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, to aetiology, environmental exposure to dusts, such as in coal mining and after the Kobe earthquake, increases the risk of disease. Two ANCA antigenic targets are specifically associated with vasculitis, the 29kd serine protease, proteinase 3 (PR3), and myeloperoxidase (MPO).

Table 1. Classification of vasculitis (1)

<table>
<thead>
<tr>
<th>Size of predominant vessel involvement</th>
<th>‘ANCA-associated’ (usually ANCA positive)</th>
<th>‘ANCA negative’</th>
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<tbody>
<tr>
<td>Small ‘microscopic’</td>
<td>Wegener’s granulomatosis</td>
<td>Henoch Schönlein purpura</td>
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<td></td>
<td>Microscopic polyangiitis (renal-limited vasculitis)</td>
<td>Cryoglobulinaemic vasculitis</td>
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<td>Cutaneous vasculitis</td>
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<tr>
<td>Medium (muscular arteries)</td>
<td>Churg-Strauss angiitis</td>
<td>Polyarteritis nodosa Kawasaki disease</td>
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<tr>
<td>Large</td>
<td></td>
<td>Giant cell arteritis Takayasu’s arteritis</td>
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been proved to be clinically safe, suppress disease activity for at least 1 year, and reduce the total dose of immunosuppressive agents. Fatal side effects, especially infections, can be avoided by using intravenous immunoglobulin (IVIg) therapy.

The use of immunoglobulin in therapy is based on the association of ANCA with vasculitis. ANCA and IgG3 ANCA are detectable in the circulation. Their importance is unclear but their enrichment in bodies or 'anti-idiotype' antibodies for ANCA are detectable in the circulation. The persistence of ANCA or the return of ANCA after drug withdrawal indicates 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 anti-ANCA and IgG subtypes is present and preliminary reports have observed IgM ANCA levels. The persistence of ANCA or the return of ANCA to normal 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.

Several animal models have confirmed the pathogenic 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.

**REFERENCES**


