LETTERS TO THE EDITOR

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 a clinical picture resembling eosinophilic fasciitis, accompanied by polyneuropathy, chronic fatigue, and psychological dysfunction.[3 4]

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.[2 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.[2 5 6]

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 Cilursu and colleagues[8] 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 subspecificity was tested by specific enzyme linked immunosorbent assay (ELISA) using proteinase 3 (PR3), MPO, lactoferrin, lysozyme, elastase, and cathepsin G as antigens.[9] For distinction between pANCA and antinuclear antibodies (ANA), sera were also examined on cultured human cells.[10]

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 the case in 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 a low rate and in low titres in a number of other chronic inflammatory diseases.[7]

A strong association of ANCA with secondary vasculitis has not yet been found.[7 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 have a pathogenetic role in this disorder.

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1 Carr L, Ruether E, Berg P A, Lehnert H. Eosinophilia-myalgia syndrome in Germany: An epidemiologic review. *Mayo Clin Proc* 1994; **69:** 620–5.
2 Martin R W, Duffy J, Engel A G, *et al.* The clinical spectrum of the eosinophilia-myalgia syndrome associated with L-tryptophan ingestion. *Ann Int Med* 1990; **113:** 124–34.
3 Kaufman L D, Gruber B L, Gregersen P K. Clinical follow-up and immunogenetic studies of 32 patients with eosinophilia-myalgia syndrome. *Lancet* 1991; **337:** 1071–4.
4 Schnabel A, Reinhold-Keller E, Wolff H H, Gross W L. Fasziitis-Sklerodermie-Eosinophilie-Syndrom durch Tryptophan. *Dtsch Med Wochenschr* 1991; **116:** 1180–5.
5 Smith S A, Roelofs R I, Gertner E. Microangiopathy in the eosinophilia-myalgia syndrome. *J Rheumatol* 1990; **17:** 1544–50.
6 Tazelaar H D, Myers J L, Strickler J G, Colby T V, Duffy J. Tryptophan-induced lung disease: an immunophenotypic, immunofluorescent, and electron microscopic study. *Mod Pathol* 1993; **6:** 56–60.
7 Gross W L, Schmitt H H, Csernok E. ANCA and associated diseases: immunodiagnostic and pathogenetic aspects. *Clin Exp Immunol* 1993; **91:** 1–12.
8 Cilursu A M, Goeken J, Olson R R. Detection of antineutrophil cytoplasmic antibody in a patient with L-tryptophan induced eosinophilia-myalgia syndrome [correction in *Ann Rheum Dis* 1992; **51:** 928]. *Ann Rheum Dis* 1991; **50:** 817–9.
9 Hagen E C, Andrassy K, Csernok E, *et al.* The value of indirect immunofluorescence and solid phase techniques for ANCA detection. A report on the first phase of an international cooperative study on the standardization of ANCA assays. EEC/BCR Group for ANCA Assay Standardization. *J Immunol Methods* 1993; **159:** 1–16.
10 Schnabel A, Csernok E, Isenberg D A, Mrowka C, Gross W L. Anti-neutrophil cytoplasmic antibodies—prevalence, specificities, and clinical significance. *Arthritis Rheum.* In press.

Clinical associations of antineutrophil cytoplasmic antibodies (ANCA)

	cANCA	*anti-PR3*	*pANCA*	*anti-MPO*
Wegener's granulomatosis (n = 445)	358 (80%)	292 (66%)	5 (1%)	2 (0·4%)
Microscopic polyangiitis (n = 44)	8 (18%)	3 (7%)	33 (75%)	28 (64%)
Churg-Strauss syndrome (n = 17)	5 (30%)	5 (30%)	2 (12%)	1 (6%)
EMS (n = 45)	0	0	0	0

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 discolouration of fingers and toes. Ankle jerks were absent. Standard blood tests showed: leucocyte count $9{\cdot}6 \times 10^9$/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 15–90 U) with MB isoenzyme 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) antineutrophil cytoplasmic antibodies (diffuse cytoplasmic fluorescence) in the serum; b) pansinusitis demonstrated by computed tomography scan; c) multineuritis on electrophysiological examination; d) necrotising vasculitis on skin biopsy. Lupus anticoagulant and anticardiolipin antibodies were absent. Antithrombin III, protein C and