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Atypical Familial Mediterranean Fever Presenting with Recurrent Upper Back Pain: A Case Report

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Familial Mediterranean fever (FMF) is a genetic autoinflammatory disease that is characterized by recurrent episodes of fever, serositis, and synovitis. FMF synovitis attacks resemble the clinical presentation of acute monoarthritis with pain and hydrarthrosis, which always resolve spontaneously. In most cases, colchicine will prevent these painful arthritis attacks in FMF. However, distinguishing these arthritis episodes from other febrile attacks with various clinical manifestations, including serositis, is important. We describe a Japanese patient with FMF who presented a febrile attack with severe abdominal and upper back pain (peri-scapula lesion), without any other joint involvement. A 44-year-old female patient presented with recurrent episodes of fever with abdominal and back pain. She carried heterozygous variants in exon 3 of the *MEFV* gene (P369S/R408Q). She was diagnosed with FMF according to Tel-Hashomer's diagnostic criteria for FMF. Colchicine treatment improved her febrile attcks with peritonitis, however, severe back pain was sustained. This unique aspect of severe pain attack was successfully resolved by canakinumab treatment, which is a specific interleukin-1β monoclonal antibody, and was finally diagnosed as FMF-related shoulder joint synovitis. Further investigations were needed to evaluate the effectiveness of interleukin-1 antagonists against colchicine-resistant arthritis in FMF patients.

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Introduction

Familial Mediterranean fever (FMF) is a genetic autoinflammatory disorder that is characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints associated with periodic fever (Ben-Chetrit and Levy 1998). FMF has been known to affect mainly Mediterranean and Middle Eastern populations (Tunca et al. 2005). However, recent studies demonstrated that FMF is a worldwide disease, including Japan (Migita et al. 2012). Acute arthritis attacks were reported to be complicated in patients with FMF, and be characterized by short-duration, self-limited episodes (Jarjour and Dodaki 2011). Large joints of the lower extremities are most frequently involved (Yenigun et al. 2022). The radiographic appearance is not specific and is characterized by soft tissue and joint space narrowing or destruction had been demonstrated in FMF patients with protracted arthritis (Sneh et al. 1977). Oral colchicine administration is usually used for FMA-associated arthritis attacks as a preventive therapy (Jarjour and Dodaki 2011). We describe a case with FMF who developed colchicine resistant atypical arthritis manifested as severe back pain, which could finally be controlled by an interleukin-1 (IL-1) inhibitor, canakinumab.

Case Presentation

A 44-year-old Japanese woman with unexplained, recurrent episodes of high fever, abdominal pain, and back pain occurring over the previous 2 years was referred to our department. She had no family history of periodic fever. Two years prior to the first visit to our hospital, she was admitted to the emergency hospital due to abdominal pain, diarrhea, and fever and be treated with antibiotics under the diagnosis of pyelonephritis for one week. However, she was readmitted to this hospital due to a recurrent febrile attack (> 40°C) and pleural effusion 1 month later.

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Laboratory tests revealed increased inflammatory markers [C-reactive protein of 9.3 mg/dL and serum amyloid A (SAA) of 1,800 μg/mL, reference value < 8.0 μg/mL]. Other immunological tests, including rheumatoid factor, anti-cyclic citrullinated peptide antibody, and autoantibodies, were insignificant. *MEFV* gene analysis was performed by direct sequencing, and compound heterozygous variants (P369S/R408Q) were detected in exon 3 of the *MEFV* gene. Clinical diagnosis of the complete type of FMF was made since she fulfilled Tel-Hashomer's diagnostic criteria according to the presence of major criteria (recurrent febrile episodes accompanied by peritonitis) (Livneh et al. 1997). She was started on colchicine at 1 mg/day, and the dose was increased to 1.5 mg/day. Her symptoms (febrile attack with abdominal pain) had improved significantly since colchicine was started. However, she had a low-grade fever (approximately 37.5℃) with persistent back pain radiating to the left shoulder and difficulty in raising the left arm once or twice a month, and was referred to our department for further examinations. Table 1 shows the laboratory findings when referred to our department. No inflammatory findings were observed since she was in FMF attack-free phase.

Fig. 1 summarizes the clinical course. Colchicine treatment was effective against peritonitis attacks; however, did not completely control the low-grade fever, and recurrent monthly attacks of back pain were sustained. Musculoskeletal ultrasonography of the left shoulder was performed during the febrile attack with back pain. It showed blood flow at the supraspinatus tendon (Fig. 2A). However, chest computed tomography (CT) revealed no abnormal shadows or pleural effusions suggestive of pneumonia or pleurisy (Fig. 3). Additionally, the CT scan showed no abnormalities in the thoracic spine or shoulder joints. The inflammatory changes were observed in the musculoskeletal ultrasonography, so we estimate the cause of the back pain based on the inflammatory changes seen on musculoskeletal ultrasonography. She was judged to have colchicine-resistant FMF; thus, treatment with canakinumab, which is a specific IL-1β monoclonal antibody (Ilaris at 150 mg, subcutaneous injection every 4 weeks), was initiated in November 2022. Since that time, she has remained asymptomatic, and FMF-related back pain was eliminated, after canakinumab induction. After three months after the initiation of canakinumab, ultrasonography of the left shoulder joint was reevaluated. The blood flows suggestive of inflammation disappeared (Fig. 2B).

Informed consent was obtained from the patient. Because of a case report of a single patient, ethical approval was waived for the institutional review board at Fukushima Medical University.

Table 1. Laboratory findings on admission.

Peripheral blood		Sodium	138 mEq/L (138-145)
Red blood cells	$432\times10^4/\mu$L	Potassium	3.8 mEq/L (3.6-4.8)
Hemoglobin	13.5 g/dL	Chloride	105 mEq/L (101-108)
Hematocrit	41.5%	Ferritin	58 ng/mL (50-200)
Platelets	$21.5\times10^4/\mu$L	Immunoserological tests	
White blood cells	4,900/μL	C-reactive protein	< 0.01 mg/dL (< 0.30)
Neutriphil	46%	Serum amyloid A	< 2.0 μg/mL (< 8.0)
Eosinophil	5%	IgG	1,104 mg/dL (861-1,747)
Monocytes	5%	C3	87 mg/dL (73-138)
Lymphocytes	43%	C4	18 mg/dL (11-31)
Basophil	1%	CH50	26.2 U/mL (25.0-48.0)
Blood chemistry		ANA	< × 80 (0-159)
Total protein	7.0 g/dL (6.6-8.1)	Anti-ds-DNA antibodies	(−) (< 9.9)
Total bilirubin	0.9 mg/dL (0.4-1.5)	RF	< 5 IU/mL (0-15)
Albumin	4.3 g/dL (4.1-5.1)	Anti-CCP antibodies	< 0.6 U/mL (< 4.5 U/mL)
Asparate aminotransferase	33 IU/L (13-30)	Infection	
Alanine aminotrans ferase	24 IU/L (10-42)	HBs Ag	(−)
Lactate dehydrogenase	219 IU/L (124-222)	Anti-HCV antibodies	(−)
Alkaline phosphatase	118 IU/L (106-322)	β-D glucan	< 6.0 (0-11.0)
Amylase	113 U/L (44-132)	Human parvovirus B19 IgM	(−)
Creatine kinase	120 IU/L (59-248)	Urinalysis	normal
Blood urea nitrogen	11 mg/dL (8-20)	Blood culture	(−)
Creatinine	0.60 mg/dL (0.65-1.07)		

Reference values are shown in the parentheses. ANA, anti-nuclear antibody; C, complement; CCP, cyclic citrullinated peptide; CH50, homolytic complement activity 50; ds-DNA, double-stranded deoxyribonucleic acid; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; Ig, immunoglobulin; RF, rheumatoid factor.

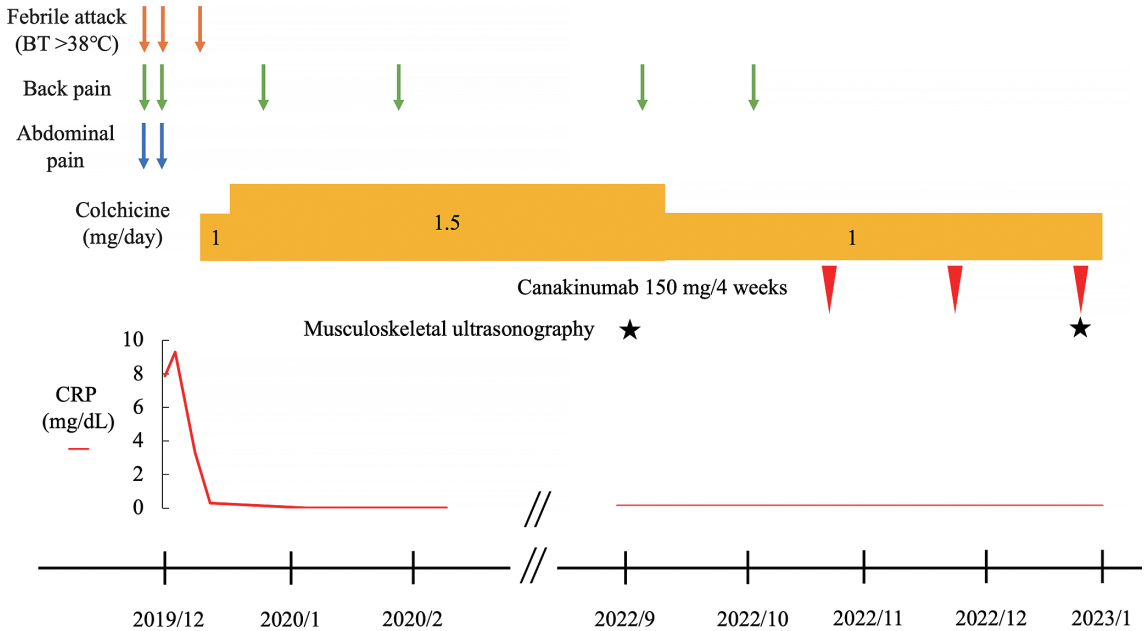

Fig. 1. Clinical course.
Colchicine treatment was effective against peritonitis attacks; however, did not completely control the low-grade fever, and recurrent attacks of back pain were sustained. For colchicine-resistant FMF, treatment with canakinumab was initiated and recurrent attacks were disappeared. BT, body temperature; CRP, C-reactive protein.

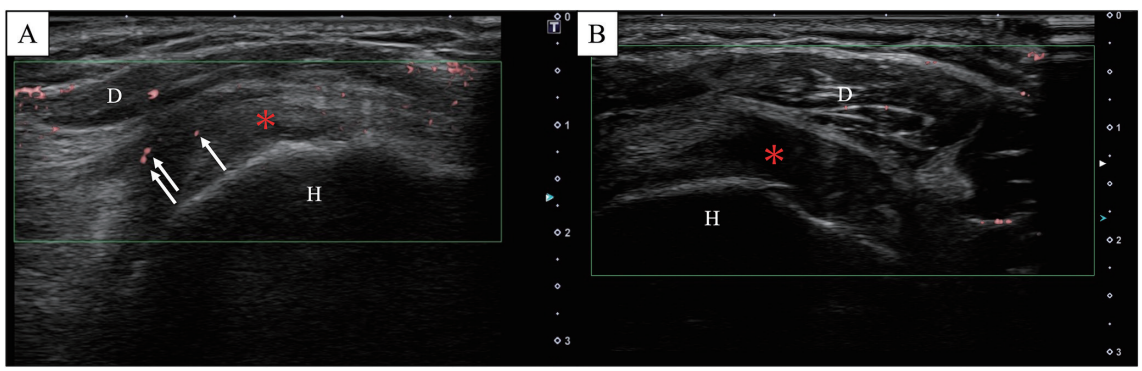

Fig. 2. Musculoskeletal ultrasonography findings of the left shoulder.
(A) Musculoskeletal ultrasonography showed blood flow (white arrows) at the supraspinatus tendon (*). (B) After three months of induction of canakinumab, the blood flow at the supraspinatus tendon, suggestive of inflammation, disappeared. D, deltoid muscle; H, humerus.

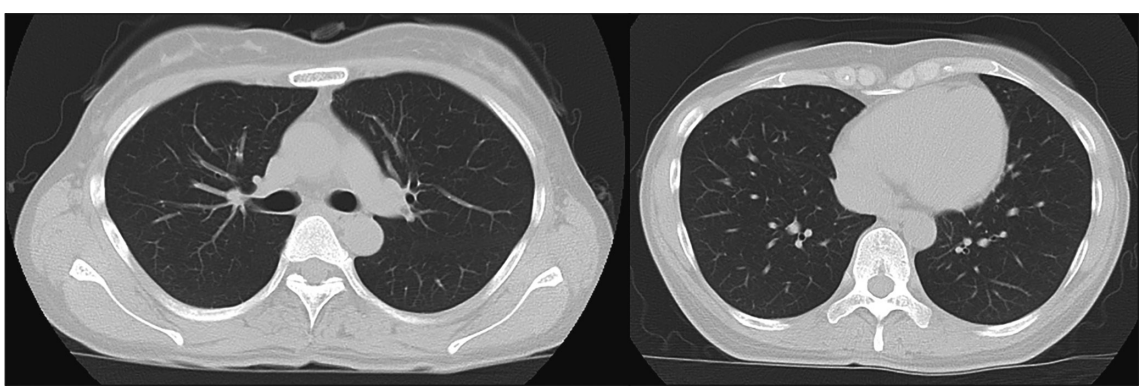

Fig. 3. Chest CT findings.
Chest CT showed no abnormal shadows or pleural effusions suggestive of pneumonia or pleurisy.

Discussion

FMF is a genetic autoinflammatory disease that is characterized by self-limited recurrent attacks of fever with serositis (Ben-Chetrit and Levy 1998). Musculoskeletal involvements in FMF, mostly in the form of arthritis or arthralgia, are the fourth most common manifestation of FMF and its frequencies accounts for 31.3% of Japanese patients with FMF (Migita et al. 2012). FMF-related arthritis usually develops as an acute monoarthritis form, mainly involving articular districts of lower limbs (hip, knee, and ankle) (Jarjour and Dodaki 2011). Herein, we present a case of FMF with recurrent localized shoulder monoarthritis as an unusual FMF attack. FMF diagnosis is usually made clinically since laboratory tests or imaging studies are not useful for FMF diagnosis (Ozen et al. 2016). However, proper FMF diagnosis is needed based on specific clinical manifestations and the treatment response based on continuous prophylactic administration of colchicine, preventing febrile attacks. FMF diagnosis was suspected based on the typical febrile attack with abdominal and back pain associated with the partial response to colchicine in the present case. We did not capture the increase in CRP/SAA after the introduction of colchicine, but this may be due to the fact that the attacks were short-term and the patient lived far away from our hospital and could not visit our hospital immediately at the time of the attack. Genetic tests are not necessarily mandated, and pathogenic *MEFV* mutations could be partially detected in Japanese patients with FMF (Tomiyama et al. 2008). P369S/R408Q variants seen in the present case are low-penetrance and might not be sufficient to diagnose FMF (Kishida et al. 2014). FMF patients carrying P369S/R408Q variant are associated with highly variable phenotypes and are infrequently associated with typical FMF symptoms (Ryan et al. 2010). However, the present case fulfilled the diagnostic criteria for FMF complete type according to the nature of febrile attacks with abdominal pain in addition to the synovitis with atypical particular districts.

Arthritis in FMF patients usually responds to colchicine (Farag et al. 2020). Although her high fever was partially improved by colchicine treatment, the painful arthritis attack of the shoulder was resistant to colchicine and was sustained. Colchicine is the mainstream treatment for FMF; however, colchicine resistance or intolerance may result in chronic inflammation, resulting in the development of AA amyloidosis in few patients with FMF (Ozen et al. 2016). The goals of FMF treatment in clinical practice include acute attack prevention and elimination of subclinical inflammation to reduce the risk of complications, including AA amyloidosis, as well as to improve the activities of daily living (ADL) (Ozen et al. 2016). Colchicine-resistant FMF patients complicated with protracted arthritis can be treated with methotrexate or anti-tumor necrosis factor inhibitors (Ozgocmen et al. 2006; Nakamura et al. 2007; Kobayashi et al. 2018). However, European League Against Rheumatism (EULAR) recommends anti-IL-1 therapy is promising second-line therapy in colchicine-refractory or intolerant FMF patients (Ozen et al. 2016). Therefore, IL-1 biological inhibitors act on the inflammatory cascade and prevent synovitis attack as well as AA amyloidosis (Varan et al. 2019). IL-1β plays a major role in FMF pathogenesis, and IL-1 blockade provides therapeutic control of colchicine-resistant FMF (Hentgen et al. 2020). Canakinumab, which is a human anti-IL-1β monoclonal antibody, has shown promising efficacy in treating colchicine-resistant FMF (Mitroulis et al. 2011). The periodic shoulder monoarthritis seen in the present case suggests that IL-1β-mediated autoinflammatory processes are involved in the FMF-related synovitis attack. Colchicine controls systemic inflammation in the present case. However arthritis attacks under adequate colchicine treatment were sustained, this refractory arthritis could be resolved by canakinumab in the present case.

In conclusion, arthritis of FMF has diverse clinical presentations. Arthritis in FMF typically occurs as monoarthritis of the lower leg joints. However, shoulder joint synovitis can be presented as severe back pain in a few patients with FMF. Clinicians should consider FMF-related monoarthritis as a possible differential diagnosis of back pain in patients with fever, even in the absence of pleuritis. Canakinumab was effective in bringing a rapid resolution of back pain, as well as in improving shoulder joint synovitis, suggesting the major role of IL-1 in the pathogenesis of FMF-related acute monoarthritis.

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Conflict of Interest

The authors declare no conflict of interest.

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