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CASE REPORT

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Familial Mediterranean fever responds well to infliximab: single case experience

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Abstract The most common arthritic involvement in familial Mediterranean fever (FMF) is acute recurrent monoarthritis; however, sometimes spondyloarthropathy-like findings or typical ankylosing spondylitis may also ensue. Reported here is our favorable experience with infliximab in an FMF patient who had been resistant to colchicine and disease-modifying antirheumatic drugs (sulfasalazine and methotrexate) treatments. A 72-week follow-up of the patient yielded complete remission of the febrile abdominal episodes, and spondylitis responded well. The patient's bilateral aseptic necrosis of the femoral head deteriorated and caused hip pain, discomfort, and disability. Overall, we believe that tumor necrosis factor (TNF) alpha has an important role in the disease pathogenesis and also that anti-TNF may represent a promising robust treatment alternative in FMF.

Keywords Aseptic necrosis · Familial Mediterranean fever · Infliximab · Spondylitis

Introduction

Familial Mediterranean fever (FMF) is a genetic disease with autosomal recessive inheritance, affecting people of Mediterranean origin, particularly, non-Askhenazi Jews, Armenians, Turks, and Arabs [1, 2]. The disease is characterized by recurrent, self-limiting painful febrile episodes of peritonitis, pleuritis, and synovitis. The arthritis of FMF consists of acute attacks of mono-oligoarthritis predominantly involving the large joints of the lower extremities [1–5]. Permanent joint disease can occur, especially at the hips. It can be related to either FMF or to a coexisting chronic inflammatory disease—frequently a spondyloarthropathy (SpA) including ankylosing spondylitis (AS) [1, 4, 6–8]. SpA is one of the well-known musculoskeletal manifestations of FMF and usually requires a specific treatment other than merely colchicine [1, 4, 6, 8]. Tumor necrosis factor-α (TNF-α) blockade has recently been demonstrated to be effective in patients with AS and in other forms of SpA [9–12]. Herein, we report our experience with infliximab treatment in a case of FMF with spondylitis, sacroiliitis, and bilateral osteonecrosis of the hip joints.

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Case report

Our patient, a 35-year-old woman, had been followed for FMF since 1992 and she had been diagnosed to have spondylitis and bilateral protracted arthritis in her hip joints since 2001. Her sister is also an FMF patient under colchicine treatment. In 2001, when she was first referred to our clinic, she was suffering from febrile abdominal attacks and she also complained of inflammatory pain in her lower back and ankle joints. She was using colchicine 1.5 mg daily. The medical history was unremarkable for psoriasis, inflammatory bowel disease (IBD), or eye involvement. The family history was negative for SpA. The physical examination was, then, consistent with bilateral painful and limited hip motions and pain and swelling in her ankles. The small joints of the hands and feet, knee, elbow and wrist joints were free of any arthritis. Lumbar motions were limited, and spinous processes of lumbar vertebrae were tender to palpation. Straight leg raising and femoral stretching

tests were bilaterally negative. Neurological examination was normal. The sacroiliac (SI) joints were painful during palpation; Gaenslen and Mennel tests were bilaterally positive. Lumbar Schober was 3.1 cm and chest expansion at the fourth intercostal space was 4 cm. Radiological examinations disclosed bilateral sacroiliitis and destructive hip joint lesions. Pelvic magnetic resonance imaging (MRI) demonstrated bilateral arthritic involvement in the hip joints and destruction of the femoral head and irregular SI joints with hypointense T1-weighted and T2-weighted signal changes consistent with sclerosis (Fig. 1a). Lumbar MRI demonstrated low signal intensity in L1-2, L2-3, and L3-4 discs in T2-weighted images, decreased disc spaces and post-contrast focal enhancement at L2-3 and L3-4 levels (discitis), and Schmorl nodules at L2, L3, and L4 vertebrae superior end plates. There were also hyperintense changes at L2, L3, and L4 vertebra corpus end plates in T1-weighted and T2-weighted images (Fig. 2a). Computed tomography of the SI joints was relevant with bilateral grade 3 sacroiliitis. Laboratory evaluations were as follows: erythrocyte sedimentation rate (ESR) 76 mm/h, C-reactive protein (CRP) 33.2 mg/l, rheumatoid factor (RF) 59 U/ml, hemoglobin (Hb) 10 g/dl, platelets (Plt) 443,000/ml, and white blood cells 8500/ml. Antinuclear antibodies (ANA) and HLA-B27 were negative. She was maintained on 1.5 mg/day colchicine and sulfasalazine was commenced; her previously started prednisolone was gradually decreased.

On follow-up, she was observed to experience FMF attacks every 2–3 months despite colchicine and the arthritic findings could not be controlled sufficiently. Thereafter, methotrexate (15 mg/week) was added to her treatment regimen. Simultaneously performed rectosigmoidoscopy and rectal biopsy were noncontributory for either IBD or amyloidosis, nor did she have any proteinuria in several controls. In June 2002, she had morning stiffness for 2 h and the laboratory evaluations yielded ESR 82 mm/h, CRP 32 mg/l, Hb 9.4 g/dl, Plt 463,000/ml, and RF 56.7 U/ml. She was then on started treatment with 3 mg/kg infliximab at weeks 0, 2, and 6 and repeat infusions every 6 weeks. The combination of colchicine 1.5 mg/day, sulfasalazine 2 g/day, and methotrexate 15 mg/week was also maintained.

After the 14th week of treatment, she started to feel tremendously better. At the 26th week, laboratory parameters were as follows: ESR 32 mm/h, CRP negative (<6 mg/l), Plt 340,000/ml, and Hb 10.8 g/dl. The patient's laboratory results and overall pain measured using a visual analog scale (VAS) at different time points during the treatment are shown in Table 1). Although the hip pain was found to be persisting, her low back pain and morning stiffness improved significantly. During the infusions, she suffered from genitourinary infections twice and she responded well to treatment with appropriate antibiotics according to the culture results. At week 72 (13th dose), she experienced a recurrence—with increased hip pain and CRP levels increased to 16 mg/l, ESR 75 mm/h, Hb 10.4 g/dl, Plt 385,000/ml, and RF 100 U/ml. She complained of morning stiffness and low back pain lasting more than 2 h. The limitations of her hip joint motions had increased and the chest expansion was 3 cm. The SI joint maneuvers were negative; however, there was tenderness on palpation of the lumbar spinous processes. On the other hand, since the onset of infliximab therapy, her previously persistent febrile abdominal FMF attacks had never occurred and had completely vanished. The control hip joint MRI unmasked an overt worsening of the osteonecrosis and the hip destruction and uncovered a regression in the aforementioned SI joint findings (Fig. 1b). The involvement of the lumbar vertebrae was still present on lumbar MRI (Fig. 2b).

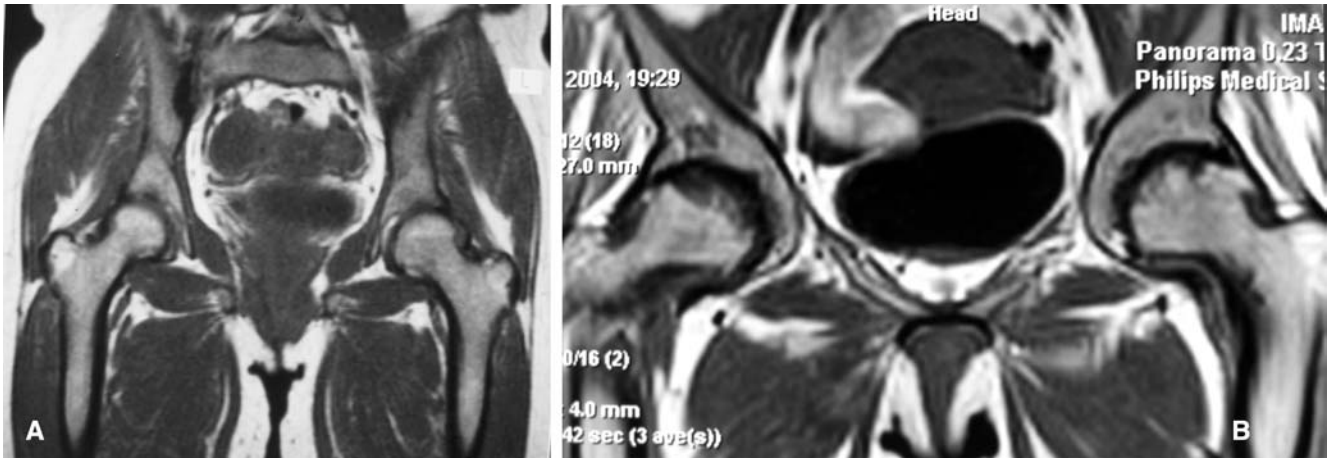

Fig. 1 **a** Coronal T1-weighted MR image shows bilateral decreased hip joint space and irregular femoral heads with heterogeneous signal intensity (May 2001). **b** Coronal T1-weighted MR image shows bilateral decreased height in the femoral heads and hypointense T1-weighted signal changes with aseptic necrosis. In comparison with the previous MRI there was significant worsening (March 2004).

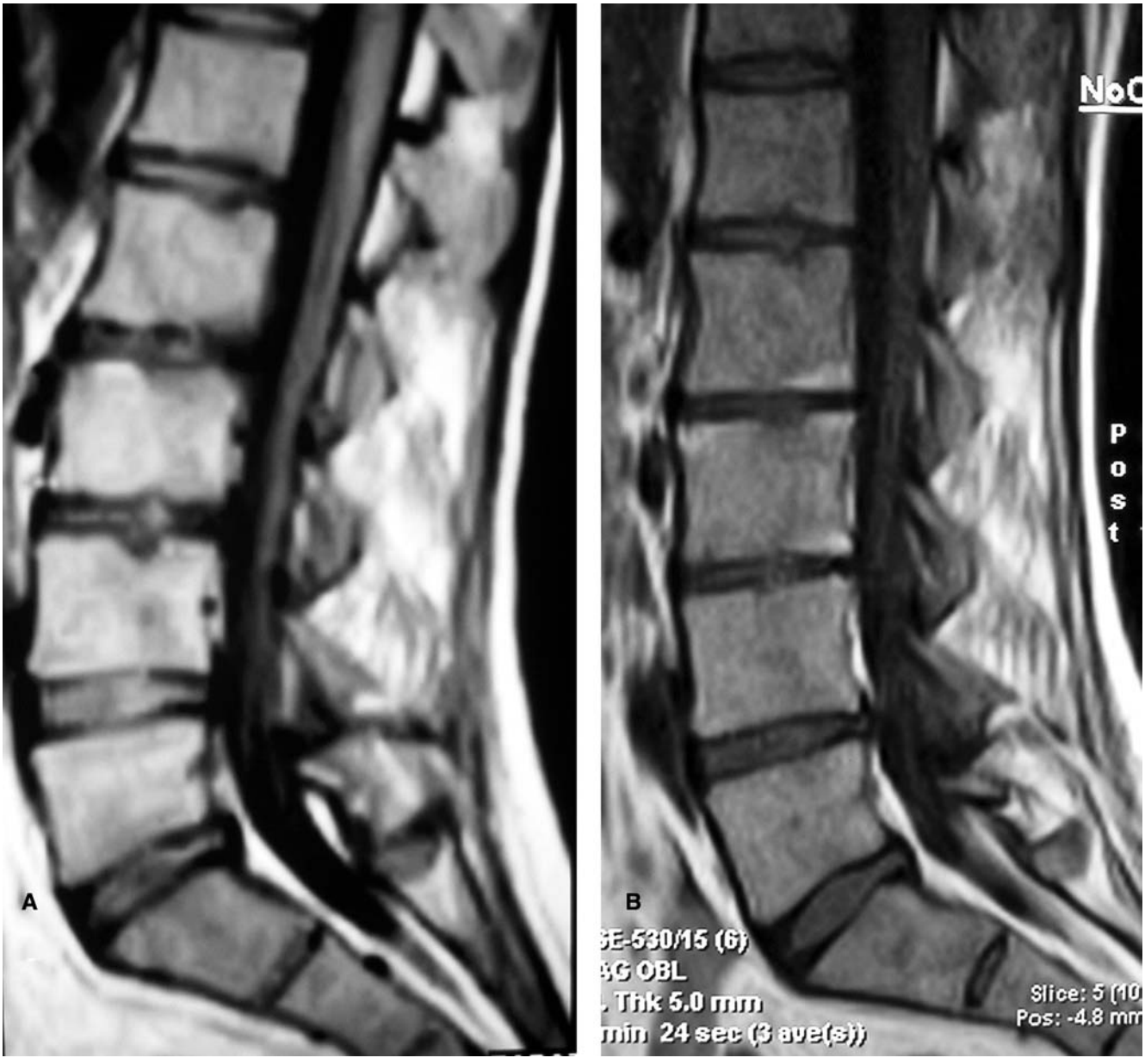

Fig. 2 **a** T1-weighted sagittal MR image shows decreased disc spaces and end plate irregularities (discitis) at L2-3 and L3-4 levels (June 2001). **b** T1-weighted sagittal control MR showing the same findings with similar severity (March 2004).

Discussion

Familial Mediterranean fever is the most prevalent periodic fever syndrome and also known as recurrent polyserositis or periodic fever. Articular involvement ensues in approximately 70–75% of the patients and in one-third of those even can be the presenting manifestation [13]. Though these arthritis attacks generally subside in 2–3 days and do not leave any sequelae [3, 13], a protracted course—mainly affecting the hip and knee joints—can be seen in 5% of the cases [3, 5, 13]. A less likely involvement can be in the form of HLA-B27-negative SpA. These patients usually have unilateral or bilateral sacroiliitis, recurrent enthesitis, and inflammatory neck/low back pain with minimal radiological spinal involvement [1, 6]. Some of them can also display an AS-like clinical course whereby chest expansion and lumbar motions are found to be restricted and typical radiological findings exist [1, 7, 14]. Either seronegative SpA or FMF patients normally have negative RF. In our case, we always detected low-titer IgM-RF positivity. Rheumatoid factor can rarely be positive in FMF patients [15, 16] and likewise in AS [17]. In this regard, our seropositive FMF patient—also consistent with AS criteria—presents an interesting clinical scenario.

Hip involvement has been reported previously in FMF [4, 8] and it is known that protracted attacks cause

Table 1 Patient's results at different time points during the treatment with infliximab

	06/02	08/02	02/03	05/03	09/03	12/03
Hb (g/dl)	9.4	10.1	10.8	10.8	10.3	10.4
Platelets	463,000	382,000	340,000	360,000	372,000	385,000
CRP (mg/l)	32	12		8	12	16
ESR (mm/h)	82	42	32	38	36	75
VAS-pain (mm)	83	41	30	35	45	60

cartilage destruction and, in some cases, aseptic necrosis [4, 8, 18]. Sneh et al. [19] have mentioned that the poor prognosis during hip involvement may be due not only to the underlying metabolic aberration of the disease but also to the impairment of the femoral head blood supply secondary to the recurrent synovial exudation. Thus, they have suggested early aspiration in preventing aseptic necrosis. We must note in addition that our patient also had an important risk factor—steroid use—for aseptic necrosis of the femoral head. Although our patient's spondylitic findings responded well to infliximab treatment, a more satisfactory result might have been overshadowed by unrelenting hip pain and disability, which could be attributed to osteonecrosis and hip destruction.

The role of TNF-α in FMF has not yet been clarified. The pertinent reports mention decreased/slightly increased TNF-α levels during acute attacks or normal/increased levels between the attacks [20–23]. Gang et al. [24] have found increased levels of soluble TNF receptor fusion protein p55 (sTNFr p55) and p75 (sTNFr p75) during attacks. Besides, it is also known that the MEFV gene is upregulated by TNF-α [25]. These data present an insight towards a better understanding of the possible benefit of anti-TNF treatment in FMF.

In closing, we overcame the FMF attacks of our patient with infliximab, a murine-human chimeric monoclonal antibody. Although the clinical findings of our patient pertaining to spondylitis improved, we could not achieve a significant change in the persistent hip pain which was thought to occur due to osteonecrotic destruction. In any case, a favorable effect of infliximab on the structural destruction of the vertebral end plates and the hip—which had been detected in the beginning and had also persisted in the control MRIs—was not expected. It is suggested that contrast enhancement—which has a better capability for evaluating the disease activity—and short τ inversion recovery (STIR) sequences could be used for better delineation of the disease activity.

Overall, we believe that our results further highlight the important role TNF-α plays in the pathogenesis of FMF and that therapies targeting TNF-α have the potential to be a cornerstone in the treatment of FMF.

Take Home Message

The arthritis in FMF may sometimes resist colchicine and DMARD treatments. The clinical scenario may comprise spondylitic involvement and also seropositivity. Our case may shed light on the possible role of TNF-α in the disease pathogenesis. This way, we believe that anti-TNF therapy may reasonably be a future target in FMF treatment.

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