Sir, By 1988 many authors described antiphospholipid antibodies (aPL), such as anticardiolipin (aCL) and/or anti-β2-glycoprotein I (anti-β2-GPI) antibodies, in patients with polymyalgia rheumatica (PMR) and/or giant cell arteritis (GCA), with positivity rates between 7.5 and 63.6% of cases [1–12]. Nonetheless, as far as we have been able to ascertain, aPL syndrome (APS) has been reported in only one patient affected with GCA [13].
Evident clinical and serological signs in keeping with the diagnosis of APS were found in three of 248 (1.20%) patients seen in our hospitals [187 females and 61 males, with mean age 73.53 yr ± 7.77 standard deviation (s.d.) and range 50–92 yr], 212 affected with PMR, five with GCA, and 31 with PMR and GCA. PMR was diagnosed as the presence of typical clinical features, including pain in the shoulder girdle, pelvic girdle and neck muscles, stiffness after rest, elevation of erythrocyte sedimentation rate (ESR), and prompt clinical response to corticosteroid treatment. Classification of GCA was made on the basis of the American College of Rheumatology criteria [14]. Diagnosis of APS was based on the criteria of Harris et al. [15], including venous and arterial thromboses, recurrent fetal loss and thrombocytopenia as clinical features, and at least one positive aPL test, confirmed at least 8 weeks later as serological features. Patients were considered affected with APS when at least one clinical and one serological finding were present contemporaneously.

Assays for aPL included aCL, anti-β2-GPI and lupus anticoagulant (LA) assessment. Ig (immunoglobulin) G aCL, IgM aCL, IgG anti-β2-GPI and IgM anti-β2-GPI were determined by a home made enzyme-linked immunosorbent assay (ELISA), using the mean values of 100 healthy subjects + 2.5 s.d. as cut-off points. LA was identified in platelet-poor plasma samples by the dilute Russell viper venom time and partial thromboplastin time with low phospholipid content. Specimens shown to be abnormal were also evaluated using mixing and confirmatory tests.

The features of the three patients are briefly reported here.

Case 1. A 56-yr-old woman was admitted in May 1991 for attacks of dyspnœa and swelling and pain in her left leg. Venous Doppler ultrasound showed deep vein thrombosis (DVT) of the femoral and popliteal veins of the lower left limb, and a lung perfusional scintiscan found segmental perfusion defects, suggesting multiple bilateral pulmonary emboli. She showed no signs of systemic lupus erythematosus and antinuclear antibodies, C3, C4 and serum immunoglobulins were all within the normal range. Acenocumarol therapy was started with benefit. In April 1995, the patient was hospitalized for convulsive seizures. Electroencephalogram revealed signs of epileptic foci in the right frontal and parietal areas, and brain magnetic resonance imaging showed several small foci with high signals in the subcortical white matter, bilaterally scattered in the frontal and parietal areas. Epilepsy with ischaemic cerebrovascular disease was diagnosed, and phenobarbital (100 mg/day) and carbamazepine (800 mg/day) were administered in addition to anticoagulant therapy, with subsequent disappearance of seizures. Testing for aPL was performed at that time, showing positivity for IgM aCL (17.5 MPL, cut-off point 7.5) and IgM anti-β2-GPI (0.600 OD, cut-off point 0.282). Positivity of both was confirmed 2 months later. In October 1996, the patient presented low-grade fever, together with aching and morning stiffness in the shoulder and hip girdles and diffuse arthralgias. ESR was 89 mm/h and C-reactive protein (CRP) was 19.4 mg/dl (normal value <0.5). Assays for aPL confirmed the positivity for IgM aCL (15.8 MPL) and IgM anti-β2-GPI (0.779 OD). Diagnosis of PMR was made and prednisone (25 mg/day) was started in addition to anticoagulant and antiepileptic therapies followed by appropriate clinical and laboratory responses.

Case 2. In 1990, a 71-yr-old man rapidly developed scalp tenderness and frontal headache, followed by the visual symptom of flashing lights. Temporal artery biopsy revealed acute GCA. Prednisone was started at a dosage of 50 mg/day and gradually reduced over the next 2 yr as the patient showed excellent benefit. In February 1997, he was hospitalized for pain and diffuse swelling of the right leg, mild fever and cough. Diagnosis of DVT involving the right popliteal femoral and iliac veins was confirmed by venous Doppler ultrasound, and a perfusion lung scan revealed diffuse hypoperfusion of the left lung and of the middle right lobe, in keeping with pulmonary thromboembolism. Signs or symptoms of GCA flare-up were not found. Testing for aPL showed positivity for IgM aCL (13.7 MPL) and for IgG anti-β2-GPI (0.309 OD, cut-off point 0.278). The patient was subjected to more testing for occult malignancy in order to exclude a paraneoplastic connection to the thromboembolic events. Cytological examinations of expecoration and urine, serological markers of neoplasm and occult blood in stools all proved negative. Thyroid, abdomen and pelvis ultrasonography, and X-ray barium examination of the gastrointestinal tract were normal. Anticoagulation with warfarin was carried out and the oedematous right leg and hypoperfused lung areas showed prompt recovery. At control the aPL pattern was characterized by positivity for IgG and IgM anti-β2-GPI (0.328 and 0.632 OD, respectively).

Case 3. In April 1995 a 72-yr-old woman developed myalgias in the shoulder and hip girdles together with right temporal headache and jaw pain. Temporal artery tenderness without nodularity was found by palpation. ESR was 108 mm/h. Diagnoses of PMR and GCA were made, and oral corticosteroid therapy (prednisone 25 mg/day) was started, followed by rapid improvement of symptoms and a reduction of ESR levels. Subsequently, the dosage was gradually decreased. In September 1995, in the absence of clinical symptoms of PMR and GCA, swelling and pain in her left leg were reported. Venous Doppler ultrasound revealed thrombosis in the left popliteal and superficial femoral veins. The patient was treated with subcutaneous calcium heparin for 15 days with significant benefit. One month later, livedo reticularis on the skin of lower extremities and necrotic cutaneous lesions on the left leg occurred. Doppler ultrasound showed partial reopening of previously obstructed veins and severe stenosis of the tibial anterior artery. Histopathological examination of cutaneous lesions revealed sclerosis and thrombosis of arterial and venous dermal vessels without infiltration. Tests for aPL showed positivity for IgG aCL (25 GPL, cut-off point 11.6), subsequently confirmed by aPL control.
assays. Administration of acenocoumarol therapy was followed by regression of ischaemic symptoms.

This study shows that APS may be present in patients affected with PMR and/or GCA. However, despite the significant prevalence of aCL and anti-β2-GPI in the blood of subjects with PMR and/or GCA [3–7, 9–12], finding these diseases and APS in the same patient represents a rare clinical event. Indeed, only three of 248 patients affected with PMR and/or GCA also had overt clinical and serological features of APS. These subjects presented clinical manifestations such as venous and/or arterial thrombosis, whereas thrombocytopenia was not found. Moreover, all satisfied the serological criteria because aPL positivity was concomitant to the thrombotic process and persisted during the follow-up period, lasting between 13 and 29 months. This aPL trend is unlike that described in patients with PMR and/or GCA, in whom these antibodies disappear after clinical response to corticosteroid treatment [4, 6, 7, 10–12]. Antibody levels were moderate, Ig classes were G and/or M, and type included aCL and/or anti-β2-GPI, whereas LA activity was never found.

It is interesting to observe that other than venous and arterial thrombosis the clinical features of APS in patient 3 included livedo reticularis and thrombosis in the microcirculation of the dermal layer. Biopsies of the corresponding cutaneous lesions were in keeping with the diagnosis of APS, disclosing thrombi in dermal vessels without infiltration of inflammatory cells. These histological alterations were very different from those found in GCA characterized by dense granulomatous vascular infiltration.

Regarding the relationship of PMR/GCA with APS, we observed that the latter occurred either after (cases 2 and 3) or before (case 1) PMR and/or GCA. Moreover, PMR and/or GCA flare-up was never concomitant with APS manifestations, and anticoagulant treatment alone was able to control the clinical complications of APS, without increasing steroid therapy. These observations indicate that APS could be considered an independent disease.

aPL are considered a factor in the pathogenesis of the thrombotic process in APS [15], while their correlation with the pathogenesis of the vascular complications is unclear in PMR/GCA [3–13, 16, 17]. Perhaps, as recently affirmed [10, 11], they could act as reactive antibodies to endothelial phospholipid exposure, due to vascular inflammation. These data are in keeping with the present study, in which APS and PMR/GCA appear to be different and independent diseases, rarely present in the same patient.

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