ANNALS OF THE RHEUMATIC DISEASES

Antineutrophil cytoplasmic antibodies and the eosinophilia myalgia syndrome

The eosinophilia myalgia syndrome (EMS) is an inflammatory multisystem disease which emerged in epidemic form in 1989 and was linked to the ingestion of L-tryptophan.1 In the acute form of the EMS, severe myalgia and pronounced blood eosinophilia are accompanied by widespread necro-inflammatory lesions, including systemic vasculitis, fever, weight loss, and encephalopathy.2

We found none of the 45 sera to be positive for ANCA. Likewise all sera were negative by ELISA testing for the above mentioned antibody specificities. A number of sera produced fluorescent staining on the alcohol fixed granulocytes; however, this was attributable to ANA. In a Chang cell assay, 19 of 45 sera (42%) tested positive for ANA.

The strongest clinical associations of ANCA have been shown to be that of anti-PR3 with Wegener’s granulomatosis (WG) and of anti-MPO with microscopic polyangiitis (MPA) and pauci-immune rapidly progressive glomerulonephritis (RPGN).3 These disorders have been categorised as the ANCA-associated vasculitides. In WG, 80% of patients are positive for cytoplasmic ANCA (cANCA); in generalised disease this is in the more than 90%, with anti-PR3 being the most frequent antibody subspecificity (table). The association between pANCA or anti-MPO and MPA or pauci-immune RPGN is less strong—approximately 65% of MPA patients are anti-MPO-positive. While anti-PR3 is highly specific for WG, anti-MPO has also been found at low rates and low titres in a number of other chronic inflammatory diseases.4

A strong association of ANCA with secondary vasculitis has not yet been found.5 6 The present results conform with this; notably, no serum showed anti-PR3 or anti-MPO reactivity. These results thus add to the evidence that anti-PR3 and anti-MPO are important markers for the classification and clinical diagnosis of primary systemic vasculitides, but not secondary vasculitides. The low prevalence of ANCA in the EMS makes it unlikely that ANCA have a pathogenetic role in this disorder.

Clinical associations of antineutrophil cytoplasmic antibodies (ANCA)

<table>
<thead>
<tr>
<th>ANCA</th>
<th>anti-PR3</th>
<th>pANCA</th>
<th>anti-MPO</th>
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</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis (n = 445)</td>
<td>358 (80%)</td>
<td>292 (66%)</td>
<td>5 (1%)</td>
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<tr>
<td>MPO</td>
<td>20 (4%)</td>
<td>37 (8%)</td>
<td>33 (7%)</td>
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<tr>
<td>Churg-Strauss syndrome (n = 17)</td>
<td>5 (30%)</td>
<td>5 (12%)</td>
<td>5 (12%)</td>
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<tr>
<td>EMS (n = 45)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

cANCA = Cytoplasmic ANCA; pANCA = perinuclear ANCA; PR3 = proteinase 3; MPO = myeloperoxidase; EMS = eosinophilia myalgia syndrome.

SILENT MYOCARDIAL INFARCTION IN WEGENER'S GRANULOMATOSIS

At postmortem, patients with Wegener’s granulomatosis (WG) frequently show a clinically overlooked and diffuse disease process. Cardiologically, many such patients have been asymptomatic but present histological findings of specific heart involvement. We report two cases of silent myocardial infarction related to WG—a feature which, to our knowledge, has not been reported in clinical series.

Patient 1. A 42 year old man was admitted to hospital because of severe vasculitis flare. He had an eight month history of arthritis and lower limb dysaesthesia. Examination showed an acutely ill patient with a 39°C fever. He had oral ulcers, haemorrhagic gingival hyperplasia, bilateral haemorrhagic nasal discharge with crusts, diffuse necrotic purpura and black discoulouration of fingers and toes. Ankle jerks were absent. Standard blood tests showed: leucocyte count 9.6 × 10⁹/l; serum creatinine 112 μmol/l; C reactive protein 278 mg/l; fibrin 12 g/l; total creatine kinase (CK) concentration 1102 U (normal range 15–60 U). Chest X-ray showed a wedge shaped opacity in the right upper lobe, and 130 U. Cholesterol, triglyceride and blood glucose values were within the normal range. Microscopic haematuria was present at 15/HPF. The electrocardiogram showed ST segment elevation and loss of R waves in leads V₁, V₂, and V₃. Silent anterior myocardial infarction was diagnosed and WG was suspected. It was confirmed by: a) anti-neutrophil cytoplasmic antibodies (diffuse cytoplasmic fluorescence) in the serum; b) pannusitis demonstrated by computed tomography scan; c) multineuritis on electro-physiological examination; d) necrotising vasculitis on skin biopsy. Lupus anticoagulant and anticardiolipin antibodies were absent. Antithrombin III, protein C and...
protein S plasma concentrations were normal. Initial treatment comprised intravenous administration of methylprednisolone, cyclophosphamide and sodium heparinate. Other drugs included dinitrosoride and enalapril. The short term course was uneventful. At day 14, the patient had a sudden rupture of the spleen. Splenectomy was performed. Histological analysis of the spleen showed widespread necrotising vasculitis with haemorrhagic infarction. At day 30, coronaryography was normal. At month 24, the patient had no active sign of WG nor any recurrence of myocardial ischaemia.

**Patient 2.** A 41 year old woman was admitted for suspected systemic vasculitis. She had a two year history of clustered rhinitis with relapsing sinusitis and antibodies against the heart. Physical examination showed a febrile, disoriented, acutely ill woman with nasal obstruction, bilateral ear chondritis, diplopia, right upper eyelid ptosis, dysaesthesia and paresthesia in the left foot, and a left hip tenderness and ankle jerk. Chest auscultation was normal. Standard blood tests showed: leucocyte count 16.7 × 10^9/L, creatinine 52 μmol/L, C reactive protein 252 mg/l, fibrin 10 g/l, total CK concentration 179 U with MB isoenzyme 179 U. Cholesterol, triglycerides and blood glucose values were within the normal range. Low grade haematuria was present at 10/HPF. The electrocardiogram showed ST segment and T wave elevation in leads V4 and V5, with loss of R waves in the anterior leads. Echocardiography showed septal akinesia and diffuse hypocontractility without dilation of the left ventricle. Silent acute anterosetal myocardial infarction was diagnosed. A diagnosis of severe WG was further supported by: a) antineutrophil cytoplasmatic antibodies (diffuse cytoplasmatic fluorescence) in the serum; b) mononeuritis multiplex on electromyography study; c) multiple bilateral infarcts of the white matter on cerebral magnetic resonance imaging; d) typical granulomatous necrotising vasculitis on nasal biopsy. Tests for antiphospholipid antibodies were negative. Treatment included intravenous pulses of high-dose prednisolone followed by oral prednisone, monthly intravenous cyclophosphamide, and supraventricular tachycardia, and cardiac mass.

Our two patients had myocardial infarction clearly related to WG because: a) myocardial infarction was novel, with no angina in the past; b) myocardial infarction accompanied severe generalised WG flare, c) the extent of clinical systemic vasculitis was unusually diffuse (distal limb necrosis and splenic infarction in patient 1 and cerebral vasculitis in patient 2); d) atheroma could be rejected as the cause of myocardial infarction because of normal coronaryography in patient 1 and absence of any risk factor in patient 2; and e) no cardiac ischaemic event was observed during a two year follow up under immunosuppressive therapy.

In the literature, we could find only two reports of myocardial infarction recognised in alive WG patients. Gatenby et al report the fulminating course of WG in a 28 year old man who died from painful and massive myocardial infarction. Pathological examination of the heart showed vasculitis with fibrinoid necrosis of the media and partial occlusion of the lumen by pale antemortem thrombus in all coronary vessels. In the other case reported in the literature, an embolic mechanism rather than vasculitis could account for the symptomatic myocardial ischaemia.

Wegener's granulomatosis is defined as a small vessel vasculitis. The severity of the condition, and occasional associated death, might be related to the progression of vasculitis and thrombosis to larger sized vessels. Coronary wall inflammation and formation of lumens blood clot are two mutually non-exclusive processes that may have been responsible for myocardial ischaemia in our two patients.

In practical terms, cardiac enzymes and electrocardiography should be repeatedly monitored in a patient with WG flare.