

[CASE REPORT]

Familial Mediterranean Fever without Fever

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Abstract:

Familial Mediterranean fever (FMF) is an autosomal recessive hereditary disease commonly observed around the Mediterranean basin presenting as recurrent febrile episodes. We herein describe a Japanese case of genetically-confirmed FMF, in which fever was lacking during attacks. An otherwise healthy 34-year-old man presented with frequent episodes of abdominal pain, which resolved spontaneously. During the attacks, the patient was afebrile, but the inflammatory marker levels in his blood were increased. Abdominal CT demonstrated enhancement of the jejunal membrane. After the initiation of colchicine therapy, the patient experienced no attacks for more than one year. The diagnosis of FMF was confirmed by a genetic analysis.

Key words: afebrile, colchicine, diagnosis, familial Mediterranean fever, mutation

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Introduction

Familial Mediterranean fever (FMF), an autosomal recessive hereditary disease, is characterized by a high prevalence of affected families around the Mediterranean basin and its clinical course of recurrent febrile episodes (1-3). We herein describe a Japanese case of genetically-confirmed FMF, in which fever was lacking during attacks.

Case Report

A 34-year-old man with frequent episodes of abdominal pain was referred to Matsushita Memorial Hospital for examination. Approximately 10 years prior to his presentation, the patient had lower abdominal pain and soft stool, which had lasted for a few days and spontaneously resolved without any treatment. Similar attacks developed at an interval of one to two months, but he had not sought medical care because the symptoms were tolerable and spontaneously resolved within a few days. Two years prior to his presentation, the patient presented to another clinic with a two-day history of lower abdominal pain. His C-reactive protein level was elevated to 19.22 mg/dL, while his white blood cell

count was 6,780/ μ L. Colonoscopy revealed no abnormalities, and his laboratory data soon normalized with conservative treatment, without antibiotics. Abdominal computed tomography (CT) performed at another hospital almost one year before presentation reportedly revealed no remarkable findings. His medical history was otherwise unremarkable. The patient was taking no medications at the time of his presentation. He drank beer (average, 500 mL/day), smoked (11.3 pack-years), and had no known allergies. His father had pharyngeal cancer.

On examination, he was asymptomatic and did not seem sick. He was 1.69 m in height and weighed 63.0 kg. He was afebrile (36.1°C) and the other vital signs were normal. There was no mass, rebound, or rigidity in the abdomen. All other examination findings were normal. His white cell count was 8,000/ μ L with 62.1% neutrophils. His hemoglobin level was 14.7 g/dL, and his platelet count was 258,000/ μ L. The patient's C-reactive protein level was 0.49 mg/dL, his erythrocyte sedimentation rate was 11 mm/h, and his uremic acid level was 8.9 mg/dL. The results of liver and renal function tests were normal, as were his blood glucose and electrolyte levels. Contrast-enhanced abdominal CT revealed normal findings with the exception of a thickened abdominal membrane and edematous jejunum (Figure A, B).

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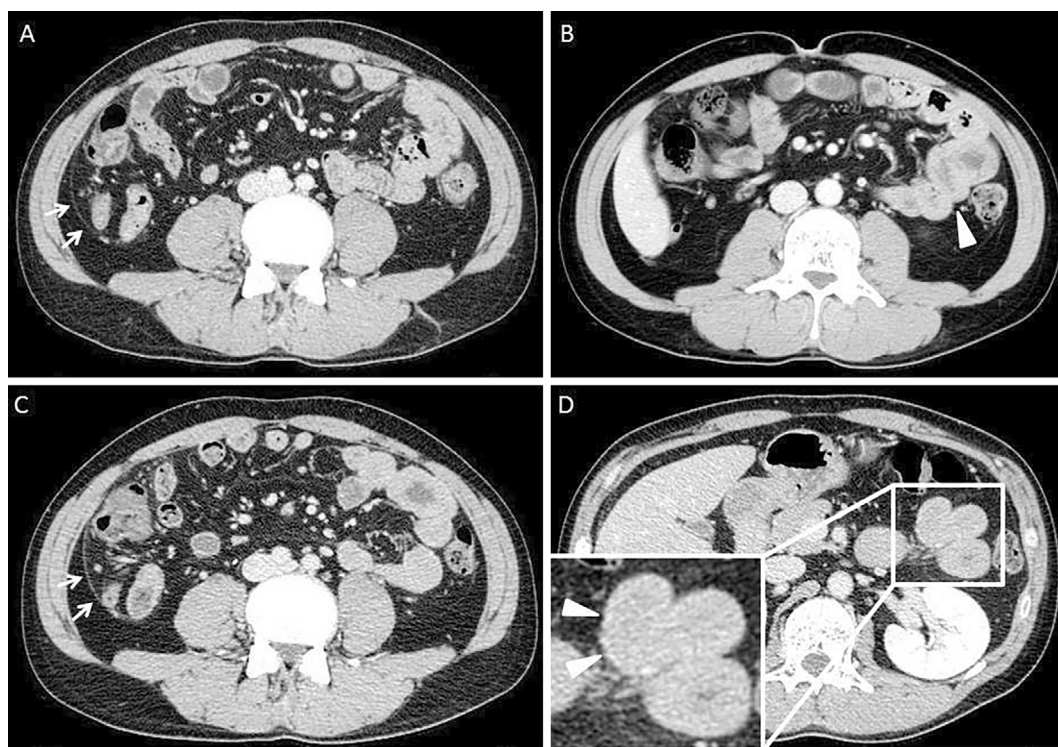


Figure. Contrast-enhanced abdominal CT images. An axial image of the abdomen on presentation, and during an attack showing a thickened abdominal membrane (A, arrows) and edema of the jejunum (B, arrowhead). The thickening was more prominent at one month after presentation and during an attack of lower abdominal pain (C, arrowheads), accompanied by enhancement of the serosa of the jejunum (D, arrowheads). The inset in D is an enlarged image of the area inside the white square.

Gastrointestinal fibroscopy and capsule endoscopy were performed, and revealed normal findings.

An attack of lower abdominal pain developed one month after the patient's presentation. A laboratory analysis at the time revealed the following: white blood cell count, 10,900/ μL (67.0% neutrophils); C-reactive protein, 12.37 mg/dL; and serum amyloid A protein, 1,090 $\mu\text{g/mL}$ (reference, ≤ 8), although he was afebrile (36.3°C), as noted during the previous attacks. Abdominal radiography revealed no abnormalities, and abdominal CT only showed a thickened abdominal membrane, which was more prominent than on previous imaging, as well as enhancement of the jejunal membrane (Figure C, D). The symptoms resolved spontaneously but recurred within two weeks. A preliminary diagnosis of FMF was made, and colchicine (2.0 mg, daily) was prescribed. After the initiation of colchicine therapy, the patient did not experience lower abdominal pain attacks for more than a year. The patient is currently doing well with colchicine (1.0 mg, daily). It was later confirmed by genetic analysis that the patient had exon 2 (E148Q) and exon 10 (M694I) abnormalities, which are diagnostic for FMF. His sister was found to have the same symptoms and is scheduled to receive colchicine. Neither the patient's sister nor his parents have undergone a genetic analysis.

Discussion

The current case presented typical symptoms suggestive of FMF, with the exception of fever. The symptoms disappeared after the administration of colchicine. The patient was finally diagnosed with FMF based on a genetic analysis.

FMF was first reported more than a century ago (4) and was described as a distinct entity in 1945 (5). FMF is commonly observed in areas surrounding the Mediterranean basin, such as Italy, Greece, Turkey, Armenia, and in Arabic communities, with a prevalence of 0.1% to 0.5% in these populations (1, 6). A nationwide multicenter study of 2,838 patients reported a mean age of 23.0 years (ranging 2 to 87), a slight male predominance (ratio: 1.2:1), and several symptoms, including fever and serositis (e.g., peritonitis, arthritis, pleuritis, myalgia, and erysipelas-like erythema) (7). The diagnosis is based on these clinical symptoms, and is also supported by the ethnic origin and family history of the patient because there is no specific test for FMF (8). Based on its name, it is intuitive that fever is one of the most important features of this condition. In analyses of 80 Japanese patients with FMF (9), high-grade fever was observed in 98.8% of patients.

The diagnosis of FMF in the current case was made based on the identification of genetic abnormalities, due to a

lack of fever, which is required for the diagnosis of FMF (9, 10). The Mediterranean fever (MEFV) gene, which consists of 10 exons in 16p13.3 and encodes a 781-amino acid pyrin/marenostrin protein is the main gene responsible for FMF called (11). In the current case, genetic abnormalities were found in exon 2 (E148Q) and exon 10 (M694I), both of which are in MEFV. Migita et al. (12) examined genotype-phenotype correlations in Japanese patients with FMF, and found that 43% of the patients were classified as having an atypical FMF phenotype, according to the Tel Hashomer criteria (13). In patients with atypical FMF, fever episodes are reported to be less frequently observed (12), although the current case was diagnosed as typical FMF according to the gene analysis (9, 10).

Our case carried M694I and E148Q mutations in the MEFV gene. In an analysis of five common MEFV gene mutations (E148Q, M680I, M694 V, M694I, and V726A) in 202 patients with FMF, the most frequent mutation was M694 V (heterozygous in 51% and homozygous in 22.2%), followed by E148Q, M680I, V726A, and M694I, according to the frequency (14). Another study consisting of 594 patients who were positive for MEFV gene mutations, reported that heterozygous, compound heterozygous, and homozygous mutations were observed in 61.11%, 29.46%, and 9.43% of patients, respectively (15). Given that the most commonly encountered gene mutations in the compound heterozygous group were E148Q+M694I (20.6%) (15), our patient was suggested have compound heterozygous E148Q and M694I mutations, but we cannot rule out other possibilities because no gene analysis was performed for his family members. In addition, attention should be paid because ethnic differences have been found in the allele frequency of the MEFV gene (2, 7, 14, 15).

It remains uncertain why our patient was afebrile during the FMF attacks. Mutations in the genes encoding pyrin are associated with the distinct interleukin-1 β (IL-1 β)-mediated autoinflammatory conditions of FMF (16). IL-1 β is likely to be the main cause of fever, but attention should be paid to coexisting conditions, such as microsomal prostaglandin E synthase-1 (17). It is reported that the febrile response to lipopolysaccharide-induced IL-1 β was lost in chimeric mice that only expressed the microsomal prostaglandin E synthase-1 in hematopoietic cells (18). These factors have not been assessed in the present case, and additional research is needed to examine the mechanism in afebrile patients with FMF.

The most prominent complication of FMF is amyloidosis, which may affect several organs (e.g., the kidneys, gastrointestinal tract, and heart) (3). This condition was reported to occur in approximately one-quarter of FMF patients and to cause death in more than half of FMF patients. Of note, 90% of patients died before 40 years of age (19). As medications are available to prevent or ameliorate amyloidosis in patients with FMF (20, 21), an early diagnosis is highly important, but is often not made. A mean period of 6.9 years from the disease onset to the diagnosis was reported for pa-

tients with FMF (7). In our case, the diagnosis was made almost 10 years after the first onset of symptoms, which may have been long enough for amyloidosis to develop. A histological examination was not performed, since the patient had no signs suggestive of amyloidosis. Further research is warranted to examine whether a histological analysis would be clinically effective for the early detection of amyloid deposition or for predicting the prognosis of patients with FMF.

The delayed diagnosis of FMF may be explained by several reasons. First, physicians outside endemic areas may be unfamiliar with this condition. However, this under-recognition is unacceptable because FMF is infrequent in other ethnic groups. In Japan, more than 300 patients with FMF have been reported (12). Second, the symptoms associated with FMF are non-specific and self-limiting (i.e., lasting from 1 to 3 days) (1, 3), similar to findings of viral infection. Third, the severity and frequency of symptoms usually decreases as the patient ages (3), although the recurrence interval varies from one week to several months or less (1, 3). Patients with FMF otherwise appear healthy. Finally, no diagnostic laboratory test has been established in clinical practice, and genetic analyses are only available in limited facilities. In the current case, the absence of fever during the attacks made the diagnosis more difficult.

In conclusion, the current case highlights the importance of the recognition of this rare condition, even outside the endemic areas of FMF. Further research is warranted to examine the clinical features in Japanese patients with FMF.

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

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