Buerger's disease and antiphospholipid syndrome

Sir: Casellas et al reported a patient in whom arteriolar occlusions were found in association with anticardiolipin antibodies.1 The authors discussed the diagnosis of Buerger's disease (thromboangiitis obliterans) and the relation with the antiphospholipid syndrome.

Buerger's disease is an uncommon vasculitis of unknown cause, in which tobacco is implicated. Diagnosis is difficult because clinical, anatomopathologic, and arteriographic features are not specific. Cell-mediated sensitivity to collagen was reported to be helpful in diagnosis,1 but was not specified in the diagnostic criteria that have been proposed.2 Adar and Mozes suggested that positive and negative criteria might be used for diagnosis.3 Thus these authors considered that other causes of arteriolar occlusions, such as coagulation disorders, systemic diseases, or embolism, rule out the diagnosis of Buerger's disease.2

The patient described by Casellas et al presented with repetitive intratracheal fetal deaths, mild thrombopenia, and a significant level of anticardiolipin antibodies without evidence of systemic lupus erythematosus. A diagnosis of primary antiphospholipid syndrome could be made. The major arteriolar lesions of the patient were in agreement with those now well recognised in the antiphospholipid syndrome.2,3 The range of histopathological changes seen in antiphospholipid vascular pathology is quite different from changes in Buerger's disease.4

The acute lesions of Buerger's disease are associated with an intense mixed cell infiltrate. This is not present in patients with antiphospholipid vasculopathy, in whom thrombosis appears at various stages of thrombus organisation, and not vasculitis.5

We conclude that the patient described by Casellas et al, even if she fulfilled the criteria of probable Buerger's disease according to McPherson, should not be considered to have this disease. The negative criteria of Adar and Mozes should have been acceded to, thus preventing overdiagnosis of Buerger's disease and avoiding the risk of misdiagnosis of a disease with a common and delayed delay of urgent specific treatment.

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AUTHORS' REPLY: Puichal et al suggest that the patient we described recently in the Antiphospholipid syndrome" (APS) rather than Buerger's disease. The authors adduce histological differences between these two conditions: in Buerger's disease the primary lesion is vasculitis, whereas in APS it is thrombosis. Although correct, this fact does not exclude, in our opinion, a possible association: it is theoretically possible that vasculitis, by causing endothelial cell damage, might have triggered the reaction of antiphospholipid antibodies with negatively charged phospholipids on these cells, as described by Alarc6n-Segovia et al.2 Puichal et al suggest, based on the negative criteria of Adar and Mozes, that diagnosis of another associated disease should exclude Buerger's disease. The paper published by Alarc6n-Segovia et al.2 intended to examine the possible relationship between Buerger's disease and atheroembolization by clinical and radiological analysis of young patients with ischaemic disease of the lower extremities.1 Patients with evidence of embolism, trauma, or collagen disease were excluded from the study group, but, in our opinion, these diseases were not defined as negative criteria for the diagnosis of Buerger's disease. A clinical diagnosis of Buerger's disease was made by Adar when, in addition to ischaemic manifestations in the legs, two or more of the following systemic manifestations were present: marangas and leg oedema, osseous elements—such as Raynaud-like phenomena—in hands or legs, or both; and ischaemic manifestations in the arms.

Although there were grounds for diagnosing Buerger's disease in our patient in accordance with McPherson, we did in fact point out in our paper that the clinical picture might be attributed entirely to APS. However, given the possible association, we tested 13 patients diagnosed in our hospital as having Buerger's disease over the past three years for the presence of antiphospholipid antibodies; these were absent in all cases. Although this suggests that these two conditions are not related, further studies are needed to confirm this. Otherwise there will be a risk of failing to establish a possible, though unlikely, association between two conditions of as yet unknown cause.
a two year history of recurrent painful violet erythema nodular lesions associated with high levels of RF (latex; range 1048–2000 U/ml). She denied asthma, weight loss, fever, and had no respiratory or articular complaints. On physical examination many scattered, painful, tender and slightly raised violet subcutaneous nodules were found on the posterior aspects of both calves. The patient was afebrile. Results of cardiopulmonary and abdominal explorations were unremarkable. White blood cell and platelet count were normal. The haemoglobin was 126 g/l and erythrocyte sedimentation rate 18 mm/1st h. Urea nitrogen, creatinine, glucose, bilirubin, aspartate transaminase, alkaline phosphatase, cholesterol, triglycerides, calcium, and phosphorus were all normal. A positive purified protein derivative skin test, antinuclear antibodies, cryoglobulins, and serum complement (C3 and C4) were unremarkable. Serum RF determined by turbidimetric immunoassay was 2048 U/ml (Quantex RF plus—laxet, WHO units). Rheumatoid factor determined by haemagglutination on slide (modified Waaler-Rose procedure) was 256 U/ml (Celarik AR, Biokit SA, Spain; WHO units). Chest films showed a fibroproductive pattern affecting both upper lung lobes without paratracheal or peripheral adenopathies. Microscopic examination of three sputum specimens stained by Ziehl-Neelsen’s method disclosed no acid-fast bacilli. A wedge biopsy of one skin nodule was performed and pathological examination disclosed a granulomatous panniculitis consistent with erythema induratum (figure). Ziehl-Neelsen and auramine-rhodamine stains were negative. Sputum cultures in Löwenstein-Jensen medium grew M. tuberculosis.

Specific daily treatment with rifampicin 600 mg, isoniazid 300 mg, and pyrazinamide 1500 mg was started and continued for two months. Rifampicin and isoniazid was continued for four more months at the same dose. The two Mantoux tuberculin skin tests (5 tuberculin units of purified protein derivative) performed while the patient was receiving chemotherapy were negative. At the end of the first, third, and sixth months of treatment, RF had decreased to 600, 200, and 442 U/ml respectively. The patient remained asymptomatic, and skin lesions healed leaving a pigmented scar.

Erythema induratum, included in the tuberculos, is not a ‘true’ manifestation of skin tuberculosis because acid-fast bacilli are not found. Although M. tuberculosis has occasionally been isolated when erythema induratum coincides, most authors support its actiological role. Nodular vasculitis is a form of multifactorial lobular panniculitis which may coexist with a tuberculous focus (erythema induratum of Bazin) or may not (nodular vasculitis erythema induratum complex). Throughout the two year follow up of our patient no nodule became ulcerated and the lesions healed completely after chemotherapy.

Rheumatoid factors in low titres are found in a small percentage of young adults. A high prevalence of RF is also found in patients with chronic infections, such as syphilis, leprosy, and tuberculosis. These observations have suggested that extensive or persistent exposure to antigens and immune complex formation induces the synthesis of RF. M. tuberculosis antigens can induce the production of RF, and several reports have demonstrated the autoimmune capacity of some proteins of this microorganism, particularly heat shock protein 60.

Immune complexes seem to have an important pathogenic role in nodular vasculitis. They have been found in patients with Henoch-Schönlein purpura associated with active tuberculous infection. It should be pointed out that in rare cases of autoimmune diseases with increased RF levels, such as rheumatoid arthritis, Sjögren’s syndrome, cryoglobulinaemia, and autoimmune liver disease, were excluded. Moreover, after treatment was started RF progressively fell to nearly normal values.

The persistent negativity of the Mantoux skin test deserves a special mention. It is unlikely that the patient had disseminated tuberculosis or any other immunosuppressive condition. A negative Mantoux skin test has been described in patients with erythema induratum. There is no doubt about the importance of the skin biopsy as it allows histological demonstration of erythema induratrum and helps to establish the differential diagnosis with erythema nodosum, syphilis, foreign body granuloma, and skin tuberculous. Finally, we strongly believe that the finding of erythema induratum should prompt a diagnostic search for pulmonary or extrapulmonary involvement of tuberculous infection.

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**CREST syndrome with pericardial but not peripheral calcification**

**Sir:** The CREST subgroup of systemic sclerosis is a mild or slowly progressive form of the disease characterised by calcinosis, Raynaud’s phenomenon, oesophageal dysfunction, and telangiectasia. Anticentromere antibodies detected on the Hep-2 substrate appear highly selective for this group of patients. In the Johns Hopkins series calcinosis was present in all patients with CREST, being peripheral or atrophic joint in the majority. Patients with CREST may develop internal organ manifestations but usually only in the second and third decades of the disease. We report a case of the CREST syndrome who presented with dyspnoea due to calcific pericarditis without peripheral calcification.

A 65 year old white female smoker presented to her general practitioner with shortness of breath in August 1989. He detected an expiratory wheeze and prescribed amoxycillin. Her pulse was 160 beats/min, and she was referred to a cardiologist. She was in atrial flutter with 2:1 block and had signs of ‘mild congestive heart failure’. The jugular venous pressure was raised 9 cm. A chest radiograph showed a cardiorheocathartia ratio of 58% with upper lobe aeration. She was anticoagulated and cardioverted but atrial flutter recurred, and her ventricular rate was controlled with verapamil, digoxin, and a diuretic. The patient had a six year history of Raynaud’s phenomenon and was noted to have facial telangiectasia and mild sclerodactyly. Further investigation showed a positive anticentromere antibody and negative antinuclear and ScI-70 (topoisomerase 1) antibodies. A barium study showed markedly reduced oesophageal motility. A diagnosis of CREST syndrome was made, though no calcification had been detected either clinically or radiologically. She gained symptomatic relief from wearing heated gloves and using cisapride, being intolerant of H₂ blockers.

Although there was improvement in her dyspnoea, the jugular venous pressure remained raised. In March 1991 she reported increasing shortness of breath on exertion and swelling of the legs. Her jugular venous pressure was 8 cm raised with a positive Kussmanl’s sign and pulsus paradoxus of 30 mmHg. A lateral chest radiograph showed marked pericardial calcification (figure) that had not been apparent on previous postero-anterior views. There was no history of tuberculous or tuberculotic contacts. The possibility of an operation to relieve her tamponade was discussed, but the patient refused.