

Letters to the Editor

MEFV-related mutations may explain why amyloidosis due to BD is more common in Middle East and Mediterranean countries than in Japan.

The frequency of MEFV mutations among patients with BD-related amyloidosis has not been investigated previously and our study showed a frequency of 32%. Although the patient with homozygous M680I did not have sufficient clinical findings for FMF, it was not possible to exclude type 2 FMF (4, 5). The main shortage of this study is the absence of a control group (BD patients without amyloidosis), but we can compare our finding with previous studies evaluating MEFV mutations in BD. The frequency of MEFV mutations may vary between regions, countries and ethnic groups and as far as we know, there are three studies evaluating MEFV mutations in BD (one from Turkey, one from Israel and one an international study) (6-8). In an international collaborative study in which we have also participated, the M694V, V726A and E148Q mutations were found to be 2.6%, 2.6% and 5.2%, respectively (7). The other two studies, one from Turkey (6) and one from Israel (8), reported MEFV frequencies of 26% and 30%, respectively. Atagunduz *et al.* have concluded that MEFV mutations are increased in BD and are associated with vascular involvement (6).

A significant difference regarding the frequency of MEFV mutations among patients with BD-related amyloidosis was not found in our study and the absence of a control group does not affect our interpretation. In addition, it should be kept in mind that different ethnic groups, unmentioned patient characteristics (presence or absence of amyloidosis), and differences in the number and type of mutations screened in these studies may influence the integrity of the comparison.

The relationship between rheumatological diseases and MEFV mutations has been reported previously (9, 10). The presented data does not offer conclusive data on MEFV mutations being one of the risk factors for the development of amyloidosis in another inflammatory disease, BD. However, larger studies are needed to clarify whether the altered inflammatory response introduced by the pyrin mutations are one of the predisposing modifying genetic factors for the development of amyloidosis in a patient who already has an inflammatory disease.

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New-onset acute heart failure and ventricular tachycardia after therapy with a tumor necrosis factor antagonist

Sirs,

Numerous adverse effects have been reported with TNF antagonists, mainly infections and lymphomas (1). Other potential adverse effects, cardiac in particular, must be kept in mind (2). We report one case of new onset acute heart failure and one case of ventricular tachycardia during treatment with infliximab.

A woman aged 52 was followed for Behçet's disease. She had no history of cardiovascular disorder. Because of severe joint involvement in spite of treatment with methotrexate, intravenous infliximab 3 mg/kg was prescribed. Initial electrocardiogram and echocardiography were normal. Fifteen minutes after the start of the fourth infusion,

she presented an acute heart failure with dyspnea and crepitant rales of both lungs, bilateral alveolar opacity on chest radiograph and sinus tachycardia on electrocardiogram. After immediate discontinuation of infusion, treatment with intravenous furosemide and nasal oxygen, the episode resolved in a few hours. Search for the cause of this episode by Holter monitoring, echocardiography and cardiac angiography was negative.

A man aged 50 was followed for spondylarthropathy. His only cardiovascular history was arterial hypertension controlled by ramipril. Because of severe axial and peripheral inflammation in spite of treatment with methotrexate, intravenous infliximab 5 mg/kg was prescribed. The initial electrocardiogram was normal. Twenty-four hours after the 9th infusion, he presented lipothymia with a sudden fall in blood pressure, revealing ventricular tachycardia on the electrocardiogram, which was immediately reduced by external electric shock. An implantable defibrillator was placed to prevent recurrence. Search for the cause of this episode revealed signs of lower supra-epicardiac ischemia on the electrocardiogram, a coronary artery spasm reproducing the ventricular tachycardia on cardiac angiography and minimal sequelae of lower necrosis on myocardial scintigraphy.

Behçet's disease may be complicated by pericarditis, myocarditis, endocarditis or coronaritis. Our patient had no such cardiac involvement and no cardiovascular history. Search for the cause of the episode of new-onset acute heart failure was negative. These findings and the chronology suggest a serious adverse event which can be attributed to infliximab. TNF antagonists are contra-indicated in patients with NYHA class III and IV heart failure. This contra-indication results from the premature discontinuation of the ATTACH study which evaluated infliximab in the treatment of heart failure, because of increased mortality and hospital admissions for cardiac decompensation in patients treated with infliximab (3), and from the premature halting of the RECOVER and RENAISSANCE studies which evaluated etanercept in the treatment of heart failure, because of inefficacy of etanercept (4). TNF antagonists may also induce heart failure even in the absence of any cardiovascular history. A recent study revealed 38 cases of new-onset heart failure in patients treated with TNF antagonists, which partially or totally resolved when this treatment was stopped (2).

Spondylarthropathies may be complicated by aortic insufficiency or conduction disturbances. Increased frequencies of myocardial fibrosis and arrhythmias have also been

reported. These arrhythmias manifest mainly as supraventricular or ventricular extrasystoles (5). Our patient had no cardiovascular history apart from arterial hypertension and the search for the cause of this episode of new-onset ventricular tachycardia revealed subclinical ischemic cardiopathy, a risk factor for ventricular arrhythmia. However, the chronology raises the possibility of an adverse event which could be attributed to infliximab. A review of the literature showed only one case of sudden death, less than 24 hours after an infusion of infliximab, in a man aged 64 who had rheumatoid arthritis and a history of conduction disturbances (6).

The physician must bear in mind that TNF antagonists are contra-indicated in patients with heart failure and that they can induce new-onset heart failure. Initial cardiac evaluation and regular clinical surveillance are mandatory to detect cardiac side effects (7).

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Chondrosarcoma in Paget's disease of bone

Sirs,

A 60-year-old patient was diagnosed with Paget's disease of bone (PDB) after having a fracture of the humerus. He had suffered another fracture at the same site when he was 30.

Radiographs showed a predominantly osteolytic pagetic lesion involving the left proximal humerus. Bone scintigraphy showed uptake on the left humerus, the seventh rib, the eighth dorsal vertebra, lumbar vertebrae and the sacrum (Fig. 1). The serum alkaline phosphatase concentration was 1026 IU/L (normal range, 98-279). He was treated first with alendronate 30 mg daily for 6 months and after that with risedronate 30 mg daily for 2 months, and the serum alkaline phosphatase decreased to almost normal values. Two years later a painful mass was observed on the proximal region of the left superior limb. The serum alkaline phosphatase concentration was 599 IU/L, slightly increased respect to previous analysis. Plain radiographs of the humerus were similar to the previous x-ray, except for an image of increased density out of the cortical bone near the former fracture. MRI showed an area of decreased signal intensity in both T1 and T2-weighted images with irregularity of the cortical and a soft tissue mass, which involved the surrounding muscles and subcutaneous cellular tissue. Histopathologically this mass was a grade 3 chondrosarcoma. The patient was treated with radical surgery in addition to chemotherapy and local radiotherapy. Fifteen months later he suffered pulmonary metastasis.

Sarcomatous transformation in PDB is a very rare event nowadays (0.7% to 5%) (1, 2), probably due to a good control of the disease with bisphosphonates. Our patient was appropriately treated over the previous 2 years, but the disease was very extensive at the time of the diagnosis. Osteosarcoma associated with PDB is the most common histological type, and chondrosarcoma is very rare. Little more than 20 cases have been reported in the literature (3-8). Our patient had previously had two fractures, both of them in the same site where the chondrosarcoma would develop years later. Sarcomatous transformation of pagetic bone at the site of a previous trauma has been reported in up to 10% of cases of sarcomas in PDB (4). In chondrosarcomas a calcified matrix of the lesion, as in the current case, has



Fig. 1. Radionuclide examination showing pagetic extension.

been described on plain x-rays (5). The estimated 5-year survival rate is about 3-8% (1, 4), although a few patients enjoy a longer survival (6, 7). Treatment must be instituted as early as possible, and include radical surgery and subsequent radiotherapy and chemotherapy.

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