INTERNAL MEDICINE

□ CASE REPORT □

Familial Mediterranean Fever Occurring in an Elderly Japanese Woman with Recent-onset Rheumatoid Arthritis

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Abstract

A 60-year-old woman with a two-year history of rheumatoid arthritis (RA) developed recurrent two- to three-day attacks of fever (>38℃) accompanied by monoarthritis of the right hip joint. The first attack occurred two months after beginning anti-tumor necrosis factor-α therapy. Since a diagnosis of infectious arthritis was suspected, the therapy was discontinued. Thereafter, the patient repeated similar episodes; however, oral colchicine effectively controlled the attacks. The patient was diagnosed to have familial Mediterranean fever (FMF). The clinical manifestations of FMF mimic infectious complications during anti-RA therapy. Clinicians should therefore consider the possibility of FMF development in RA patients exhibiting recurrent febrile attacks.

Key words: familial Mediterranean fever, rheumatoid arthritis, *MEFV*, colchicine, infectious arthritis

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive, hereditary, autoinflammatory disorder characterized by recurrent one- to three-day attacks of fever and paroxysmal serositis, usually involving the peritoneum, pleura and synovial joints (1, 2). This disease is prevalent in individuals of Mediterranean descent, such as non-Ashkenazi Jews, Armenians, Turks and Arabs, and is quite rare in Japan. Approximately 90% of all cases occur before 20 years of age. Almost all FMF patients carry mutations in the pyrin-encoding gene *MEFV* on chromosome 16p13.3 (3, 4). Mutated forms of pyrin proteins may be involved in alterations of inflammatory processes that ultimately result in the uncontrolled expression of the potent proinflammatory cytokine, interleukin-1β. In turn, overexpression of IL-1β leads to dysregulated neutrophil activation and bursts of systemic inflammation (5). Recently, the presence of an association between *MEFV* mutations and the occurrence of rheumatic diseases, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and ankylosing spondylitis, has been suggested (6-8). Two studies have shown that RA patients carrying *MEFV* mutations have higher severity scores than non-carriers (9, 10). Nevertheless, no cases of coexisting RA and FMF have hitherto been reported. We herein report a case of FMF occurring in an elderly Japanese woman with a two-year history of RA who was receiving immunosuppressive anti-RA therapy.

Case Report

In February 2007, a 60-year-old woman was diagnosed to have early RA at our outpatient clinic. At that time, a physical examination revealed five swollen and six tender small joints, including both wrists. She also complained of morning stiffness in and around these joints lasting longer than one hour. These symptoms had persisted for two months. Plain radiographs of the hands showed evidence of bone erosion and joint space narrowing. Given these findings, the patient met five of the seven 1987 American College of Rheumatology criteria for RA diagnosis. Both the serum C-reactive protein (CRP) levels and the erythrocyte sedimentation rates were high. The patient was also positive for anti-

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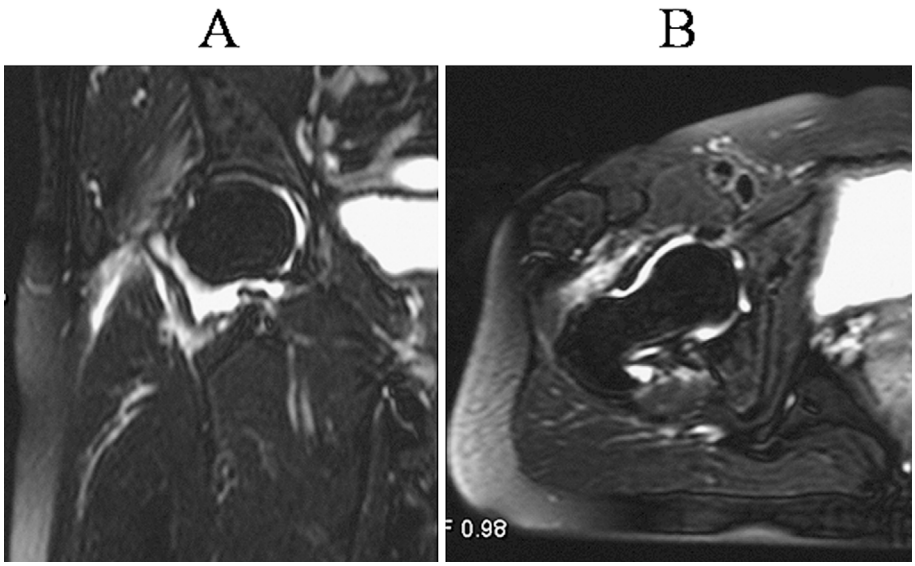

Figure. **Magnetic resonance imaging scans obtained during the patient's first febrile attack. Fat suppression T2-weighted (FS-T2W) images in the coronal (A) and axial (B) planes show high signals in the right hip joint. The findings suggest the presence of joint effusion and thickened synovium. High signals are also seen in the soft tissues around the joint, thus reflecting inflammatory changes.**

cyclic citrullinated peptide antibodies (57 IU/mL); however, she exhibited a negative result for rheumatoid factor. The disease activity score for 28 joints (DAS28) was 5.1 and Steinbroker's stage was II. The patient carried two copies of shared epitope-positive HLA-DRB1 alleles (*0101/*1001). Following treatment with 8 mg/week of methotrexate (MTX), she achieved low disease activity.

In April 2009, anti-tumor necrosis factor-α (anti-TNFα) therapy with infliximab (3 mg/kg) was initiated in combination with MTX because the patient's RA had deteriorated (DAS28: 6.05). She responded well to this therapy: the DAS 28 score fell to 2.11 immediately before the third infusion. Two months later, the patient visited our hospital due to a high fever of 39℃ and severe pain in the right hip joint. Neither pulmonary complications nor abdominal symptoms were observed. The white blood cell (WBC) count was elevated with neutrophilia (12,650/μL), and the level of CRP was also high (10.8 mg/dL). The serum levels of hepatic aminotransferases, blood urea nitrogen and albumin were within the normal ranges. Tests for serum endotoxin, β-D glucan and procalcitonin were negative. Neither renal dysfunction nor proteinuria were observed. There was no radiographic evidence of erosion or destructive involvement of the hip joint. Magnetic resonance imaging scans of the hip joint revealed massive amounts of fluid and synovial hypertrophy (Figure). Joint aspiration performed during the attack revealed sterile pyogenic synovial effusion without calcium pyrophosphate deposition or uric acid crystals. Cultures did not produce any bacteria. The patient's hip joint pain and a high fever >38℃ continued for three days, then subsided and disappeared. Although the origin of the fever was unknown, infliximab therapy was discontinued. Alternative anti-RA treatment consisting of 1 mg/day of tacrolimus and MTX was introduced, and the patient remained in remission.

In September 2009, the patient developed recurrent two-day fever episodes (>38℃) accompanied by severe pain in the right hip joint. The WBC count and CRP level both increased during these attacks. Since a diagnosis of FMF was suspected, colchicine (1 mg/day) was administered, and the attacks were effectively controlled. This therapy was continued until August 2010. In May 2011, the patient once more experienced recurrent attacks of high fever (>38℃) and severe right hip joint pain lasting two days; as before, she responded very favorably to colchicine. Considering the typical feverish attacks accompanied by monoarthritis of the hip joint, as well as the adequate response to colchicine, the patient fulfilled one major and one minor criterion of the Tel Hashomer criteria for a diagnosis of FMF (11). A definitive diagnosis of FMF was therefore given to the patient. The patient exhibited no cutaneous, mucous, eye, or neurological involvement. Neither xerostomia nor dry eye were observed. The patient did not complain of gastrointestinal or respiratory symptoms. There was no laboratory evidence suggesting that the patient had developed renal dysfunction, hepatic impairment or a hematological disorder. A urinalysis by dipstick showed no abnormal findings. Therefore, we excluded the possibility that the patient's recurrent febrile attacks were due to autoinflammatory diseases, including Sjögren's syndrome, Behçet's disease, systemic lupus erythematosus, vasculitis and inflammatory bowel disease. In addition, the patient presented with no clinical findings that raised the suspicion of lymphoma, such as lymphadenopathy, lymphopenia, splenomegaly or cryoglobulinemia.

The patient denied having had any recurrent fever episodes prior to the first visit to our clinic. According to an

interview regarding the patient's family health history, none of her first-degree relatives had experienced typical FMF symptoms. A mutation analysis was performed by sequencing all exons of the *MEFV* gene (exons 1-10) as described elsewhere (12). We found that the patient was heterozygous for the E148Q allele in exon 2. Until the time of submission, the daily administration of colchicine was continued without any attacks of fever.

Discussion

Considering that the attacks of fever and hip joint monoarthritis occurred within the first two months of infliximab therapy, we suspected a diagnosis of infectious arthritis, which led to discontinuation of this therapy. Anti-TNFα therapy increases the risk of septic arthritis in RA patients compared with nonbiological disease-modifying antirheumatic drugs (13, 14). Since septic arthritis is potentially life-threatening, this decision was inevitable. However, consideration should be given to the possibility of FMF development in RA patients exhibiting recurrent attacks of fever, although it is unclear whether the coexistence of FMF and RA is a mere coincidence or whether there is an association between these two diseases. FMF manifestations can mimic many common infectious diseases. We believe that a therapeutic trial with colchicine is justified in such cases. It has recently been shown that anti-TNFα agents are effective in treating colchicine-resistant FMF cases (15). Our patient, however, developed the clinical symptoms of FMF during infliximab therapy. The role of TNFα in FMF pathogenesis remains to be clarified.

It is now known that the *MEFV* gene is associated with several rheumatic diseases, not only FMF (6-8). Coexistence of systemic lupus, JIA, Sjögren's syndrome, and polymyositis with FMF has been reported (12, 16-18). As for RA, carriage of *MEFV* mutations, and the E148Q mutation in particular, has been reported to be an independent modifier for clinical manifestations in Israeli patients (9). In a Turkish cohort, *MEFV* mutations appeared to be an aggravating factor for RA severity (10). Conversely, no significant associations between the presence of these mutations and the development of RA or RA-related amyloidosis were found in a Japanese population (19). It is uncertain whether differences in the genetic backgrounds of these ethnic groups are responsible for this discrepancy. The present patient experienced her first FMF episode two years after the onset of RA. When RA patients develop recurrent fevers and monoarthritis in large joints such as the hip, ankle and knee, then the concurrence of FMF should be considered as a possible cause.

FMF patients experiencing disease onset after 60 years of age are extremely rare (20-22). The cause of late-onset FMF is unclear; however, heterozygosity of *MEFV* mutations may contribute to this phenotype. The present patient carried the heterozygous E148Q allele in the *MEFV* gene. Since FMF has traditionally been considered an autosomal-recessive disease, a heterozygote is expected to be a carrier and to lack the clinical phenotypes of FMF. However, several research groups have suggested that carriers of one *MEFV* mutation may have a tendency to develop certain manifestations due to having an increased baseline of inflammation and may develop rheumatic diseases more often than 'healthy' populations (6, 23-25). Recently, two groups reported the existence of a significant subset of FMF patients who are carriers of only one *MEFV* mutation, thus suggesting that having the heterozygous mutation is sufficient to express the typical clinical features of FMF (26-28). In another study, the clinical presentations of patients with recurrent fever and only one *MEFV* mutation appeared to resemble those of homozygous patients, and most of the cases required colchicine treatment (29). In either case, mutation analyses of *MEFV* and therapeutic trials with colchicine should be considered in patients exhibiting recurrent febrile attacks, even among those over 60 years of age.

Whether the E148Q allele in the *MEFV* gene is a true disease-causing mutation or a benign polymorphism remains controversial. The E148Q allele appears to confer an inflammatory phenotype in Turkish individuals (30). In a Greek population, the E148Q allele was found to be significantly more frequent in FMF patients than in healthy controls (31). These findings suggest that the E148Q allele is a disease-causing *MEFV* mutation. In a Jewish population, however, the frequency of the E148Q allele was similar between FMF patients and healthy controls, favoring the concept of a non-causative role (32, 33). Tomiyama et al. showed that the E148Q and M694I alleles are most frequently detected in Japanese patients, although the impact of the E148Q allele on FMF manifestations is low (34). Nevertheless, the present patient developed the FMF phenotype in her sixties. There may be an unknown factor or event capable of triggering the disease through interactions with IL-1β-related inflammatory pathways.

Fortunately, our patient shows no evidence of developing serious complications to date, and her RA remains in remission. Since inflammation can persist, even during attack-free periods, in many FMF patients, providing careful monitoring of inflammatory markers and adequate control of chronic inflammation is required to prevent the development of complications such as life-threatening amyloidosis (35). Although the present patient's symptoms had been well controlled for one year, her attacks of fever returned after cessation of colchicine treatment. Daily lifelong administration of colchicine is required to prevent both attacks of fever and silent amyloid deposition (2).

In conclusion, FMF can occur in RA patients. The clinical manifestations of FMF mimic infectious complications, which can delay FMF diagnosis for many years and can occasionally subject patients to unnecessary examinations and inadequate treatments. Clinicians should therefore be aware of the possible coexistence of FMF in RA patients exhibiting recurrent febrile attacks. Conducting a therapeutic trial with colchicine is thus considered to be justified in such cases.

The authors state that they have no Conflict of Interest (COI).

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