANCA is associated with GPA. GPA, MPA, and CSS differ in their clinical presentation. Patients with GPA have more frequent relapses, and often present with granulomatous necrotizing inflammation of the upper airways, nasal passages, and sinuses.[3] Those with MPA have similar vasculitic features, but without granulomatous upper-airway involvement, whereas those with CSS have vasculitis, asthma, and eosinophilia. Although GPA, MPA, and CSS share important similarities,

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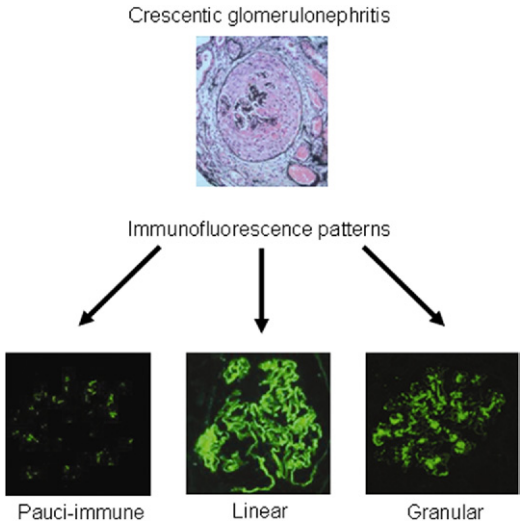

Figure 1. Silver stain showing a crescentic glomerulus (top). Immunofluorescence pictures show the three characteristic patterns of IgG deposition in crescentic glomerulonephritis.

the clinical features are heterogeneous, and it is unclear to what extent they share the same pathogenetic mechanisms.

Pathogenicity of ANCA

ANCA originally were recognized as a biomarker of pauci-immune crescentic glomerulonephritis in the 1980s.[4,5] Subsequently, two characteristic autoantigens were identified as PR-3[6] and MPO.[7] These autoantigens are serine proteases expressed in the azurophilic neutrophil granules and monocyte lysosomes. In GPA, PR3-ANCA has a high sensitivity (93% in active disease) and specificity (93%).[8] Increasing titers of PR3-ANCA were present in 81% of patients with a relapse in one prospective study, but 11 of 38 increases were not followed by a relapse.[9] MPO-ANCA has a high specificity in the right clinical context,[10] but also has been described in other diseases such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma, and inflammatory bowel disease.

Cytokine-primed neutrophils and monocytes express the target antigens PR3 and MPO on their cell membranes. ANCA bind to their target antigen by $F(ab')_2$ specificity,[11] but also co-aggregate activating Fc gamma receptors on the surface of myeloid cells,[12] thereby activating the cell. Neutrophils and monocytes activated by ANCA release oxygen radicals, lytic enzymes, and inflammatory cytokines, such as interleukin (IL)-8.[13,14] In co-culture experiments, ANCA stimulated neutrophil killing of endothelial cells.[15] When neutrophils were passed over endothelial cell surfaces in vitro in a flow chamber, the presence of ANCA in the medium promoted adhesion and transmigration of primed neutrophils across tumor necrosis factor–stimulated endothelium.[16] The normal process of noninflammatory clearance of apoptotic neutrophils by phagocytes is disrupted by ANCA, which also may enhance their proinflammatory effects.[17] Monocyte activation also has been shown in AAV, with increased levels of IL-6 and neopterin.[18,19]

A recent publication showed that ANCA depend on glycosylation for their function because deglycosylation attenuated their ability to activate neutrophils and ameliorated disease in a mouse model.[20]

The most direct evidence that ANCA are pathogenic in human beings comes from a single case report of pulmonary hemorrhage and glomerulonephritis in a neonate with transplacental transfer of MPO-ANCA from a mother with active MPO-positive vasculitis.[21] There is no report of PR3-ANCA being transferred in this way to date.

Animal models of vasculitis in rats and mice have provided valuable information about the pathogenesis of the disease. A rat model of MPO-positive vasculitis has been developed in our laboratory by immunizing Wistar Kyoto (WKY) rats with human MPO. The rats developed ANCA with a pauci-immune glomerulonephritis and lung hemorrhage.[22] Intravital microscopy of mesenteric venules showed that intravenous injection of rat MPO-ANCA induced neutrophil rolling, adhesion, and transmigration in the cytokine-activated vessels, together with injury to the venules causing hemorrhage.[23] This confirms the in vitro findings described earlier in an in vivo setting. Xiao et al[24] developed a passive mouse model of MPO-ANCA–induced AAV by immunizing MPO-deficient mice with murine MPO, and transfer of purified immunoglobulin or splenocytes to a naive host. Both purified immunoglobulin and splenocytes were able to induce disease, indicating that MPO-ANCA antibodies alone can be directly pathogenic.[24] However, disease was more severe when a splenocyte population was transferred, suggesting that both humoral and cellular arms of the immune system are involved. Further work implicated neutrophils and the alternative pathway of complement in the pathogenesis of disease in this model.[25,26] Summers et al[27] showed the importance of Toll-like receptor 4 stimulation in increasing glomerular neutrophil infiltration after injection of MPO-ANCA.

In contrast, no convincing model of systemic vasculitis owing to PR3-ANCA has been developed to date. Human PR3 and murine PR3 are structurally different, and antibodies to them do not cross-react and cannot be used in passive transfer experiments. Anti-PR3 antibodies were increased in PR3/neutrophil elastase-deficient mice, but passive transfer of these antibodies did not produce systemic disease, although local dermal inflammation was enhanced.[28]

Infection, Molecular Mimicry, and AAV

A role for infective episodes preceding relapse of AAV has long been suggested.[29] Stegeman et al[30] described an association between nasal carriage of *Staphylococcus aureus* and relapses of PR3-ANCA–associated AAV, and prophylactic treatment with co-trimoxazole resulted in a 60% reduction in relapses.[31] Low-grade infection in the