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Necrotizing Glomerulonephritis-Vasculitis and Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA)

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The purpose of this paper is to briefly review the clinical setting and types of renal lesions associated with vasculitis in which ANCAs may lead to a diagnosis. I will review published work on this subject as well as work in progress regarding the value of ANCAs in the nephrology practice at Mayo.

Renal involvement is an important clinical manifestation of systemic necrotizing vasculitis[1-4]. The vasculitides encompasses a heterogeneous group of disorders that involve the vessels either as the primary target or as a secondary feature of diseases such as rheumatoid arthritis, lupus erythematosus, congenital hypocomplementemia, cryoglobulinemia, relapsing polychondritis, and Henoch-Schönlein purpura. Vasculitis that involves the vessels as the primary target include the polyarteritis group, Wegener's granulomatosis, and Strauss-Charg vasculitis.

Necrotizing vasculitis is usually defined by the presence of fibrinoid necrosis and acute inflammatory cellular infiltrate within the wall of the vessel. Focal segmental necrotizing glomerulonephritis is characterized by necrosis either involving the glomerular capillaries in some, but not all, glomeruli (focal) or involving a segment of the glomerulus (segmental). The glomerular changes characteristically show «capillaritis» (disruption of the capillary wall, presence of fibrin and inflammatory cells); and frequent crescents[4-6]. Conceptually, we consider focal segmental necrotizing glomerulonephritis a vasculitis involving glomerular capillaries[5]. Traditionally, vasculitis has been classified according to the size and type of vessel affected. Classic polyarteritis nodosa is viewed as necrotizing vasculitis of medium-sized arteries with or without aneurysm formation. Microscopic polyarteritis usually denotes small vessel vasculitis (mainly arterioles and capillaries) of major visceral organs. Segmental necrotizing glomerulonephritis is defined here as vasculitis involving visceral capillaries. Clinicians and pathologists prefer the term «hypersensitivity vasculitis» to indicate cutaneous vasculitis involving the small vessels[7]. Some studies, including ours, documented involvement of the vasculature of both small and medium-sized vessels, so-called overlap syndrome of idiopathic vasculitis[5,8]. Table I shows the types of vasculitis observed on renal biopsies at the Mayo Clinic that involve the vessels and glomeruli as the primary target. The immunofluorescent findings are either negative of showed only small amounts of immunoglobulin and/or complement deposition without any specific pattern, referred by some as «pauci-immune» glomerulonephritis[9]. In our study of patients shown in table I, the immunofluorescent findings were negative in 42 % specimens, while 58 % showed trace to 1 + immunoglobulin deposition with or without complement component deposition, usually in a focal and segmental pattern.

Several authors have recognized the relationship between *crescentic* glomerulonephritis and systemic idiopathic vasculitis[10-12]. My colleagues and I studied all patients with crescentic glomerulonephritis, defined as ≥ 30 % of crescents on the renal biopsy, who were seen at the Mayo Clinic during a 15-year period[10]. Fifty-one percent of these patients had a systemic illness consistent with vasculitis proven on tissue biopsy of the kidney or other organs in more than 25 % of the patients. Furthermone, the renal biopsies of those patients with necrotizing vasculitis and glomerulonephritis in table I showed glomerular crescents in many, but not all, biopsies. Thus glomerular crescents are a characteristic feature of necrotizing renal vasculitis but the frequency of crescents is variable.

Table I. Necrotizing Glomerulonephritis and Vasculitis. A Study of 198 Patients and Renal Biopsies

Classification	Frequency %
Capillaritis only (FSNGN) *	54
Microscopic polyarteritis	17
Polyarteritis nodosa	15
Wegener's	14

* FSGN: Focal segmental necrotizing glomerulonephritis.

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ANCAs are very helpful in the diagnosis of these types of renal lesions, that is, idiopathic (pauci-immune) crescentic glomerulonephritis and necrotizing vasculitis. Most, but not all, affected patients have a rapid loss of renal function consistent with the clinical syndrome of rapidly progressive glomerulonephritis.

The clinical features of systemic idiopathic vasculitis have been reviewed elsewhere[4]. Both sexes are equally at risk; vasculitis has a distinct predilection for patients between 50 an 70 years of age. In general, patients with arteritis have a more prominent clinical course than do patients with small-vessel vasculitis, that is, those who have focal segmental necrotizing glomerulonephritis. Patients with arteritis have a clinical course manifested by more frequent fevers; constitutional symptoms such as malaise, myalgias, and arthralgias; pulmonary involvement; and abdominal pain. The overlap of these findings in patients with arteritis with those patients with small-vessel vasculitis is such that they are of little differential diagnostic value for an individual patient[5]. The survival of patients with systemic idiopathic vasculitis has improved remarkably during the last 30 years, since the first patient with vasculitis was treated with glucocorticoids at the Mayo Clinic. Our studies of patients with necrotizing vasculitis and glomerulonephritis showed a one-year survival rate of 81 %, 65 % at 5 yrs, and 40 % at 10 yrs[5]. These results were obtained using high dose prednisone in all patients treated and, cyclophosphamide plus prednisone in about 20 % of patients with severe renal disease or lack of adequate response to steroids. Intravenous pulses of methylprednisolone are helpful during the acute phase of the disease[10].

Ante-neutrophil cytoplasmic autoantibody test (ANCA) in the diagnosis of idiopathic necrotizing crescentic glomerulonephritis and renal vasculitis. Anti-neutrophil cytoplasmic autoantibodies (ANCA) are serologic markers for a disease spectrum characterized by necrotizing vascular inflammation in patients with renal and extrarenal involvement[9, 14]. The association of ANCA test results with systemic or organ-specific vasculitides varies depending on the organ systems studied. For example, ANCA associated with pulmonary syndromes are predominantly cytoplasmic (c)-ANCA[15], whereas in glomerulonephritis they are predominantly nuclear or perinuclear (p)-ANCA[14]. Several methods have been used to detect ANCA. Proteinase 3 is the antigen recognized as c-ANCA by immunofluorescence. There is a good correlation between this immunofluorescent pattern and the antigen-specific, solid-phase assay for antibodies to proteinase 3[16-18]. Myeloperoxidase (MPO) is the major antigen recognized as p-ANCA by immunofluorescence. As a result of problems with interpretation of p-ANCA, the correlation between this immunofluorescent pattern and the solid-phase assay for MPO-ANCA is less satisfactory[16-18].

We *prospectively* examined the value of c-ANCA tested by indirect immunofluorescence and antimyeloperoxidase autoantibodies (anti-MPO) measured by a solid-phase assay in the diagnosis of idiopathic (pauci-immune) necrotizing-crescentic glomerulonephritis (NCGN) and renal vasculitis at our institution[19]. A diagnosis was established on the basis of clinical and renal biopsy findings. Patients were followed for at least six months. One hundred eleven patients were studied: 28 had NCGN and renal vasculitis. The combination of the enzyme-linked immunofluorescence assay for antimyeloperoxidase autoantibodies (MPO-ANCA) and the immunofluorescence assay for cytoplasmic anti-neutrophil cytoplasmic autoantibodies (C-ANCA) had a 78 % sensitivity and 84 % specificity. A firm diagnosis was established before the anti-neutrophil cytoplasmic autoantibody determination in 26 of 28 patients with NCGN and renal vasculitis. The antimyeloperoxidase autoantibody values would have suggested the diagnosis in the other two patients. Five of the 28 patients had negative anti-neutrophil cytoplasmic autoantibody tests. High antimyeloperoxidase autoantibody values were detected mainly in patients with NCGN and renal vasculitis whereas lower values were less specific and were detected in some patients with in anti-glomerular basement membrane antibody disease and lupus glomerulonephritis.

In this prospective study, we have shown that 1) there is a good correlation between idiopathic NCGN and renal vasculitis and ANCA, specifically anti-MPO autoantibodies determined by solid phase assay and antiproteinase-3 antibodies determined by immunofluorescence (c-ANCA); 2) these assays have good sensitivity and specificity for the diagnosis of idiopathic NCGN and renal vasculitis in patients with parenchymal renal diseases; 3) high anti-MPO values are more specific for this diagnosis of NCGN and renal vasculitis made on the basis of information from the renal biopsy. These results support the conclusion in other studies[14-16]. ANCA test are an important addition to the serologic screening of idiopathic (pauci-immune) necrotizing glomerulonephritis and vasculitis and may lead to an early diagnosis. This is important because these patients undergo a rapid deterioration of renal function and the response to therapy is gratifying.

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