INTERNAL MEDICINE

□ CASE REPORT □

Protracted Febrile Myalgia Syndrome in a Japanese Patient with Fasciitis Detected on MRI

Keita Fujikawa[1], Kiyoshi Migita[2], Toshiaki Tsukada[1], Atsushi Kawakami[3] and Katsumi Eguchi[4]

Abstract

Protracted febrile myalgia syndrome (PFMS) is a rare manifestation of familial Mediterranean fever characterized by prolonged severe myalgia. We herein describe a case of PFMS with fasciitis on magnetic resonance imaging. The response to corticosteroid therapy was prompt, as is typical for PFMS. An MEFV gene analysis revealed the patient to be homozygous for E148Q and compound heterozygous for P369S-R408Q. This is the first case report of a Japanese patient with PFMS. MRI findings may help to diagnose such cases.

Key words: autoinflammatory disease, familial Mediterranean fever, protracted febrile myalgia syndrome, MRI

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Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by recurrent fevers, serositis and synovitis attacks (1). Colchicine is the established first-line therapy for disease control in cases of FMF (2). Protracted febrile myalgia syndrome (PFMS) is a rare manifestation of FMF characterized by prolonged excruciating and symmetric muscle pain and tenderness, a high-grade fever and elevated levels of acute-phase reactants, necessitating treatment with corticosteroids (3). On muscle biopsies, the most striking changes appear in the fascia, including an increased amount of collagen fibrils and infiltration by fibroblasts, macrophages and a few mast cells (4). We herein present the case of a patient with PFMS fasciitis detected on magnetic resonance imaging (MRI).

Case Report

In June 2013, a 22-year-old Japanese man was referred to our hospital with a fever and prolonged myalgia of the upper and lower extremities lasting for three weeks, accompanied by cervical lymph node swelling, headaches, abdominal pain and diarrhea. The muscle pain was so severe that standing or walking was impossible, and the patient was forced to use a wheelchair. The laboratory data revealed elevated levels of C-reactive protein (1.32 mg/dL; normal limits 0-0.1 mg/dL), aldolase (6.6 IU/L; normal limits 2.7-5.9 IU/L) and ferritin (566 ng/mL; normal limits 12-60 ng/mL), although the white blood cell count and creatine phosphokinase (CPK) level were within the normal range. Infectious causes (hepatitis B and C, cytomegalovirus, Epstein-Barr virus and human immunodeficiency virus) were ruled out. Thickening of the fascia was observed on short-time inversion recovery (STIR) images of plain MRI (Figure). The patient's younger sister had a history of recurrent episodes of fever lasting for two or three days with arthralgia, erythema, headaches, chest pain and abnormal pain starting at 10 years of age, typical of FMF. Therefore, the patient's symptoms and clinical manifestations were suggestive of the atypical type of FMF. Treatment with colchicine was promptly instituted, and the dose of the drug was increased to 1.5 mg/day. The patient's symptoms of fever, myalgia and abdominal pain partially improved; however, they soon recurred. He was therefore given prednisolone (20 mg/day) for the diagnosis

[1]Department of Rheumatology, Japan Community Health Care Organization (JCHO), Isahaya General Hospital, Japan, [2]Department of Rheumatology, NHO National Nagasaki Medical Center, Japan, [3]Department of Rheumatology, Unit of Translational Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Japan and [4]Department of Internal Medicine, Sasebo Municipal Hospital, Japan
Received for publication March 12, 2014; Accepted for publication June 2, 2014
Correspondence to Dr. Keita Fujikawa, keitafj@gmail.com

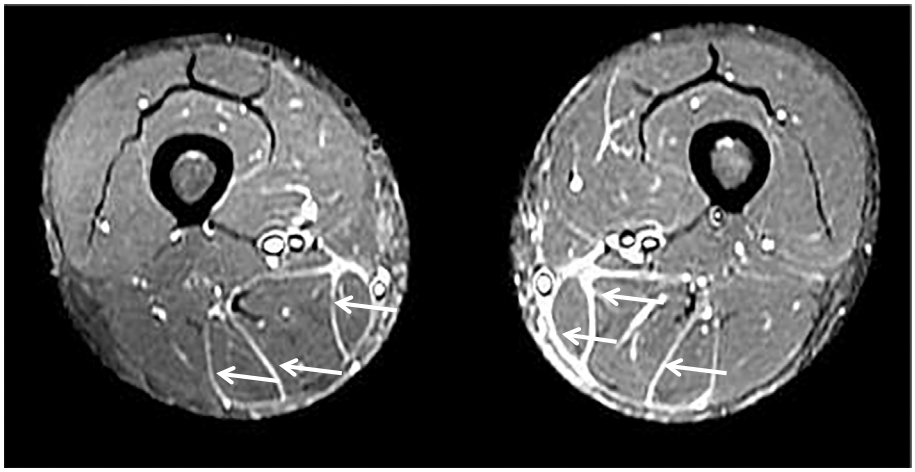

Figure. **Plain STIR MRI of the muscle in the thigh. The arrows indicate sites of thickening of the fascia.**

of PFMS, at which point his symptoms quickly disappeared. The dose of prednisolone was subsequently tapered and discontinued six weeks after the start of treatment. The patient experienced no further episodes of recurrence, without treatment with colchicine, during a follow-up period of six months. On a genetic analysis of the MEFV gene, he was found to be homozygous for E148Q and compound heterozygous for P369S-R408Q, while his sister was homozygous for E148Q.

Discussion

Myalgia is a common manifestation in patients with FMF, occurring in approximately 25% of cases of FMF (5). Exercise-induced myalgia is the most common form of the condition; it is not severe, subsides with rest and lasts from hours to 2-3 days, without a fever or elevated levels of acute-phase reactants. On the other hand, there are sporadic case reports of severe, prolonged myalgia in patients with FMF, called PFMS. This entity was first described by Schapia et al. in 1988 (4), and its clinical manifestations were defined by Langevitz et al. in 14 patients (6). According to Schapia and colleagues' characterization of the disease, severe debilitating myalgia of the extremities and a high fever are occasionally accompanied by abdominal pain, diarrhea, arthritis/arthralgia and transient vasculitic purpura. In 33% of cases, PFMS occurs as the first sign of FMF (7). The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level is elevated in such patients, whereas the creatine kinase (CPK) level is normal (7). Electromyography (EMG) typically shows nonspecific inflammatory myopathy. Although PFMS can develop despite the administration of colchicine therapy, the response to corticosteroid treatment is prompt (6). Muscle biopsies typically demonstrate thickening of the endomysial and perimysial spaces with infiltration of inflammatory cells, such as fibroblasts, macrophages and mast cells (4). In the present case, thickening of the fascia was detected on MRI. These findings suggest that inflammation in the setting of PFMS occurs in the fascia rather than the muscle fiber and that the myalgia experienced by PFMS patients is caused by fasciitis.

Of course, it is difficult to diagnose PFMS based on MRI findings alone. Thickening of the fascia on MRI is also observed in various autoimmune/auto-inflammatory diseases, including polyarteritis nodosa (8), eosinophilic fasciitis (9), inflammatory myopathy with abundant macrophages (IMAM) (10) and monocytic fasciitis in TRAPS patients (11). Accordingly, there are few characteristic features of PFMS in clinical or laboratory data that can be used to differentiate this condition from fasciitis of other etiologies. Therefore, it is essential to diagnose PFMS comprehensively by referring to other findings, such as episodes of periodic fever, the patient's family history and the results of genetic analyses and muscle biopsies. In the current case, the diagnosis of PFMS was made based on clinical and genetic evidence and the patient's family history of FMF according to the criteria for a working diagnosis (7). In patients with FMF who exhibit symptoms such as prolonged myalgia and fever, MRI findings may be useful for diagnosing PFMS.

The results of genetic analyses of PFMS have been reported in Jews and Arabs (12-14). The most frequent mutation is homozygosity for M694V (42-83%), although there is one case report describing a patient homozygous for the E148Q mutation (15). While M694V and V726A are the most common mutations in Mediterranean FMF patients (16), they are infrequent in Japanese FMF patients (17, 18). The E148Q, P369S and R408Q mutations, which were detected in the present patient, have been reported in patients with atypical FMF in Japan (19). Importantly, the MEFV mutations of PFMS have not been studied in Japanese subjects, and such mutations may differ between Mediterranean and Japanese individuals.

To our knowledge, this is the first case report of a Japanese patient with PFMS. The diagnosis of PFMS should be made based on clinical manifestations and the findings of MEFV gene analyses, as well as by ruling out other diseases

caused by fasciitis. MRI may also be helpful in such cases, and the role of this modality in diagnosing PFMS should be explored in a larger series of patients.

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

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