Antiproteinase 3 antibody in adult-onset Still's disease

Sirs,

Adult-onset Still's disease (ASOD) is a rare condition that typically affects young adults aged 16-35 years. Although it is characterized by febrile illness, typical rash and arthropathy, other systems may also be involved by the disease process. The diagnosis rests on the combination of clinical and laboratory findings. Diagnostic criteria have been developed by various investigators and those established by Cush *et al*. 1987 (1) and by Yamaguchi *et al*. 1992 (2) are frequently used for this purpose. Typically, rheumatoid factor (RF), and antinuclear factor (ANF) are negative in patients with AOSD (1, 2).

Moreover, two groups of antineutrophil cytoplasm antibodies (ANCA) are now recognized: perinuclear (pANCA), which is non-specific for a single disease and is seen in a wide spectrum of conditions, and cytoplasmic (cANCA) (3). The major autoantigen for cANCA is proteinase 3 (PR3). The antibody to PR3 is known to be highly sensitive and specific for Wegener's granulomatosis (WG) (4, 5). In this brief communication, we report the occurrence of PR3 Ab in a patient who did not suffer from WG but appeared to have AOSD instead.

A 47-year-old Arab engineer with mild controlled hypertension presented with a 2-day history of left-sided chest and upper abdominal pain and sore throat. For just over 2 months he was suffering from episodic bilateral polyarthritis affecting the wrists, elbows, shoulders and the right knee which was accompanied by mild morning stiffness. He also complained of intermittent sore throat with occasional fever spikes at home and during his admission to hospital a week earlier. He had been regularly taking diclofenac since the beginning of his symptoms, but with only modest improvement. In addition, he received two courses of amoxicillin for a presumed bacterial throat infection. The patient had been on atenolol for the last 10 years.

On physical examination he was in moderate respiratory distress, but was not cyanosed or febrile. The BP was 145/90. His throat looked congested. Moderate features of bilateral synovitis were noticed in the shoulders and knees. A pleuretic rub was heard at the left base posteriorly on chest auscultation and mild, non-tender hepatomegaly was elicited on abdominal palpation. There was no evidence of cardiac tamponade, rash or a change in skin turgor and there was no pain elsewhere. The rest of the examination was unremarkable. There was no family history of similar illnesses.

The chest radiograph revealed bilateral, plate-like atelectasis in the lower zones, but spiral CT showed pericardial effusion, a thickened pericardium and mild pleural collection on the left side, in addition to alveolar infiltrates in both lower lobes consistent with inflammatory alveolitis. Pleural fluid was not accessible for tapping. The echocardiography was confirmatory of pericardial disease.

Laboratory findings included Hb 11 g/dl , neutrophil leucocytosis (%95 of 18.5 x 10^3 u/L), thrombocytosis (523 x 10^3 u/L), CRP (170 mg/L, N < 10), ESR (120 mm/hr), serum ferritin (1484 ng/ml, N 30-400), albumin (2.3 g/dl), hypergammaglobinaemia, ALT (86 U/L, N 10-55), urea (109 mg/dl), creatinine (1.6 mg/dl), 24 hour urinary protein (0.750 g/day, N 0.05–0.1), creatinine clearance (24.2 ml/min/m^2) and sodium in spot urine test (53 mmol/L N < 10). The ANF, RF, anti-dsDNA, extractable antigens (ENAs), C3 and C4, blood cultures x3 sets, throat swab, ASO titre, hepatitis B and C serology, *M. pneumonaie* Abs, EBV Abs, parvovirus B19 Abs, herpes simplex Abs HIV serology and urine examination for haematuria or red cell casts were all either negative or not detected. A Mantoux test was negative. Abdominal ultrasonography showed diffuse hepatic enlargement. A ^{99m}Tc-EC diuretic renal scan revealed mild renal tubular dysfunction.

Despite the absence of the typical skin rash, the patient satisfied 7 (4 major and 3 minor) of the criteria of Cush *et al*. (1) and at least 5 (2 major and 3 minor) of the criteria of Yamaguchi *et al*. (2) for the diagnosis of AOSD. The associated pleuro-pericarditis, hepatic and renal dysfunctions are well known to occur as part of the systemic process of the disorder. Evanescent rash occurs in 86% of patients, pleuritis in 40% and pericarditis in 26-30%. Pneumonitis is found in about 20% of patients and often presents a diagnostic challenge (6). Nearly 40% are found to have hepatomegaly and nearly 70% demonstrate hepatic enzyme abnormalities (7). Renal involvement is uncommon, but many patients may manifest minor or transient proteinuria. Chronic proteinuria may indicate amyloidosis (8), Interstitial nephritis, subacute glomerulitis and, most recently, collapsing glomerulopathy have also been reported (9).

The patient declined a liver and renal biopsy. A course of iv pulse steroids (1 g methylprednisolone per day for 3 days) was commenced, followed by oral corticosteroid tapering. Within 2 weeks there was a remarkable clinical recovery with full resolution of the arthropathy and cardiopulmonary disease.

The first indirect immunofluorescence assay (IFT) for ANCA carried out by Merieux Laboratories (Lyon, France) was positive. This was followed by a positive test for c-ANCA (titre 1:20, N < 1:2) performed by Biocientia Laboratories, Germany. Further assays for PR3-ANCA by direct ELISA (IgG) using the International Reference Laboratory (Euroimmune, Lübeck, Germany) (5) was positive at levels of 380 and 400 u/ml, (N < 15) on separate occasions. The anti-myelopyroxidase (MPO) ELISA (IgG) was negative.

The patient showed no evidence at any point during his illness or the follow-up to suggest Wegner's granulomatosis (WG) according to the 1990 ACR classification criteria of Leavitt *et al.* (10). We therefore felt strongly that the presence of the highly specific PR3-ANCA did not justify revising the initial diagnosis of AOSD. Now, nearly 10 months have passed in the follow-up without the patient developing new physical manifestations. Apart from minimal proteinuria, renal and hepatic functions, ESR, CRP and serum ferritin have been normal on subsequent testing. Concomitantly, PR3-ANCA has significantly dropped to 80 u/ml, while the MPO-ANCA, ANF, anti-dsDNA and RF remained negative.

In our opinion this case falls within the category of clinical heterogeneity of antiPR3-associated diseases, in which the high specificity of anti-3PR to WG is challenged. Perhaps this finding is peculiar to non-Caucasian populations so far. In a recent interesting report by Lee *et al.*, among a group of predominantly Chinese patients with positive PR3, only 22% had WG. The diagnosis in the remaining patients varied from systemic vasculitis to renal disease possibly related to underlying vasculitis, livedo reticularis, amyloidosis, relapsing polychondritis, mononeuropathy and some unclassifiable cases (11). Therefore, it appears that testing for c-ANCA and anti-PR3 can certainly provide valuable and supportive information for the diagnosis of WG, but they alone should not lead the clinician to such diagnosis in the absence of the respective criteria. To the best of our knowledge, we are not aware of any similar associations having been reported in the English literature.

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Catastrophic antiphospholipid syndrome presenting with renal thrombotic microangiopathy and diffuse proliferative glomerulonephritis

Sirs,

The catastrophic variant of the antiphospholipid syndrome (APS) is an unusual but often lethal form of presentation of this syndrome characterized by a rapid development of multiorganic failure, mainly due to thrombotic microangiopathy in several organs (1). Since the early description of the catastrophic APS (1), more than 300 cases have been collected, being the kidney one of the more commonly affected organs (70%) (2). However, there are no previous reports of the simultaneous presence of diffuse proliferative lupus glomerulonephritis and renal thrombotic microangiopathy (TMA) as the first manifestation of catastrophic APS.

A 29-year-old Caucasian man was admitted at the Emergency Department in June 2004 due to the appearance of generalized oedema in the last 4 weeks accompanied by decrease in urine output. He had been diagnosed as having systemic lupus erythematosus (SLE) in 2002 due to a history of Evans' syndrome, recurrent leg ulcers, presence of antinuclear antibodies (ANA) (1/160), anti dsDNA antibodies (42 U/mL [normal < 7 U/mL]), and lupus anticoagulant (LA), and was on treatment with aspirin alone at the time of admission. Physical examination revealed marked *livedo reticularis* in the lower extremities and a generalized oedema. During the first hours of admission, he presented seizures with a cerebral computed tomography (CT) scan that showed a cortico-subcortical ischaemic lesion and a lacunar infarct in the right semioval region. Transthoracic echocardiography disclosed severe decrease in left ventricular ejection fraction (LVEF) (35%), mild aortic and mitral regurgitation, and a moderate pericardial effusion. Laboratory tests at admission showed microangiopathic haemolytic anaemia (Hb 8.5 g/dL) with schistocytes, elevated serum creatinine (5.6 mg/dL), and prolonged activated partial thromboplastin time. LA was positive, whilst IgG and IgM anticardiolipin antibodies (aCL) were negative. Anti ds-DNA antibodies were positive (> 200 U/mL) and C3, C4 and CH50 complement levels were low. He was admitted at the Intensive Care Unit (ICU) where i.v. methylprednisolone (1 g per day for 5 days) and i.v. cyclophosphamide (1,250 mg) were started. One week later, percutaneous renal biopsy was performed disclosing the presence of diffuse proliferative lupus glomerulonephritis and TMA (Figure 1). A diagnosis of definite catastrophic APS was made (3) and anticoagulation and plasma exchange (PE) sessions were started. One month later, he was discharged of the ICU because of progressive improvement of his clinical condition, including the heart involvement (LVEF > 60%). However, 4 months later, he was admitted again because of fulminant hepatic failure. The patient's clinical condition progressively deteriorated in the following days and died due to multiorgan failure. Autopsy showed multiple liver infarcts, inferior vena cava thrombosis (6.0 x 0.4 cm) and signs of bilateral pneumonia, as well as persistence of the renal TMA previously described.

In the present case, a "double" renal injury was produced probably due to an immune-complex glomerular deposition (SLE nephritis) and an ischaemic glomerular damage (TMA induced by APS) and this was the first clinical manifestation of a catastrophic APS in a patient with SLE, a combination that has not been previously described. Although there are few reports describing the simultaneous presence of proliferative glomerulonephritis and renal TMA in SLE patients (4-7), none of them fulfil the recently proposed criteria for the classification of definite catastrophic APS (3).

This variant of the APS is a life-threatening condition with an elevated mortality rate (around 50%) that requires high clinical awareness. Therefore, it is essential that it should be diagnosed early and treated aggressively. The combination of high doses of heparin plus steroids plus PE and/or intravenous gammaglobulins is the treatment of choice in patients with catastrophic APS (2).

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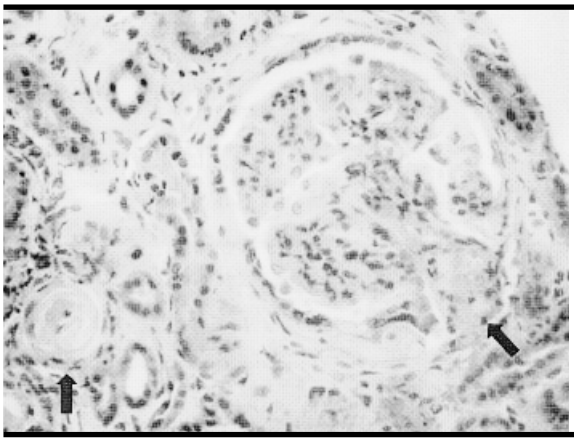

Fig. 1. Percutaneous renal biopsy specimen showing prominent diffuse endocapillar hypercelularity (type IV [WHO classification] lupus glomerulonephritis). Luminar thrombi can be seen in arterioles (**arrows**), small arteries, arterioles and glomerular capillaries. (Hematoxylin & eosin, original magnification x 400).