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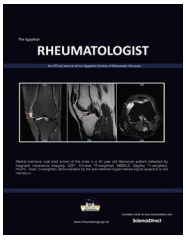

CASE REPORTS

Diagnostic challenge in a Tunisian patient with Familial Mediterranean Fever, sacroiliitis and coxitis

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KEYWORDS

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Abstract *Introduction:* Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disease. The most common joint attack is an acute large joint monoarthritis most often affecting the knee or hip and lasting for several days. Rarely, a more protracted arthritis may occur.

Case report: Herein, we describe a 47-year-old man with FMF in whom a few years elapsed before a definitive diagnosis could be made. The patient presented, since the age of 25, with a history of recurrent episodes of fever, abdominal pain, bloody diarrhea and intermittent attacks of acute bi-arthritis of hips. At the age of 40, he was referred under the suspicion of Spondylarthritis (SpA); in view of an inflammatory back pain, talalgia and bilateral coxitis. The result of blood tests suggested the presence of a high level of inflammation without leukocytosis. Human leukocyte antigen (HLA-B27) was negative. X-ray and computerized tomography of the pelvis showed an overall bilateral joint space narrowing of the hips and grade 3 bilateral sacroiliitis. During the hospitalization, he developed an acute episode of fever, abdominal pain and muscle contracture, spontaneously resolved in 12 h. We suspected FMF based on the clinical course and family history, as one of his brothers had suffered similar abdominal crises since childhood. Molecular analysis for

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FMF was done, and demonstrated a homozygote mutation of M649V. A definitive diagnosis of FMF was then made. Oral administration of colchicine was followed by a remission.

Conclusion: Clinicians should consider FMF with sacroiliitis and coxitis in the differential diagnosis of spondyloarthritis.

1. Introduction

Familial Mediterranean Fever (FMF) is a hereditary auto inflammatory disease which mainly affects ethnic groups living at the Mediterranean basin [1]. Recurrent peritonitis, fever, arthritis, pleuritis, myalgia and erysipelas-like erythema are the principal clinical features. Joint involvement is the second most common manifestation following abdominal pain; which often makes the definitive diagnosis difficult. Typically, it consists of acute self-limiting monoarthritis affecting the large joints of the lower limbs [2]. Five percent of FMF patients develop protracted arthritis, mostly in the hips or knees [2]. These features of the disease resemble spondyloarthritis (SpA) [3]. The gene responsible for FMF (*MEFV*) is located on the short arm of chromosome 16. Many studies have revealed that an increased significant frequency has been noted in this M694V allele among patients with ankylosing spondylitis (AS). All these data may make the diagnosis of FMF difficult to differentiate from AS. Herein, we report a case of FMF with bilateral coxitis and sacroiliitis, in which a few years elapsed before a definitive diagnosis could be made.

2. Case presentation

A 47-year-old Tunisian man presented, since the age of 25, with a history of recurrent episodes of fever, abdominal pain, bloody diarrhea and intermittent attacks of bilateral acute hip arthritis. He was first seen at the gastroenterology department, Charles Nicolle Hospital, El Manar Tunis University, where Crohn's disease (CD) was initially suspected. Both upper endoscopy and colonoscopy revealed no abnormal findings, so CD was considered to be highly improbable.

At the age of 40, he was referred to the rheumatology department under the suspicion of Spondylarthritis (SpA); in view of an inflammatory back pain, talalgia and bilateral coxitis. Further investigation showed a negative human leukocyte antigen-B27 (HLA B27). A pelvic CT was performed to assess the sacroiliac joints and scored bilateral sacroiliitis grade 3. Six years later, he was referred again to the rheumatology department with recurrent episodes of fever, bilateral inguinal pain and left shoulder pain. On admission, the patient presented with fever and limited motion of the hips and left shoulder. The result of blood tests suggested the presence of a high level of inflammation (C-reactive protein: 228 mg/dl) without leukocytosis. X-ray of the pelvis showed an overall bilateral joint space narrowing of the hips, with small areas of bilateral increased density and irregularity over the sacroiliac joints; indicating grade III bilateral sacroiliitis (Fig. 1). MRI of sacroiliac joints showed sclerosis on the left side of joint but no sign of activity (Fig. 2).

During hospitalization, he developed an acute episode of fever, abdominal pain and abdominal muscle contracture that spontaneously resolved in 12 h. We suspected FMF based on the clinical course and family history, as one of his brothers had suffered similar abdominal crises since childhood. Molecular analysis for FMF was done, and demonstrated a homozygote mutation of M649V. A definitive diagnosis of FMF was then made. Oral administration of colchicine was followed by a complete release of pain and a normalization of the level of the C-reactive protein (15 mg/dl). Five months later the patient is still in a remitting form. Approval of the Institutional Review Board in compliance with ethical principles of the Declaration of Helsinki and Good Clinical Practice was achieved. Patients provided written informed consent.

3. Discussion

FMF is a disease with a high prevalence rate in the Mediterranean basin and is considered to be associated with the highest morbidity among the hereditary periodic syndromes [4]. The level of awareness about this disease is far from sufficient, and it is assumed that there may be many patients with this disease who are under observation without an accurate

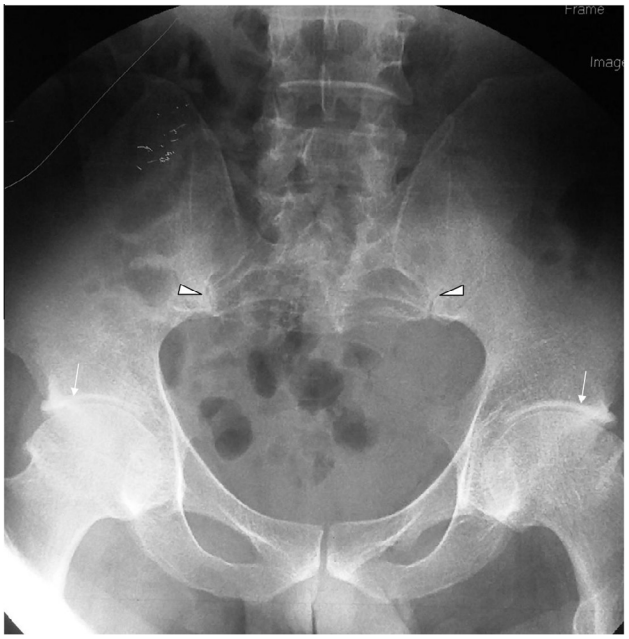

Figure 1 X-ray of the pelvis showing bilateral joint space narrowing of the hips (arrows) and increased density and irregularity over the lower portion of the sacroiliac joints (head arrows) in a patient with familial Mediterranean fever.

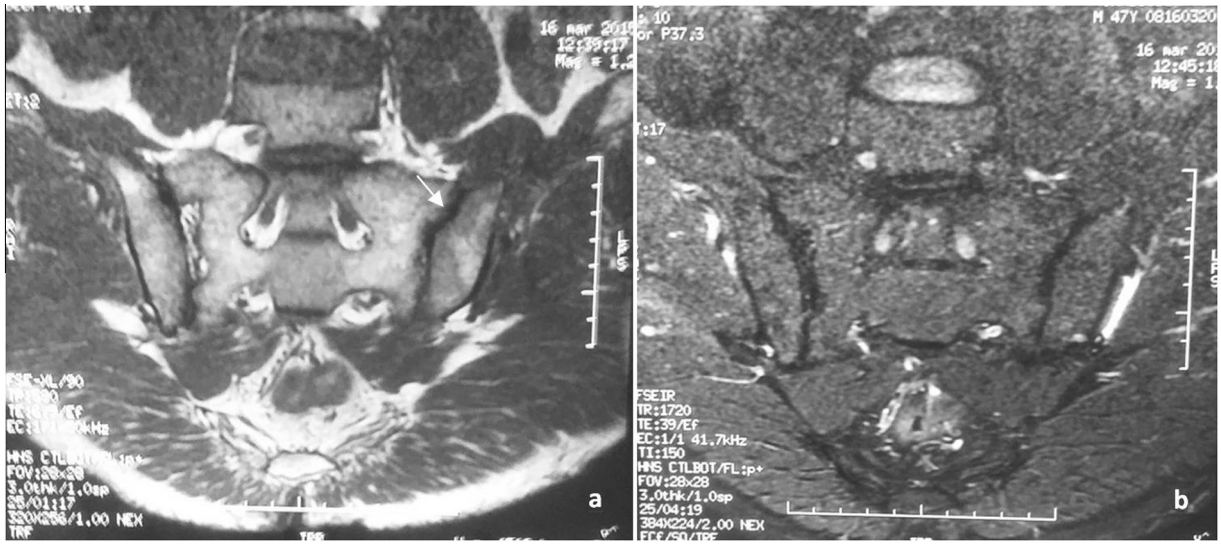

Figure 2 Magnetic resonance imaging (MRI) coronal oblique views of the sacroiliac joints in a patient with Familial Mediterranean Fever. (a) T1 weighted image: sclerosis on the left side of joint is reflected by the hyposignal bands (arrow). (b) STIR MRI sequence showing no sign of activity of the grade III sacroiliitis.

diagnosis. FMF is characterized by brief, but self limiting, attacks of peritonitis and synovitis. Diarrhea, which was observed in our patient, has been reported to occur in 10–20% of the patients [5].

Joint involvement in FMF is mostly acute self-limiting monoarthritis which typically lasts for 72 h. Hips joint involvement is uncommon in FMF. Younes et al. reported ten FMF patients who suffered from hip involvement, but only four of these patients had isolated FMF-related arthritis .They indicated the association of FMF and SpA in the remaining patients [6]. Therefore, hip involvement in FMF can result either from a process specific to this disease, or from coexisting SpA [7]. Patients with FMF are considered to have an increased risk of sacroiliitis and two FMF cases with accompanying seronegative SpA were reported [8], which further complicates the distinction that chronic inflammation of the sacroiliac joints appears to occur more commonly in FMF patients than in the general population [9]. Limited data suggest that the prevalence of sacroiliitis is increased in FMF patients. It has been reported that 7.5% of FMF patients had associated AS and none of them were HLA-B27 positive [10].

The *MEFV* gene is located on the short arm of chromosome 16. We speculate that FMF and the SpA share a common inflammatory pathogenesis which may be mediated by the M694V mutation [11]. Indeed, controlled studies have revealed that the M694V allele frequency is significantly increased in AS patients compared with controls [12,13]. There is also some evidence that the M694V variation may be more frequent in FMF patients with sacroiliitis [14]. The allele frequency of M694V was significantly high among Turkish FMF patients with radiographic sacroiliitis [10]. MEFV gene encodes a protein named pyrin, which is expressed in neutrophils and monocytes [15]. Although the function of pyrin is still unknown, it inhibits the processing of interleukin (IL)-1β to active form and nuclear factor NF-kB activation [15]. In the presence of MEFV mutations, the function of pyrin can be impaired and there is uncontrolled production of active IL1β [16]. However, M694V mutation could be associated with different clinical presentations as reported in 3 FMF sibling patients; while the sister presented with abdominal pain, one of the brothers presented with erysipelas-like erythema and the other with bilateral sacroiliitis. [17]. Colchicine is the agent of first choice for FMF, as it is highly effective [18]. Our patient responded greatly to oral administration.

The patient described herein had lower back pain with sacroiliac and hip joint involvement, miming the presentation of SpA. The ethnic origin of our patient, clinical history and the absence of HLAB27 antigen also increased the possibility of FMF. We think that the presence of homozygous M694 mutation at the MEFV gene and the good response to colchicine strongly confirm the diagnosis of FMF.

4. Conclusion

Lack of awareness of FMF among patients with sacroiliitis and coxitis may cause misdiagnosis. Molecular analysis of gene mutation and determination of HLA-B27 may be helpful in uncertain cases. We suggest that FMF with sacroiliitis and coxitis should be considered in the differential diagnosis of spondyloarthritis.

Conflict of interest

None.

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