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 organ involvement with the skin, lungs, serosal membranes, and the peripheral nervous system being involved most frequently.2,3 The chronic form of the EMS is characterised by progressive fascial and cutaneous fibrosis, leading to the development of a picture resembling eosinophilic fasciitis, accompanied by polyneuropathy, chronic fatigue, and psychological dysfunction.4,5

A spectrum of vascular lesions has been described including perivascular aggregation of mononuclear cells, intimal and medial thickening and fibrosis, ultrastructural alterations of the vascular endothelium, and frank vasculitis with mural infiltration by mononuclear cells.5,6 The last of these was found primarily in small arteries, veins and capillaries, and by immunofluorescence microscopy no deposition of immunoglobulins or complement components was found.1,5

These histopathological features resemble those of the pauci-immune small vessel vasculitides, a group of diseases strongly associated with antineutrophil cytoplasmic antibodies (ANCA).7 In the March 1991 issue of this journal Cilurzo and colleagues8 reported a patient with acute EMS and perinuclear ANCA (pANCA) with anti-myeloperoxidase (MPO) specificity together with a small vessel vasculitis in skeletal muscle. This report prompted the question whether EMS also is an ANCA associated disease.

From a nationwide collection of EMS sera, we tested a random sample of 45 sera for ANCA. The sera were from 39 females (age 30–69 years) and six males (age 51–61 years) who fulfilled the diagnostic criteria of chronic EMS.4 ANCA testing was performed in compliance with the guidelines of the European ANCA Study Group with an indirect immunofluorescence test on ethanol fixed and formalin fixed granulocytes; antibody specificity was tested by specific enzyme linked immunosorbent assay (ELISA) using proteinase 3 (PR3), MPO, lactoferrin, lysozyme, elastase, and cathepsin G as antigens.5 For distinction between pANCA and antinuclear antibodies (ANA), sera were also examined on cultured human cells.6

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).7 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 sub specificity (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 a low rate and low titres in a number of other chronic inflammatory diseases.8

A strong association of ANCA with secondary vasculitides has not yet been found.9,10 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 has a pathogenic role in this disorder.

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 15–100 U). Chest X-ray showed cardiomegaly, and bilateral pleural effusion with lung shadow measurements of 130 U. Cholesterol, triglyceride and blood glucose values were within the normal range. Microscopic haematuria was present at 15/HFP. 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) pansinusitis demonstrated by computed tomography scan; c) multinucleitis on electro-cardiographic examination; d) necrotising vasculitis on skin biopsy. Lupus anti-coagulant and antidiiodilipin antibodies were absent. Antithrombin III, protein C and

Clinical associations of antineutrophil cytoplasmic antibodies (ANCA)

<table>
<thead>
<tr>
<th>cANCA</th>
<th>anti-PR3</th>
<th>pANCA</th>
<th>anti-MPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegener’s granulomatosis (n = 445)</td>
<td>358 (80%)</td>
<td>292 (66%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Microscopic polyangiitis (n = 44)</td>
<td>8 (18%)</td>
<td>7 (17%)</td>
<td>33 (73%)</td>
</tr>
<tr>
<td>Churg-Strauss syndrome (n = 17)</td>
<td>5 (30%)</td>
<td>5 (30%)</td>
<td>12 (71%)</td>
</tr>
<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.
protein S plasma concentrations were normal. Initial treatment comprised intra-
venous administration of methypred
nisolone, cyclophosphamide and sodium hep-
arinate. Other drugs included diltiazem,
dinitroisorbide, 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 
necrotizing vasculitis with haemorrhagic 
infarction. At day 30, coronarography 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 crusted rhinitis 
with respiratory symptoms, and showed 
productive cough with bloody sputum. A 
chest radiograph showed disseminated 
cavitation, and nodules. Fibroscopy 
disclosed a pseudotumoral aspect of the 
bronchial mucosa. Microscopic examination of 
a bronchial specimen showed giant cell 
granuloma. Treatment against tuberculosis 
was started with four drugs. Because 
distressing neurological signs appeared 
investigation was transferred to our department. 
Physical examination showed a febrile, 
disoriented, acutely ill woman with nasal 
obstruction, bilateral ear chondritis, diplopia, 
right upper eyelid ptosis, dysaesthesia 
and paresis in the right arm, and absent infrapatellar 
ankle jerk. Chest auscultation was normal. 
Standard blood tests showed: leucocyte 
count 16.7 x 10⁹/l; creatinine 52 μmol/l; C 
reactive protein 252 mg/l; fibrin 10 g/l; total 
CK concentration 179 U/l; with MB isoenzyme 
179 U. Cholesterol, triglycerides and blood 
glucose values were within the normal range. 
Lowgrade 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 
aakinesia and diffuse hypococontractility without 
dilation of the left ventricle. Silent acute 
anteresetal myocardial infarction was 
diagnosed. A diagnosis of severe WG was 
further supported by: a) antineutrophil cyto-
plasmic antibodies (diffuse cytoplasmic 
fluorescence) in the serum; b) mononuertis 
multiplex on Electromyogram study; c) 
multiple bilateral infarcts of the white matter 
on cerebral magnetic resonance imaging; d) 
typical granulomatous necrotizing 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 
sodium heparinate. All symptoms remitted 
rapidly, except for mononeuritis multiplex 
that progressively deteriorated over a period 
of months. After eight cycles, cyclo-
phosphamide was changed for daily oral 
etoposide which has been considered to be 
effective in neuropathy. At month 18, 
relapse of sinusitis and pulmonary nodules 
required increased prednisone dosage and 
etoposide was combined with methotrexate. 
At month 22, the patient had no 
active sign of WG nor any recurrence of 
myocardial ischaemia.

Because Wegener's granulomatosis was once 
a uniformly fatal disease, before 
successful use of cyclophosphamide therapy, 
early reports were only of postmortem 
findings. However, reviewing 54 cases, 
found myocardial granulomata in six and focal 
coronary arteries in 15; death was retrospectively 
attributed to myocardial infarction in two 
cases. A more recent comprehensive review 
reported the most common pathological 
findings as pericarditis in 50%, focal 
myocarditis in 25%, coronary arteritis in 
50%, and myocardial infarction in 11% 
of WG postmortem cases in which the heart 
was examined.

Such high prevalence contrasts sharply 
with clinical data collected in the 
cyclophosphamide era. Only 10 (6%) of 158 WG 
patients had detectable heart involvement in 
the series reported by Hoffman et al. All had 
only specific pericarditis and no myocardial 
ischaemia was reported. Heart involvement 
was not mentioned among the causes of 
death. In contrast, there have been several 
patients published reports of WG with myocardial 
involve—heart muscle disease, heart 
block and supraventricular tachycardia, and 
cardiac mass. 1-7

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 coronarography 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 immuno-
suppressive therapy.

In the literature, we could find only two 
reports of myocardial infarction recognised 
in alive WG patients. Gatenby et al report the 
fulminant course of WG in a 28 year old man 
who died from painful and massive myo-
cardial 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. 8 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 vessels. 9 
Coronary wall inflammation and 
formation of lumen 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.

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