Renal Involvement in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Reza Zonozi, MD, John L. Niles, MD, Frank B. Cortazar, MD*

KEYWORDS

• ANCA-associated vasculitis • Granulomatosis with polyangiitis
• Microscopic polyangiitis • Rapidly progressive glomerulonephritis

KEY POINTS

- Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is the most common cause of rapidly progressive glomerulonephritis (RPGN).
- ANCAs play an important pathogenic role in the development of AAV via the activation of neutrophils.
- The hallmark pathologic renal lesion in AAV is pauci-immune necrotizing and crescentic glomerulonephritis presenting as RPGN. In many cases, however, the disease course can be indolent with a slow deterioration of renal function.
- Early initiation of treatment is paramount to prevent irreversible organ damage.
- Enhanced understating of the pathogenesis of AAV has provided the rationale for novel targeted therapies.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small-vessel vasculitis, which is the most common cause of rapidly progressive glomerulonephritis (RPGN).[1] If diagnosis or therapy is delayed, there are organ-threatening and life-threatening implications. Thus, the practicing clinician should pay special heed to this entity. This article reviews the renal involvement of AAV.

DEFINITIONS, NOMENCLATURE, AND CLASSIFICATION

AAV has traditionally been classified based on clinical and pathologic features into 4 entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA),

Disclosure Statement: F.B. Cortazar and J.L. Niles have served as consultants for ChemoCentryx. R. Zonozi has no disclosures.
Division of Nephrology, Vasculitis and Glomerulonephritis Center, Massachusetts General Hospital, 101 Merrimac Street, Boston, MA 02114, USA
* Corresponding author.
E-mail address: FCORTAZAR@PARTNERS.ORG

Rheum Dis Clin N Am 44 (2018) 525–543
https://doi.org/10.1016/j.rdc.2018.06.001
rheumatic.theclinics.com

renal limited vasculitis, and eosinophilic GPA (EGPA).[2] During the active phase of disease, greater than 90% of AAV patients with glomerulonephritis are ANCA positive.[3,4]

GPA is characterized by extravascular necrotizing granulomatous inflammation and necrotizing vasculitis with a proclivity for the upper and lower respiratory tract in addition to the kidney. GPA is more commonly associated with proteinase 3 (PR3)-ANCA than myeloperoxidase (MPO)-ANCA. MPA is distinguished from GPA by the lack of extravascular granulomatous inflammation and is more frequently associated with MPO-ANCA. Likewise, renal limited vasculitis is predominantly an MPO-ANCA disease (>75% of cases) and is defined by the lack of extrarenal manifestations of vasculitis.[5]

EGPA, like GPA, leads to necrotizing granulomatous inflammation of the respiratory tract and is distinguished from other causes of AAV by the presence of eosinophilia and asthma. Unlike the other AAV syndromes, only approximately 50% of patients with EGPA have a positive ANCA, typically MPO-ANCA.[6] ANCA-positive and ANCA-negative cases, however, have different clinical phenotypes. ANCA-positive EGPA more commonly causes glomerulonephritis and mononeuritis multiplex, whereas ANCA-negative EGPA is more commonly associated with cardiac involvement.[7]

In clinical practice, the distinction between GPA and MPA is rarely definitive, because granulomatous inflammation is apt to be missed by sampling error and biopsy is often foregone in the setting of a positive ANCA and a characteristic presentation. Rather, a presumptive diagnosis is made based on apparent clinical features. For example, patients with destructive upper airway disease or cavitary pulmonary nodules are given a diagnosis of GPA, whereas those presenting with pulmonary hemorrhage and RPGN are generally labeled as MPA. From a practical standpoint, classifying a patient as GPA versus MPA is somewhat subjective and may not add significant value to disease management.

Another way to classify AAV patients is by ANCA serotype. There is a geographic variation of the frequency of ANCA specificity, with PR3-ANCA more common in northern Europe and MPO-ANCA more common in southern Europe and Asia.[8] Genome-wide studies have demonstrated that key predisposing genetic variants correlate with ANCA serotype more strongly than clinical diagnosis (eg, GPA).[9]

In the clinical setting, ANCA serotype better predicts disease prognosis and the propensity for relapse than clinical syndrome, with PR3-ANCA patients more likely to have refractory disease and a relapsing course.[10] Finally, ANCA specificity can be associated with certain disease manifestations and clinical scenarios. For example, ANCA with interstitial lung disease, which can occur in isolation of other clinical features and masquerade as idiopathic interstitial lung disease, is essentially always an MPO-ANCA disease.[11] Similarly, drug-associated AAV occurs with MPO-ANCA with or without PR3-ANCA but virtually never with PR3-ANCA alone.[12] Due to genetic and pathophysiologic underpinnings and the superior clinical utility, many experts now propose classifying AAV patients as having simply PR3-ANCA or MPO-ANCA rather than having GPA or MPA.

PATHOGENESIS

Risk Factors for Antineutrophil Cytoplasmic Antibody Production

Although the exact mechanisms leading to the genesis of ANCA autoantibodies remain unclear, several risk factors have been implicated, including genetic predispositions, infectious insults, and medication exposures.

Given the central role of antigen presentation in the initiation of an adaptive immune response that ultimately leads to antibody production, it is conceivable that different