Familial Mediterranean fever-related spondyloarthropathy

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ABSTRACT

Familial Mediterranean fever (FMF) is an autosomal recessively-transmitted disease characterised by attacks of fever and serositis. Articular involvement is the second most common manifestation following abdominal pain. Patients with FMF are considered to have an increased risk of sacroiliitis, while the association of such abnormalities with FMF has not been accepted uniformly. We report two cases of FMF with accompanying seronegative spondyloarthropathy, a 18-year-old boy and a 29-year-old man, and review the literature for FMF-related seronegative spondyloarthropathy.

Keywords: familial Mediterranean fever, sacroiliitis, seronegative spondyloarthropathy

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INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disease affecting individuals from the Mediterranean region, particularly Jewish, Turkish and Arabic populations.[1,2] The condition is characterised by recurrent self-limited painful febrile attacks of peritonitis, pleuritis and synovitis. Articular involvement is the second most common manifestation following painful abdominal attacks.[1-3] The joint disease occurs in 70%–75% of patients, one-third of whom present with arthritis as the first sign. The arthritis of FMF presents as acute attacks of mono- or oligoarthritis predominantly involving the large joints of the lower extremities. The radiographical appearance is not specific, and is characterised by soft tissue swelling and transient osteoporosis.[4,5] Although the joint attacks are recurrent, protracted arthritis and joint damage leading to disability are not common. Approximately 5% of patients develop protracted arthritis, mostly in the hip and knees.[5] Sacroiliitis rarely occurs in FMF and can be associated with spinal involvement. Patients with FMF are considered to have an increased risk of sacroiliitis, although the association of such abnormalities with FMF has not been accepted uniformly.[3,6-8] Many earlier sporadic case reports or cases in some series suggested that a differential diagnosis of spondyloarthropathies was indicated in FMF patients with axial involvement.[6-9] We report two cases of FMF with accompanying seronegative spondyloarthropathy (SSpA) and review the literature for FMF-related SSpA.

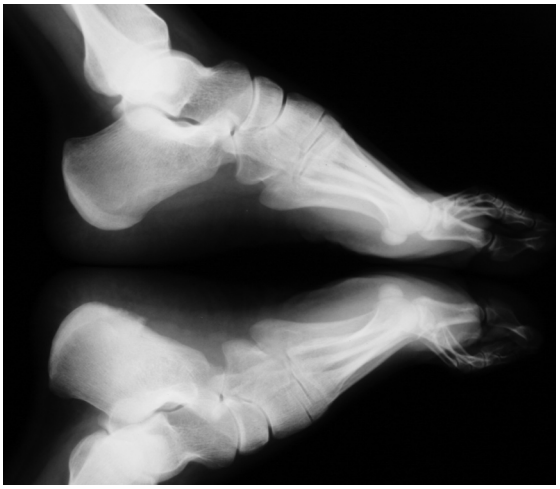

Fig. 1 Radiographs show bilateral sclerosis near the prominence of the calcaneus.

CASE REPORTS

Case 1

An 18-year-old boy was referred to our clinic with low back pain and bilateral heel pain. His complaints had persisted for three months and were exacerbated in the mornings. He had stiffness of the low back lasting for more than one hour in the mornings. In his past medical history, he had been diagnosed with FMF three years ago when he had been evaluated for abdominal pain attacks. The family history was negative for spondyloarthropathy (SpA) and the medical history was unremarkable for psoriasis, inflammatory bowel disease and eye involvement. He was a non-smoker. His articular complaints had started a few months ago. On physical examination, his body temperature was 37.3°C. His appearance was weak. Physical examination revealed restricted lumbar movements (Schoeber test 4 cm) and normal chest expansion (nipple line thoracic expansion 4.8 cm). The straight leg raising and femoral nerve stretch tests were negative. Patrick's (Faber) test as well as Gaenslen and Mennel sacral compression tests were positive bilaterally. He was tender on the plantar aspect of both heels near the prominence of the calcaneus. Neurological examination indicated normal findings. His finger to ground, occiput to wall, tragus to wall, and chin to chest measurements were within normal limits. The remainder of his physical examination was unremarkable. He had been on colchicine therapy for three years at 1 g daily.

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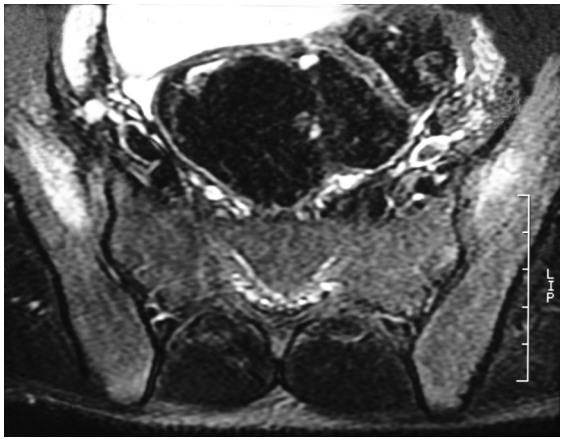

Fig. 2 Axial T2-W MR image shows sclerosis and erosive changes, especially on the iliac sides, indicating sacroiliitis.

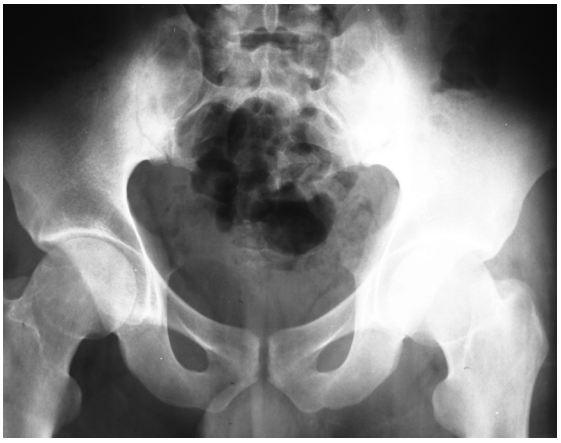

Fig. 3 Radiograph of the pelvis in the Ferguson position shows narrowing of the sacroiliac joints and hip joints.

Laboratory investigations revealed a normal complete blood cell count, urinalysis, electrolyte and immunoglobulin levels. Antinuclear antibodies by ELISA and rheumatoid factor (RF) assessed by Latex were negative. The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were slightly elevated (ESR: 27 [normal range 0–15] mm/hour, CRP 9.38 [normal range 0–0.8] mg/dL). Urine and throat cultures for bacterial growth were negative. His pulmonary function tests were within normal levels. Radiological examination of the heels showed marked sclerosis of the heel near the prominence of the calcaneus (Fig. 1). Magnetic resonance (MR) imaging of the sacroiliac joints revealed marked sclerosis and erosive changes, especially on the iliac sides, indicating sacroiliitis (Fig. 2). Molecular analysis showed that the patient was homozygous for M694V mutation at the Mediterranean fever (MEFV) gene. In light of these findings, the patient was diagnosed as having SSpA of FMF. He was hospitalised and underwent a treatment programme, that included specific posture and breathing exercises, as well as physical therapy modalities. His low back and heel pain were reduced, and he was discharged with colchicine (1.5 mg/day), a non-steroidal anti-inflammatory drug (indomethacin 75 mg/day) and a home exercise programme.

Case 2

A 29-year-old man presented with complaints of knee and hip pain. He had a history of long-standing buttock pain with low back stiffness. He had been diagnosed with FMF four years ago after an evaluation for recurrent abdominal pain attacks. He was receiving colchicum dispert 1.5 mg daily. He was a healthy-looking young man with no apparent spinal deformation. Physical examination revealed a normal range of motion in the lumbar spine. He described minimal pain and restriction on the left hip joint range of motion. He had morning stiffness lasting for more than one hour. Straight leg raising and femoral stretch tests were negative. Sacral compression, Gaenslen, Mennel and Patrick's (Faber) tests were all positive, with pain radiating from the sacroiliac joints. Other joint examinations, except for the left hip, were normal. Neurological examination revealed normal findings. Enthesopathic areas were negative for tenderness. His chest expansion was 5.5 cm at the nipple line. His occiput to wall, tragus to wall, and chin to chest distances were within normal limits. Laboratory investigations revealed that the HLA-B27 antigen and RF were negative.

Laboratory studies showed that both ESR (39 mm/hr) and CRP (11.2 mg/dL) were raised. He had a normocytic normochromic anaemia with haemoglobin of 11.7 g/dL. Assays for antinuclear antibodies, anti-dsDNA, RF, HIV, *Brucella* spp. and hepatitis antigen were negative. Urine and throat cultures were negative. Radiological examination of the pelvis in the Ferguson position showed a narrowing of the sacroiliac joint and normal hip joint (Fig. 3). A study of his genetic analysis was reported as homozygous M694V mutation at the MEFV gene. According to these findings, we diagnosed the patient as having FMF-related SpA. He was prescribed salazopyrine but developed a disseminated urticarial skin lesion on the second day. Dermatological consultation revealed leucocytoclastic vasculitis on his skin biopsy and salazopyrine was withdrawn. His colchicine dose was altered to 2 g daily. He received physical therapy modalities including ultrasound and hotpack, as well as a range of motion exercises to the left hip. The patient was discharged with indomethacin 100 mg/day and colchicine (2 mg/day) two weeks after administration. In the follow-up at four weeks, he denied any recent arthralgia, and a gradual improvement in his left hip joint complaints and morning stiffness were observed.

DISCUSSION

FMF is one of the most common periodic fever syndromes characterised by typical acute attacks of either serositis, arthritis or skin rash.[4] Musculoskeletal manifestations occur in approximately 75% of patients and generally subside within a few days without leaving any joint damage.[2,10] An involvement in the form of SpA is less likely and generally associated with a lack of HLA-B27.[6-8] Articular attacks may show variations in severity, while subacute and chronic arthritis may be seen in 5% of patients.[2,3,10,11] As indicated in previous studies, FMF patients with SpA usually have unilateral and bilateral sacroiliitis, inflammatory low back pain and recurrent enthesitis associated with minimal radiological involvement of the spine.[5-9] All previous patients with SpA were seronegative and, in contrast to ankylosing spondylitis (AS) or other SpA, were HLA-B27 negative.[2,6,8-10] Some of the previous series of FMF indicated that patients can display an AS-like clinical course in which lumbar motion and chest expansion are restricted with typical radiological changes.[12] The incidence of SpA was investigated in a series of patients with FMF and accordingly, some patients met the criteria of SSpA. Some previous cases were represented as an evident coincidence of AS and FMF and these had a positive HLA-B27.[2,7,12] They were classified as a coincidental association of FMF and AS.[7,12] The relationship between FMF and SSpA was studied by Langevitz et al in 3,000 FMF patients. 11 patients were reported to meet the criteria for a diagnosis of SSpA in FMF.[2,13] In another series of FMF patients with chronic joint involvement, 8.7% of patients met the criteria for a diagnosis of SSpA.[10,13]

The diversity and non-specificity of the various clinical manifestations of FMF arthritis can obscure the diagnosis. Our patients presented with low back pain lacking neurological findings in the clinical examination. One of our patients had enthesopathy at the heel, and the other had hip involvement and slightly restricted lumbar motion. After obtaining their history of FMF, we suggested sacroiliac joint involvement and considered AS or other SpA for the differential diagnosis. Our patients' clinical and radiological findings satisfied both the modified New York criteria for AS[14] and the European Spondyloarthropathy Study Group criteria for SSpA.[13] However, as our patients lacked some characteristic manifestations of AS including syndesmophyte, bamboo spine, square vertebrae or uveitis, we were faced with diagnostic confusion. Their chest expansion was within normal limits and they were negative for HLA-B27. AS and other SpAs are mostly associated with HLA-B27 positivity. For our patients, although the picture confirmed an AS diagnosis, it is reasonable to consider their condition as FMF-related SpA.

The exact relationship between FMF and AS remains obscure. However, SSpA was proposed as one of the causes of the possible joint involvement in FMF,[2,7,15,16] and the pathogenetic relationship between these two conditions remains unknown. Recent data suggest that pro-inflammatory cytokines including IL-10, IL-12, IL-17, IL-18 contribute to the cytokine network in the inflammatory cascade of FMF,[17-20] and indicates a relationship between chemokines and subclinical inflammation. A sustained inflammatory reaction is observed in the disease course, and cytokine levels such as IL-1, IL-6 and TNF-alpha have been shown to increase during and between the attacks.[20] As these cytokines are also known to contribute to the pathogenesis of AS, a possible connection between these two diseases can be considered to exist. There is no clear data on the relationship between the attacks of peripheral arthritis and SpA, and the cytokine network, as well as the gene expression profile in patients with FMF. However, there are case reports indicating the therapeutic effects of anti-TNF drugs in resistant arthritic episodes of FMF.[21,22] It would be valuable to investigate this relationship in future studies, in order to determine the patients at risk of contracting arthritis and to prescribe the appropriate treatment, as well as to monitor the response to therapy. We suggest that sacroiliac joint involvement and enthesopathy must be kept in mind in the differential diagnoses of patients with arthritic symptoms and who are suffering from FMF.

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