Familial Mediterranean Fever with Onset at 66 Years of Age

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Abstract

The patient was a 68-year-old woman who had experienced recurrent febrile episodes since 66 years of age. Despite various examinations and treatments, the etiology remained unclear. Further examinations following another referral failed to uncover the cause. Therefore, despite her age, it was presumed that she had familial Mediterranean fever. An analysis of the familial Mediterranean fever (MEFV) gene detected heterozygous L110P, E148Q, and R202Q mutations. No further febrile episodes occurred after colchicine treatment was initiated. Familial Mediterranean fever presenting in patients in their sixties is extremely rare.

Key words: abdominal pain, familial Mediterranean fever, febrile episodes, MEFV gene

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Introduction

Familial Mediterranean fever (FMF) is the most common, genetic, autoinflammatory disease, with a predominantly autosomal recessive pattern of inheritance. It is characterized by periodic fever and symptoms of serositis, such as abdominal pain, chest pain, and joint pain, and occurs mostly at a young age. The case of a patient who presented with FMF for the first time at 66 years of age is herein reported. An investigation of the association between genetic mutations and the age of onset reported in the Japanese literature is also presented.

Case Report

A 68-year-old woman was referred to our department for further evaluation and treatment with a 2-year history of febrile episodes ranging from 37°C to 40°C, which lasted for a few days. The febrile episodes occurred with a cycle of between one and three months. Initially, the patient was treated with antibiotics at another hospital, although the etiology of the fever was unclear despite various examinations. She was subsequently treated with non-steroidal anti-inflammatory drugs (NSAIDs) alone after it was found that her fever subsided without antibiotic therapy. She was admitted to our department for further evaluation and treatment.

The physical examination on admission showed evidence of severe anemia in the palpebral conjunctiva, a mild systolic murmur on chest auscultation, and vague abdominal tenderness. She had no abnormal neurological findings. There were no signs of a skin eruption, swelling of the lymph nodes and tonsils, or swelling or deformity of the joints. She had no joint pain even during febrile attacks. There was no pain on percussion of the spine or costovertebral angles.

At that point, the differential diagnosis of her febrile attacks included infection, malignancy, collagen disease such as seronegative rheumatoid arthritis, seronegative spondyloarthropathy or vasculitis, and arthritis from gout or calcium pyrophosphate deposition (CPPD).

Laboratory tests during febrile episodes showed evidence of increased inflammation, such as an elevated level of C-

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Treatment with a glucocorticoid (prednisolone 40 mg) was initiated on the assumption that she had had some sort of collagen disease, such as seronegative rheumatoid arthritis, seronegative spondyloarthropathy, or adult Still’s disease, because the frequency of febrile episodes increased during hospitalization. However, this did not alleviate her fever, and treatment was stopped. At the same time, a sample specimen was obtained to analyze the familial Mediterranean fever (MEVF) gene to determine whether she had FMF. Exons 1, 2, 3, and 10 of the MEVF gene, where mutations of FMF are often confirmed, were analyzed, and heterozygous L110P, E148Q, and R202Q mutations were identified in exon 2 (Fig. 1). Since FMF is sometimes complicated by AA-type amyloidosis, endoscopic duodenal mucous membrane biopsies were performed, and the serum amyloid A protein (SAA) levels were measured. Amyloid was not detected in the biopsy specimens. The SAA protein level was increased during the febrile episodes, but it did not increase during the fever-free period (Fig. 2).

Colchicine at a dose of 0.5 mg once a day was started. This was insufficient to suppress the febrile episodes, so the dose of colchicine was increased to 1.5 mg three times a day. Therapy was discontinued several times because of abdominal pain, nausea, and diarrhea, which were probably side effects of colchicine or FMF peritonitis. Low-dose colchicine at 0.25 mg once a day was eventually used after one of these discontinuations, followed by an increase to 0.5 mg twice a day. The white blood cell (WBC), CRP, ESR, and SAA protein levels decreased to within the normal limits, and the patient had no further febrile episodes. As of this time, 6 months have passed since her last febrile episode. Her blood inflammatory markers still remain within the normal limits.

Retrospectively, her symptom of vague abdominal pain tended to be seen more frequently during febrile attacks than during the fever-free period. However, this would not be surprising since there are no apparent physical signs of peritonitis in the elderly. The amyloidosis, favorable response to colchicine treatment, and recurrent febrile episodes satisfied the Tel Hashomer criteria for the diagnosis of FMF, which take into account the clinical symptoms and the efficacy of colchicine (Table 2). Therefore, the MEVF gene mutation, the patient’s clinical symptoms, and the favorable response to colchicine treatment led to a diagnosis of FMF, though the age at onset of 66 years was very unusual.

**Discussion**

A case of FMF with an age at onset of 66 years is herein described. FMF is the most common, inherited, autoimmune disease. It is inherited in an autosomal recessive pattern, and it is characterized by periodic attacks of fever, aseptic serositis, and synovitis. The Tel Hashomer criteria for FMF have previously relied on clinical signs alone, so it

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**Table 1.** Laboratory Findings during a Febrile Episode

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Biochemistry</th>
<th>Serological tests</th>
<th>Tumor markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 10200 /µL</td>
<td>T-Bil 0.3 mg/dL</td>
<td>CRP 12.6 mg/dL</td>
<td>CEA 1.1 mg/mL</td>
</tr>
<tr>
<td>seg 83 %</td>
<td>AST 14 IU/L</td>
<td>ESR 169 mm/hr</td>
<td>SCC antigen 0.9 mg/mL</td>
</tr>
<tr>
<td>lym 12 %</td>
<td>ALT 15 IU/L</td>
<td>SL-2R 761 U/mL</td>
<td></td>
</tr>
<tr>
<td>mono 4 %</td>
<td>LDH 103 IU/L</td>
<td>RF 9.8 IU/mL</td>
<td></td>
</tr>
<tr>
<td>RBC 229±10^6 /µL</td>
<td>ALP 314 IU/L</td>
<td>ANA &lt;20</td>
<td></td>
</tr>
<tr>
<td>Hb 6.1±0.04 g/dL</td>
<td>vGTP 87 IU/L</td>
<td>C3 132 mg/dL</td>
<td>[Urinalysis]</td>
</tr>
<tr>
<td>Hct 20.3 %</td>
<td>Amy 63 IU/L</td>
<td>C4 27.5 mg/dL</td>
<td>occult blood</td>
</tr>
<tr>
<td>PR 58.8±10^4 /µL</td>
<td>CK 19 IU/L</td>
<td>CH50 73.4 U/mL</td>
<td>protein</td>
</tr>
<tr>
<td>UA 4.9 mg/dL</td>
<td>IgG 140 mg/dL</td>
<td></td>
<td>glucose</td>
</tr>
<tr>
<td>TP 7.2 g/dL</td>
<td>IgM 126 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alb 2.9 g/dL</td>
<td>IgA 278 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN 20 mg/dL</td>
<td>ferritin 462 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr 1.17 mg/dL</td>
<td>FT3 1.66 pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4 1.14 ng/mL</td>
<td>TSH 1.31 IU/mL</td>
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</tr>
</tbody>
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Figure 1. DNA sequencing demonstrating the L110P, E148Q, and R202Q mutations in the patient and a healthy control.

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Reactive protein (C-reactive protein (CRP); 6.94-28.11 mg/dL), leukocytosis (9,300-31,600/µL), segmented neutrophils 73-95%, and an increased erythrocyte sedimentation rate (ESR; 160 mm/hr). In contrast, during the fever-free period, her inflammatory markers were normal or slightly increased: CRP 0.09-9.47 mg/dL; leukocyte count 3,600-16,000/µL, segmented neutrophils 39-82%; and ESR 66-159 mm/hr (Table 1). The tumor marker levels were within the normal limits, except for the fact that the ferritin level and soluble interleukin 2 receptor level were slightly increased. The plasma uric acid level was not increased. No immunological abnormalities were found. The urinalysis was normal and the fecal occult blood test was negative. X-ray examinations of the chest and abdomen, a computed tomography (CT) scan from the head to the pelvis, ultrasound examinations of the heart and abdomen, upper and lower gastrointestinal endoscopy, and laryngoscopy were all negative. In addition, positron emission tomography/computed tomography (PET/CT) and bone-marrow aspiration were performed, but they revealed no abnormalities. Repeated blood, urine, and fecal cultures were all negative. Considering the findings of the physical examination, laboratory tests, and imaging, she did not appear to have any infection, malignancy, or arthritis from gout or CPPD.
was difficult to make a correct diagnosis in patients with mild or atypical symptoms. In 1997, the MEFV gene, which is responsible for the development of FMF, was cloned. It is located on the short arm of chromosome 16 (1). The detection rate of MEFV gene mutations in FMF patients remains low, at only approximately 60% (2). Nevertheless, analyzing the MEFV gene is used as an adjunct diagnostic examination, especially when the clinical features are not distinctive, or when there is no family history of FMF.

The MEFV gene encodes a protein called pyrin, which suppresses cryopyrin, which is involved in the induction of an inflammatory reaction. MEFV gene mutations depress pyrin function, which increases the inflammatory reaction. MEFV mutations are found mostly on exons 2 and 10. L110P and E148Q on exon 2 and M680I, M694I, M694V, and V726A on exon 10 are the most common mutations. In the present patient, there was no evidence of a mutation on exon 10, such as M694I, which is the most common mutation related to MEFV in Japan. However, there were heterozygous L110P, E148Q, and R202Q mutations on exon 2. In addition to the MEFV gene mutations, the characteristic clinical symptoms and the efficacy of colchicine, which met the Tel-Hashomer criteria, led to the diagnosis of FMF.

It is well known that FMF usually occurs at a young age. The majority of patients develop FMF before 20 years of age (3). According to Sohar et al. (4), the age at 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 in 36 patients. As of October 2010, only 53 cases of FMF have been reported in Japan, including the present case (5-18). Of these, the age at onset was 0-10 years in 9 patients (16%), 11-20 years in 29 patients (56%), 21-30 years in 7 patients (13%), 31-40 years in 4 patients (8%), 41-50 years in 2 patients (3%), 51-60 years in 1 patient (2%), and 61 years (2%) in 1 patient (Table 3). The present case had the latest age at onset of FMF in Japan.

The reason why FMF develops in the elderly needs to be considered. The E148Q mutation is considered to be the mildest mutation and to result in a milder form of
FMF (19). It has also been reported that patients with homozygosity for the pyrin variant E148Q mutation have less severe symptoms and fewer attacks than those with heterozygosity for the pyrin variant E148Q/M694I mutation (15, 16). The patient in the present case was found to have a heterozygous E148Q mutation. According to our analysis of all cases reported in the Japanese literature (n=53), the age at onset of FMF with the E148Q mutation was 21.3±12.11 years (n=35), while that without the E148Q mutation was 22.2±24.28 years (n=18). There is apparently no significant difference in the age at onset of FMF based on the E148Q mutation (Student’s t-test, p=0.86) (Fig. 3).

With respect to the R202Q mutation, Giaglis et al. (20) reported that, in 152 Greek FMF patients and 140 Greek healthy controls, homozygosity for the R202Q mutation was detected in 14/152 (9.2%) FMF patients and in 1/140 (0.7%) healthy controls (p=0.001, diagnostic odds ratio = 14.1, 95% CI 2.33-84.72). Heterozygosity of the R202Q mutation was detected in 48/152 (31.6%) FMF patients and in 47/140 (33.6%) healthy controls (p=0.717, diagnostic odds ratio =0.913, 95% CI 0.560-1.49). Yamaguchi et al. (21) reported that R202Q heterozygotes were observed in 7/170 (4.1%) of randomly selected healthy Japanese subjects. They and their families had no episodes of periodic fever similar to FMF. R202Q homozygotes were not observed. In our analysis of all cases of FMF reported in the Japanese literature (n=53), R202Q heterozygotes were observed in 2/53 (3.8%) FMF patients. The rates of R202Q mutation differ between Greek and Japanese, but there is little difference between FMF patients and healthy controls in the rate of heterozygosity of R202Q. It is thus, thought that the heterozygosity of the R202Q mutation does not play a significant role in FMF. On the other hand, homozygosity of the R202Q mutation is strongly associated with FMF. However, few reports have so far analyzed the impact of the L110P mutation.

Therefore, the reasons why FMF develops in the elderly remain unclear. More analysis of the association between the mutations of MEFV, the onset of FMF, and the frequency of febrile episodes is needed. However, the present case suggests that FMF should be considered in cases of unknown fever regardless of the patient’s age.

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

References


