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Cyclosporin treatment in rapidly progressive pulmonary thromboembolic Behçet's disease

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Abstract

A patient with Behçet's disease with pulmonary thromboemboli responded to treatment with cyclosporin A and coumarin.

Behçet's disease is a rare systemic disorder of unknown cause, most often observed in Mediterranean countries, Japan, and the Middle East. It is a progressive disorder with episodes of activity and remission. The major features are oral and genital ulceration and skin and eye lesions (uveitis or hypopyon). Other characteristic features include thromboembolic disease, arthritis, neurological symptoms, gastrointestinal lesions, and a family history[1] of Behçet's disease. Pulmonary disease is rare.[2-4] We report the favourable response to a combination of cyclosporin A and coumarin treatment in a patient with extensive pulmonary thromboemboli.

Case report

A 35 year old white woman was admitted for investigation of recurrent fever and pulmonary infiltrates. Three years earlier she had had a superior sagittal sinus thrombosis, confirmed by angiography. Her erythrocyte sedimentation rate at that time was 37 mm in the first hour. She was advised to stop smoking and to discontinue oral contraception.

On admission she had recurrent episodes of fever with chills, headaches, bilateral basal chest pain, atypical upper abdominal pain, and severe constitutional symptoms, including loss of appetite and fatigue. A chest radiograph showed basal, ill defined alveolar infiltrates without pleural effusion. She had worked as a diamond polisher until shortly before admission and had never experienced any respiratory problems at work. There was no relevant family history.

Clinical examination showed an ill young woman, unable to breath deeply because of pleuritic pain. A pleural rub was present over the lower half of the left lung. She had no rash, cyanosis, lymphadenopathy, hepatosplenomegaly, or varicose veins. All other systems were found to be normal.

Investigations revealed an erythrocyte sedimentation rate of 150 mm in the first hour, normocytic anaemia, normal liver and renal function, and normal results from urine analysis. Antinuclear antibody, circulating immune complexes, and precipitating antibodies to *Aspergillus fumigatus* were absent. Complement C3d was increased and coagulation studies showed a raised fibrinogen concentration (8·56 g/l) and fibrin split products (76 mg/l). There was no lupus anticoagulant and the antithrombin III level was normal. Extensive microbiological investigations gave negative results. Lung function studies showed a restrictive defect (vital capacity 2·7 l (76% predicted), FEV_1 2·3 l (75% pred), total lung capacity 4·16 l (81% pred), transfer factor for carbon monoxide 3·96 mmol/min/kPa (44% pred). Bronchoscopic appearances, bronchoalveolar lavage fluid, and bronchial and transbronchial biopsy specimens were normal. Radioisotope studies showed patent veins in the lower extremities and multiple, predominantly lower field, perfusion defects with ventilation mismatch in the lungs.

The anticoagulation initiated previously was continued, but the local and general symptoms remained. A trial of corticosteroids produced some symptomatic relief but symptoms returned when the dose was reduced. The patient developed moderate haemoptysis, and a few months later both oral and genital aphthous ulceration. Herpes simplex virus was not isolated and there was no seroconversion for HSV1 or HSV2. A chest radiograph showed a new right upper field infiltrate and an enlarging round opacity near the right hilum (fig 1). A pulmonary angiogram showed numerous segmental perfusion defects in both lower lung fields and small perfusion defects in the right upper lung field. The hilar opacity corresponded to a pulmonary artery aneurysm (fig 2). An open lung biopsy showed pulmonary

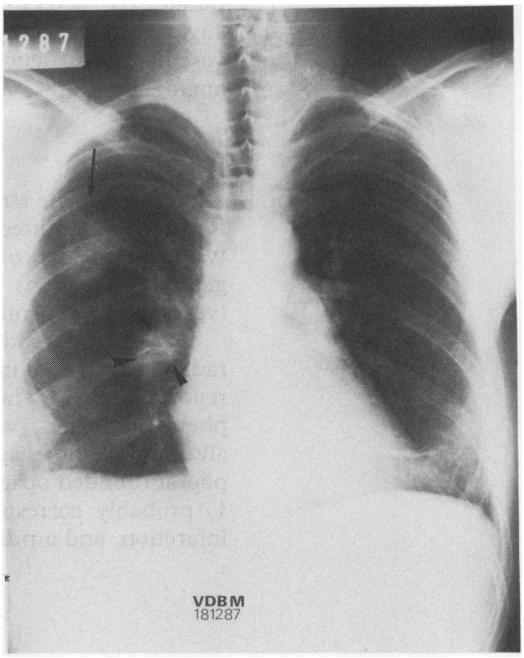

Figure 1 Posteroanterior chest radiograph showing an infiltrate in the right upper lung field (arrow) and a round opacity near the right hilum (arrow heads). A linear shadow in the left lower lung field and an ill defined infiltrate in the right lower lung field are the remains of previous thromboemboli.

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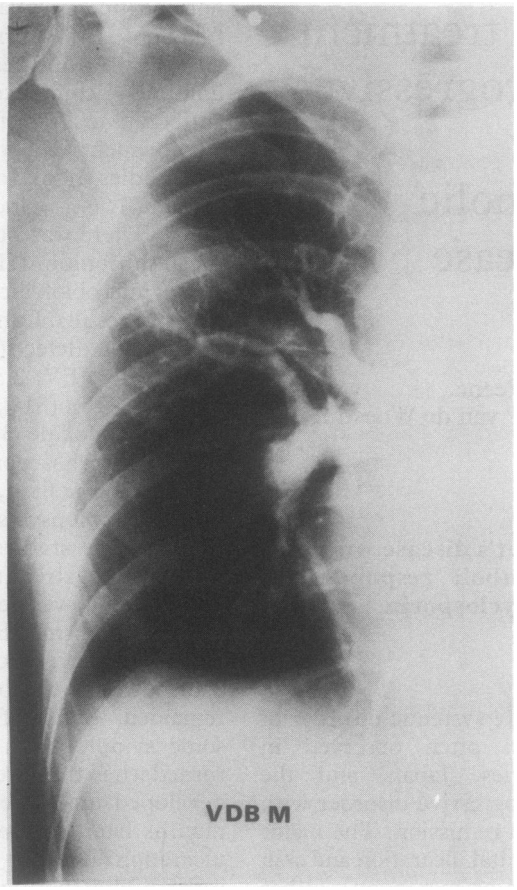

Figure 2 Pulmonary artery angiogram showing several segmental perfusion defects in the lower lung field and smaller defects in the upper lung field. The round opacity seen on the plain radiograph corresponds to a pulmonary artery aneurysm.

infarction with aspergillus superinfection, but no evidence of vasculitis.

Postoperatively a proximal iliac vein thrombosis occurred. A diagnosis of thromboembolic Behçet's disease was made and cyclosporin A and coumarin treatment was started. Fever, symptoms, and signs of inflammation disappeared; no more infiltrates have developed during almost two years of follow up. The pulmonary artery aneurysm has increased slightly in volume but no new pulmonary vascular obstructions were noted on the angiogram.

Discussion

According to the strict criteria of the Disease Research Committee of Japan,[1] our patient had two major features of Behçet's disease (oral and genital ulceration) and one minor feature (venous thromboembolic disease).

There was a striking similarity between our radiographic findings and those in six other reported cases.[5] There were ill defined peripheral infiltrates (which may correspond to alveolar haemorrhage and infarction), peripheral rounded opacities (not visible in figure 1) probably corresponding to older areas of infarction, and a pulmonary artery aneurysm. This was not a congenital aneurysm, because it was not visible on the previous radiographs, and it was unlikely to be a mycotic aneurysm because no other infectious foci were found and numerous blood cultures were negative. Similar infiltrates are seen in Wegener's granulomatosis[6] and Takayashu disease,[7] but central arterial aneurysms are not described in these conditions.

The absence of vasculitis in the lung biopsy specimen does not rule out the diagnosis of Behçet's disease because the lesions were two weeks old and because vasculitis is focal in nature. Other patients with pulmonary manifestations have been reported without[2,3] or with only focal[4,5] vasculitis.

Encouraged by the results of cyclosporin treatment in other inflammatory conditions associated with thrombosis,[8,9] we tried cyclosporin A combined with coumarin. After almost two years of follow up the clinical and laboratory features of the disorder remain suppressed. As cyclosporin A affects predominantly T lymphocytes the success of this form of treatment suggests a derangement of T cell regulatory processes in Behçet's disease.

We have found no other reports of pulmonary Behçet's disease treated with cyclosporin A.[10] Life threatening or fatal haemoptysis occurs in Behçet's disease.[4,6] Two of three patients with aneurysms in one series died of fatal haemoptysis within 13 months of diagnosis; the other aneurysm decreased in volume with treatment.[5] We are reluctant to undertake surgery in our patient because the disease appears to be well controlled; she has no haemoptysis and surgery would probably mean a pneumonectomy in a patient whose pulmonary function is already compromised as a result of lesions in the left lung. Her clinical progress and repeated angiography will determine further management.

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