

## Letters to the Editor

### The disappearance of pulmonary artery aneurysms and intracardiac thrombus with immunosuppressive treatment in a patient with Behçet's disease

Sirs,

Behçet's disease (BD) is a chronic inflammatory disease of unknown cause characterised by recurrent oral aphthous ulcers, genital ulcers, uveitis, skin lesions and arthritis. Venous and arterial thrombosis and vascular aneurysms are also prominent features of BD. Pulmonary arterial aneurysms are associated with a high frequency of deep vein thrombosis which leads to confusion in the differential diagnosis and treatment of the hemoptysis (1,2). Rarely, thrombus formation may occur in the cardiac cavities (3,4).

Here we present a patient with BD who suffered from pulmonary arterial aneurysms, intracardiac thrombi and venous thrombosis, and evaluate the duration of clinical remission and radiologic resolution of the findings following immunosuppressive and anticoagulant therapy.

In January 2000 a 19-year-old male patient was admitted to our hospital with hemoptysis, shortness of breath and occasional coughing that began 2 weeks before, associated with a history of recurrent oral aphthous and genital ulcers for the past year, and thrombophlebitis appearing in the lower extremities 6 months ago. On admission his temperature was 37.5°C. He had tachypnea, orthopnea, tachycardia, decrease of breath sounds in the basal region of the right lung,

oral aphthous lesions, healing scars of genital ulcers and pseudofolliculitis. The patient fulfilled the International Study Group Criteria for the diagnosis of BD (5).

Chest x-ray revealed diaphragm elevation on the right side, left hilar enlargement, a granular-aciner pattern and low density opacity reaching from the right hilus to the diaphragm, a pneumonic pattern in the right lower zone and retractions of the diaphragm in the left lower zone of the lung. Ventilation-perfusion scintigraphy of the lung revealed bilateral multiple perfusion defects and preservation of ventilation in the perfusion defective areas.

Computed tomography (CT) of the thorax revealed local dilatation of the left descending pulmonary artery, a hypodense view of both pulmonary arteries suggesting the surrounding thrombus (Fig. 1), and multiple consolidations lying on the pleural surface involving the basal segments of both lungs, but more pronounced on the right. Echocardiography revealed the presence of a thrombus (1.4 x 1.7 cm) in the right ventricle.

Systemic glucocorticoid 60 mg/day, colchicine 1.5 mg/day and cyclophosphamide 500 mg/m<sup>2</sup> IV pulse therapy were started for the pulmonary vasculitis signs of BD. Three days later acute thrombosis occurred in his left leg, worsening with time. Circulatory insufficiency was observed in his leg. Lower extremity venous doppler USG revealed the findings of acute-subacute thrombosis in all the deep and superficial veins of the left extremity, and also acute-subacute thrombosis throughout the left external iliac vein up to the left femoral vein. The arterial doppler USG was normal. We had to order heparin therapy, followed by oral anticoagulation, despite the presence of multiple pulmonary aneurysms. The signs in his left leg regressed within a short time. As elevation of the liver enzymes and hematuria were noticed, pulse cyclophosphamide therapy and oral anticoagulant therapy were stopped. Azathioprine (150 mg/day) and low dose aspirin were added to the glucocorticoid therapy.

A repeat CT of the thorax about at the third month revealed a marked regression of the aneurysmatic dilatation and thrombus in the left and right pulmonary arteries. Control echocardiography revealed that the dimensions of the thrombus in the right ventricle had diminished by almost one-half (1.1 x 0.7 cm).

Six months after presentation, thorax CT showed the disappearance of pulmonary aneurysms and thrombus formation, but a few small consolidation areas were seen in the basal areas. Echocardiogram also revealed the complete resolution of intracar-

diac thrombus.

Pulmonary arterial aneurysms have been reported to be associated with a high frequency of deep vein thrombosis in as many as 59% (2) and 88% (1) of patients, and ventilation perfusion scans were found to be compatible with pulmonary thromboembolism (2-4), as in our case. In general, the presence of hemoptysis, acute and subacute thrombosis in lower extremities and abnormal ventilation perfusion scans may be evaluated as compatible with thromboembolism. However, pulmonary thromboembolism is rare in BD (6), and examination of the systemic vasculature revealed strictly adherent thrombus in the inflamed vein (1). Thorax CT showed pulmonary aneurysm formation which was a cause of the hemoptysis in the patient. Anticoagulation therapy is a potential hazard to patients suffering from aneurysmatic dilatation of the pulmonary blood vessels in BD (2). We had to start the heparin therapy despite the patient's pulmonary aneurysms, because severe failure of the circulation in his left leg developed and became worse within hours. During anticoagulation no complications were seen.

A beneficial effect of therapy with cyclophosphamide plus glucocorticoid on pulmonary vasculature involvement in patients with BD has usually been observed (1,7). However, cyclophosphamide was also found to be effective in a few cases (2). Successful treatment with steroids has been reported in most patients but a relapse was observed in some cases (2). Our patient responded well to immunosuppressive treatment. Clinical remission and the disappearance of aneurysms and thrombus of the pulmonary arteries were achieved within 6 months. There was no relapse after 12 months of follow-up.

Cardiac involvement is uncommon in BD. There have been rare case reports of coronary artery disease, pericarditis, myocarditis, endomyocardial fibrosis and intracavitary thrombus formation (4, 8) which were associated with pulmonary vascular involvement (3, 4), as in our case. The abnormality of plasma fibrinolytic activity in patients with active BD has not been identified (9). There was no predisposing factor for the intra-cardiac thrombus (e.g., prolonged immobility, malignancy, anticardiolipin antibody) in our patient.

The resolution of intracardiac thrombus by means of immunosuppressive drugs and anticoagulant therapy associated with corticosteroid has been reported in the literature (4, 10). In our patient, intracavitary thrombus disappeared with immunosuppressive therapy within 6 months. In addition to this treat-



**Fig. 1.** A 19-year-old male patient with Behçet's disease. Computed tomography of the thorax revealed local dilatation of the left descending pulmonary artery and a hypodense view of both pulmonary arteries suggesting the surrounding thrombus.

ment, the anticoagulation therapy which was used for his deep venous thrombus might also have contributed to the resolution of intracardiac thrombus.

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## Is there a heterozygote advantage for familial Mediterranean fever carriers against tuberculosis infections: Speculations remain?

Sirs,

Familial Mediterranean fever (FMF) is a disease characterized by recurrent episodes of fever and serosal inflammation accompanied by a marked acute phase response (1, 2). Mutations in the MEFV gene underlie familial Mediterranean fever and code for a protein called pyrin. The carrier frequency among North African Jews has been reported to be 1/5-1/10 (3) and 1/5 (21%) among Ashkenazi Jews (1). Among Armenians it is expected to be as high as 1/3 (4). In a recent study we have shown the carrier rate in Turks to be 1/5 as well (5). The minimum prevalence of the disease is estimated to be 1/1073 in the Turkish population (2). These high numbers suggest that there is a possible heterozygote advantage to the inhabitants in the area.

A shared haplotype and mutation that is observed in Armenians, Ashkenazi Jews and Druze FMF patients suggests that this mutation dates back at least 2000 years in the eastern Mediterranean basin. The historic retracing of another mutation suggests that it again dates back to at least 2500 years ago, again when these populations were living together in Mesopotamia. The first farmers in the history of mankind are known to have settled some 8000 years ago in the Fertile Crescent, an area extending from Mesopotamia into Anatolia (the mainland of Turkey). These farmers started to live together and raise cattle. Carriers of pyrin mutations in these geographically related populations might have shared a selective advantage, having adapted a new life style. The Anatolian people may have also received mutations during the migrations before the birth of Christ or may have fostered the mutation in their own land.

It has already been shown that carriers of certain hemolytic anemias are resistant to malaria, which was an organism that caused serious historical outbreaks in this area. In a parallel manner we wondered whether there

could have been a candidate organism to offer a heterozygote advantage in the area. FMF patients and relatives have elevated CRP levels, suggesting an increased acute phase inflammatory response in these people (6). Thus the heterozygotes might simply have an advantage of mounting an augmented acute phase response to microorganisms. However, one wonders why this mutation was restricted to this area. Thus, a heightened resistance introduced by mutations in the MEFV gene to a pathogen endemic to the Eastern Mediterranean seems an attractive hypothesis to pursue.

Tuberculosis is an ancient disease caused by the tubercle bacillus. It has remained endemic in many areas for centuries. In humans the most common tubercle bacilli are *Mycobacterium tuberculosis*, which is transmitted by close contact, and *Mycobacterium bovis* that is transmitted by the consumption of milk from infected domestic animals. Thus, it would have been a new disease for the first farmers. These bacilli are intracellular pathogens. MEFV (the gene for familial Mediterranean fever) is primarily expressed in leukocytes and monocytes, and therefore might be expected to have an effect on immune function. We wanted to study whether heterozygotes for MEFV mutations had a better response to pathogens offering them a selective advantage. This pathogen would have to be some organism endemic to the Middle East. Since such a clue is not present we decided to investigate a possible advantage that could be introduced by an ancient pathogen – tuberculosis. An increased inflammatory response is required in the generation of cell-mediated immunity aimed at intracellular pathogens and to generate a delayed-type hypersensitivity response, that is characteristic of tuberculosis. In turn, patients with MEFV mutations have an augmented inflammatory response. Thus we decided to analyze whether carriers for the MEFV mutations had increased resistance to develop tuberculosis. We screened 103 patients with proven tuberculosis for the presence of MEFV mutations and compared the results with that published in 100 healthy Turkish individuals.

DNA samples were isolated from the peri-

**Table I.** Frequencies for the common mutations in the MEFV gene among tuberculosis patients, healthy controls and FMF patients (%).

	M694V	M680I	V726A	M694I	E148Q
Healthy Turkish subjects (n=100)	3	5	2	-	12
Tuberculosis patients (n=103)	3	1	4	-	9
FMF patients (n=100)	51.5	9.2	2.8	0.4	3.5