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The Clinical Features and Pathology of Vasculitis Associated with Anti-Myeloperoxidase Autoantibodies

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SUMMARY: Autoantibodies to myeloperoxidase (MPO) are associated with the autoimmune disease, systemic vasculitis, in humans. This results in severe inflammation and microscopic necrosis of multiple organs, especially the kidneys, leading to renal failure and death. The discovery of MPO autoantibodies has permitted the development of new diagnostic tests allowing earlier diagnosis and more effective therapy. Furthermore these antibodies are directly implicated in tissue injury by binding to MPO on the neutrophil cell membrane and stimulating neutrophil activation and degranulation. The causes for the breakdown in tolerance to MPO are not known although rare cases are drug-induced and remit on drug withdrawal. An understanding of the biology of MPO and its involvement in the pathogenesis of vasculitis is of importance in understanding the pathogenesis of vasculitis and the development of newer therapies.

Vasculitis implies the inflammation and necrosis of blood vessel walls, thrombotic occlusion of the lumen and infarction of distal tissue. This appearance may be localised or systemic and may have a clearly identified cause, such as an infection, or result from autoimmune dysregulation. The autoimmune or 'primary', systemic vasculitides are a group of clinico-pathological syndromes classified according to the size of blood vessel involved and the presence of circulating autoantibodies to neutrophil cytoplasmic antigens (ANCA) (Table 1). Those vasculitides associated with ANCA comprise 50 - 70% of all cases and have attracted increasing scientific and public health interest due to their increasing frequency, and high risk of death or kidney failure. Two ANCA antigenic targets are specifically associated with vasculitis, the 29kd serine protease, proteinase 3 (PR3), and myeloperoxidase (MPO).

Background: ANCA associated vasculitis (AASV) has an incidence in Western Europe of approximately 25/million/year, with a prevalence over 200/million, and it accounts for 5% of the causes of end stage renal failure (ESRD) (1,2). European and American studies point to an ethnic difference with a lower incidence in those of black African origin. Wegener's granulomatosis, associated with PR3-ANCA appears more common in Northern Europe and America, while MPO-ANCA positive microscopic polyangiitis is more common in Japan. There is only weak evidence for a genetic contribution to aetiology, environmental exposure to dusts, such as in coal mining and after the Kobe earthquake, increases the risk of disease. Rarely, MPO-ANCA vasculitis is triggered by the drugs penicillamine, hydralazine, propylthyouracil or minocycline, or occurs in association with another inflammatory disease, including rheumatoid arthritis or anti-glomerular basement membrane disease.

Clinical presentation and therapy: The kidney is involved in over 90% of cases of MPO-ANCA vasculitis, next in frequency is the lung in 50%, alveolar hemorrhage; then the skin, purpuric rash; the joints, flitting arthritis; the eye, episcleritis; the peripheral nerves, axonal neuropathy; the gut, intestinal hemorrhage or perforation and the brain, cerebral vasculitis. There is usual a prodromal period of at least 3 months characterised by increasing fatigue, polymyalgia, fevers and weight loss. These presentations are fatal when untreated but now around 90% achieve disease control with the combination of corticosteroids and the alkylating agent cyclophosphamide (3). Early mortality results from organ failure, especially lung hemorrhage, the infective complications of immunesuppression or cardiovascular disease. Kidney function at presentation is the most important predictor of outcome (Fig. 1) and is also associated with the severity of treatment-related toxicity. Many patients present in established renal failure, at which stage, the removal of MPO-ANCA by plasma exchange improves the rate of renal recovery (Gaskin, American Society of Nephrology, 2002).

The evidence base for treatment decisions has been developed from a series of randomised controlled trials in the past decade, including four trials by the European Vasculitis Study Group (EUVAS). Newer therapies, including intravenous immunoglobulin, tumor necrosis factor alpha blockade and b cell depletion provide the hope for safer, effective treatment in the future (4,5).

Pathology: The renal lesion of MPO-ANCA vasculitis is a necrotizing, crescentic glomerulonephritis (1). The glomeruli contain foci of fibrinoid necrosis caused by vascular occlusion of segmental capillaries. This excites an intense, neutrophil predominant glomerular infiltrate and the secondary formation of a circumferential crescent composed of proliferating epithelial cells and macrophages that constricts the glomerular tuft within Bowman's capsule. In contrast to other cause of crescentic glomerulonephritis, immune deposits are scanty or absent. The development of glomerular fibrosis, loss of renal tubules and their replacement by tubulo-interstitial

Table 1. Classification of vasculitis (1)

Size of predominant vessel involvement	'ANCA-associated' (usually ANCA positive)	'ANCA negative'
Small 'microscopic'	Wegener's granulomatosis Microscopic polyangiitis (renal-limited vasculitis)	Henoch Schönlein purpura Cryoglobulinaemic vasculitis Cutaneous vasculitis
Medium (muscular arteries)	Churg-Strauss angiitis	Polyarteritis nodosa Kawasaki disease
Large		Giant cell arteritis Takayasu's arteritis

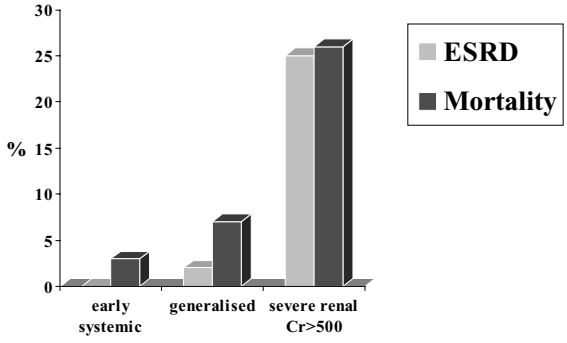

Fig. 1. Percentage mortality and those in end stage renal disease (ESRD) 1 year after diagnosis for patients with 'early systemic' vasculitis, no or mild renal disease (hematuria, normal creatinine); 'generalized' vasculitis, creatinine < 500 μmol/l; and severe renal vasculitis, creatinine > 500 μmol/l. Data from the European Vasculitis Study group.

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scarring is more evident in MPO-ANCA vasculitis than PR3-ANCA disease and indicates chronicity and a poorer outcome. A similar pathogenesis is responsible for other organ manifestations, for example, alveolar capillaritis in the lung is the cause of the lung hemorrhage.

Serology: The association of ANCA with vasculitis has provided both a diagnostic tool and an insight into pathogenesis. Initially detected by indirect immunofluorescence of patient sera on alcohol-fixed normal human neutrophils, rapid immunoassays are now available for MPO or PR3-ANCA that facilitate earlier diagnosis and identify a target for therapy. ANCA levels usually fall with therapy although it is unclear whether drug doses should be titrated against ANCA levels. The persistence of ANCA or the return of ANCA after drug withdrawal indicate a high risk of relapse. ANCA of all IgG subtypes is present and preliminary reports have observed IgM ANCA and IgG3 ANCA with more severe disease. Inhibitory antibodies or 'anti-idiotype' antibodies for ANCA are detectable in the circulation. Their importance is unclear but their enrichment in pooled normal human immunoglobulin has provided a rational for the use of immunoglobulin in therapy (4).

Several animal models have confirmed the pathogenetic role of MPO-ANCA in vasculitis. A mouse prone to spontaneous crescentic nephritis and MPO-ANCA has been bred from an MRL/lpr background. The Brown-Norway rat given mercuric chloride develops an intestinal vasculitis and MPO-ANCA. Unilateral perfusion of an MPO-immunised rat with neutrophils causes a pauci-immune glomerulonephritis, and infusion of spleen cells or MPO-ANCA from an MPO-immunized animal into a RAG knockout mouse induces a renal lesion identical to that seen in patients (6).

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