A Japanese Case of Familial Mediterranean Fever with Onset in the Fifties

Tateki Yamane¹, Kan Uchiyama¹, Daigo Hata¹, Makoto Nakamura¹, Takayuki Ishii², Shigeo Koido¹, Kiyotaka Fujise¹ and Hisao Tajiri¹

Abstract

The patient was a 63-year-old woman with attacks of fever and abdominal pain, starting from the age of 53 years and recurring every month. Despite various examinations at another hospital, the etiology remained unclear. She was under symptomatic treatment, and was referred to our department for further evaluation. Although she had onset in middle age, the clinical symptoms and examination findings suggested familial Mediterranean fever, and administration of colchicine inhibited the attacks completely. Therefore, the patient was diagnosed as having the disease. We were not able to analyze the entire MEFV gene, but detected only a heterozygous M694I mutation. Amyloidosis did not develop as a complication. The disease is rare in Japan, and its onset in the fifties is extremely rare in the world.

Key words: familial Mediterranean fever, attacks of fever and abdominal pain

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Introduction

Familial Mediterranean fever (FMF) is a genetic disease manifested by recurrent attacks of fever and pain such as abdominal pain, and very few cases have been reported in Japan (1-5). Most cases in the world occur at a young age. We report a patient whose age at onset was as old as 53 years.

Case Report

A 63-year-old woman visited our department because of attacks of fever and abdominal pain. Her past history was noncontributory. Her parents were deceased and non-consanguineous, and had reportedly had no similar symptoms. Her siblings and children were healthy. She was from Chiba Prefecture, and had had recurrent attacks of fevers between 38 and 40°C, followed by abdominal pain. The symptoms were paroxysmal, lasted for 2 to 3 days, then subsided, and she usually remained completely asymptomatic. She underwent various examinations at another hospital, but the etiology remained unclear. She was prescribed NSAIDs and antispasmodics for symptomatic treatment of attacks, and was referred to our department for further evaluation and treatment. Physical examination at the time of referral showed that she was moderately developed and well nourished, and had no anemia or jaundice. During attack-free periods, she had a normal temperature, and no abnormalities in the chest or abdomen, with normal neurological findings. Laboratory tests during the attack-free periods revealed no abnormal blood counts, biochemical abnormalities, or inflammatory reactions. Tumor marker levels were within normal limits. No immunological abnormalities were found. Urinalysis was normal. The fecal occult blood test was negative. Chest and abdominal X-rays and electrocardiograms showed no abnormalities. At the time of attacks, the abdominal pain was located mainly in the right flank and right hypochondrium, unaccompanied by muscular defense but accompanied by tenderness and sometimes by rebound tenderness. In addition, blood tests showed evidence of inflammatory reactions, such as an elevated CRP, leukocytosis with a left shift, and an increased erythrocyte sedimentation rate: 8.4-13.4 mg/dl, 9,800-12,900/μl, and 46-73 mm/hour.

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respectively (Table 1). These values during the attack-free periods were within normal limits respectively. Chest and abdominal X-rays at the time of attacks revealed no abnormalities. We suspected cholecystitis and right colonic diverticulitis, and performed abdominal ultrasound and CT, and upper and lower gastrointestinal endoscopy in the attack and attack-free periods, which showed no abnormalities. In addition, contrast imaging of the small intestine, magnetic resonance cholangiopancreatography, and whole-body gallium scintigraphy revealed no abnormalities. At the time of attacks, we also prescribed NSAIDs or antispasmodics; however, the antispasmodics were ineffective, and the NSAIDs reduced fever only transiently. We also suspected infection at the time of attacks, and administered antibiotics, which did not contribute to reducing attacks or their duration. No steroids were administered in our department or the previous hospital. We had difficulty in diagnosing the patient’s condition, and considered the possibility of periodic fever, particularly FMF, and performed genetic analysis after obtaining informed consent. Although we attempted to analyze exons 1 through 10 of the responsible gene MEFV for FMF, we could not analyze exon 2 because of the difficulty of designing primers. As a result, we were able to detect a heterozygous M694I mutation in exon 10. Since the patient’s family did not give consent, we could not analyze them genetically. FMF is sometimes complicated by AA-type amyloidosis, making the prognosis poor, with associated renal failure in many patients. The rate of complication varies with race, being high at 60% in Turks, low at 2% in Armenians, and apparently low in Japanese in that only 1 of 24 Japanese patients, including ours, was complicated by AA-type amyloidosis.

The Tel Hashomer Criteria (7) for the Diagnosis of FMF (Table 2), which take into consideration the characteristic clinical symptoms and the efficacy of colchicine, has been proposed. Since the present patient had recurrent attacks of fever accompanied by abdominal pain with occasional rebound tenderness suggestive of peritonitis, and achieved a complete response to colchicine, we made a diagnosis of FMF in light of the above criteria. Since the discovery of the MEFV gene responsible for FMF, multiple mutations in the gene have been reported, and genetic analysis is used as an adjunct diagnostic tool. The MEFV gene is located on the short arm of chromosome 16, and consists of 10 exons. To date, 29 mutations have been reported in exons 1, 2, 3, 5, 9, and 10, including 5 frequent mutations, E148Q, V726A, M694V, M694I, and M680I (6). However, since the direct analysis of DNA, instead of the entire length of the

**Table 1. Labolatory Findings during Fever Attack**

<table>
<thead>
<tr>
<th>[Peripheral Blood]</th>
<th>[Biochemistry]</th>
<th>[Serological test]</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 12500 / μL</td>
<td>T-Bil 0.6 mg/dL</td>
<td>CRP 13.4 mg/dL</td>
</tr>
<tr>
<td>Hgb 79.0%</td>
<td>AST 16 IU/L</td>
<td>ESR 67 mm/hr</td>
</tr>
<tr>
<td>Lym 17.6%</td>
<td>ALT 14 IU/L</td>
<td></td>
</tr>
<tr>
<td>Mos 3.8%</td>
<td>LDH 211 IU/L</td>
<td></td>
</tr>
<tr>
<td>RBC 4.15 x 10^12 / μL</td>
<td>ALP 243 IU/L</td>
<td></td>
</tr>
<tr>
<td>Hb 12.8 g/dL</td>
<td>γ-GTP 40 IU/L</td>
<td></td>
</tr>
<tr>
<td>Ht 39.8%</td>
<td>Amy 76 IU/L</td>
<td></td>
</tr>
<tr>
<td>Plt 18.9 x 10^12 / μL</td>
<td>CK 110 IU/L</td>
<td></td>
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</table>

**Table 2. Tel Hashomer Criteria for the Diagnosis of FMF**

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
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<tbody>
<tr>
<td>1. Recurrent febrile episodes accompanied by peritonitis, arthritis, or pleuritis.</td>
<td>1. Recurrent febrile episodes.</td>
</tr>
<tr>
<td>2. Amyloidosis of the AA-type without predisposing disease.</td>
<td>2. Erysipelas like erythema.</td>
</tr>
<tr>
<td>3. Favorable response to continuous colchicine treatment.</td>
<td>3. FMF in a first degree relative.</td>
</tr>
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</table>

Definitive diagnosis: 2 major or 1 major and 2 minor.
Probable diagnosis: 1 major and 1 minor.

**Discussion**

When pathological states presenting with attacks of fever and pain recurring at fixed intervals are encountered, periodic fevers should be differentiated. They are classified into FMF, hyper-IgD syndrome, and familial Hibernian fever (FHF). FMF is an autosomal-recessive disease characterized by attacks of fever, aseptic serositis, and synovitis. As few as 23 cases have been reported in Japan (1-5). Although the etiology has not been established, the inability of the MEFV-encoded protein pyrin to control inflammation-related substances due to mutations is considered to increase neutrophil activation and migration, mainly causing the disease (6). In many patients, colchicine with migration inhibitory activity is effective as a therapeutic agent.

FMF often has onset before the age of 20 years. The disease is manifested by paroxysmal fever, followed by symptoms such as abdominal pain, chest pain, joint pain, and skin eruptions. These symptoms last for 1-4 days, and then subside and disappear. Attacks occur at various intervals, and the symptoms always include fever, followed in frequency by abdominal pain. Laboratory findings are generally nonspecific, including only inflammatory reactions. FMF is sometimes complicated by AA-type amyloidosis, making the prognosis poor, with associated renal failure in many patients. The rate of complication varies with race, being high at 60% in Turks, low at 2% in Armenians, and apparently low in Japanese in that only 1 of 24 Japanese patients, including ours, was complicated by AA-type amyloidosis.

The Tel Hashomer Criteria (7) for the Diagnosis of FMF (Table 2), which take into consideration the characteristic clinical symptoms and the efficacy of colchicine, has been proposed. Since the present patient had recurrent attacks of fever accompanied by abdominal pain with occasional rebound tenderness suggestive of peritonitis, and achieved a complete response to colchicine, we made a diagnosis of FMF in light of the above criteria. Since the discovery of the MEFV gene responsible for FMF, multiple mutations in the gene have been reported, and genetic analysis is used as an adjunct diagnostic tool. The MEFV gene is located on the short arm of chromosome 16, and consists of 10 exons. To date, 29 mutations have been reported in exons 1, 2, 3, 5, 9, and 10, including 5 frequent mutations, E148Q, V726A, M694V, M694I, and M680I (6). However, since the direct analysis of DNA, instead of the entire length of the
mRNA, for FMF mutations is generally used, it is often difficult to evaluate the entire responsible gene. In this patient, we were able to detect only a heterozygous M694I mutation. Another mutation may be present in exon 2 that could not be analyzed, and the patient may have compound heterozygous mutations.

Careful history taking revealed that her age at onset of FMF was unusually late at 53 years. According to Sohar et al (8), the onset of FMF in 755 patients was 0-10 years in 65.5%, 11-20 years in 24%, 21-30 years in 8.2%, 31-40 years in 1.5%, 41-50 years in 0.3%, and unknown years of age in 36 patients; thus, FMF rarely has onset at a late age, and no cases of onset at ages over 50 have been documented. Similarly, in Japan, except in the present patient, it has been reported that the age at onset was 0-10 years in 8 patients, 11-20 years in 6 patients, 21-30 years in 6 patients, 31-40 years in 2 patients, 41-50 years in 1 patient, and over 50 years in no patients. Although the cause of the late onset of FMF is unclear, the present case suggests that patients in their fifties and sixties with a long history of characteristic clinical symptoms and findings should be examined for possible FMF.

References


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