Two Cases of Familial Mediterranean Fever Involving MEFV Variants: The Importance of Differentiating the Diagnosis from COVID-19

Tomohiro Nakayama¹,² and Yutaka Kozu³

Abstract:
Familial Mediterranean fever (FMF) is an inherited autoinflammatory disease associated with the MEFV gene. FMF is common in Mediterranean peoples but not highly recognized in Japan. We herein report two cases of Japanese FMF patients who were diagnosed by genetic testing for the MEFV gene during the Coronavirus disease 2019 (COVID-19) pandemic. Both patients presented with symptoms similar to COVID-19, which delayed the definitive diagnosis. Patients with a confirmed diagnosis of FMF may be eligible for physical, emotional, and financial benefits. Therefore, the COVID-19 pandemic highlights the importance of differentiating the diagnosis by genetic testing.

Key words: COVID-19, familial Mediterranean fever, MEFV gene, SARS-CoV-2

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.0414-22)

Introduction
Familial Mediterranean fever (FMF) (OMIM #249100) is an inherited autoinflammatory disease characterized by periodic fevers, peritonitis, pleurisy, and arthritis. It is common in Mediterranean peoples and inherited in an autosomal recessive manner. The gene responsible for FMF, MEFV (OMIM *608107), was identified in 1997 (1, 2). In 2002, the first case of FMF with a pathological variant of the MEFV gene was reported in Japan (3). Although FMF is considered rare in Japan, more than 300 cases have been reported to date (4), and a 2009 survey conducted by a research group commissioned by the Ministry of Health, Labour and Welfare of Japan estimated that there were approximately 500 FMF patients nationwide.

The diagnosis of FMF is generally based on a combination of clinical symptoms, such as a periodic fever, and genetic testing for the MEFV gene. One diagnostic approach is for the patient to take colchicine, which is used as a therapeutic agent for FMF, and monitor the results. Factors that trigger febrile attacks associated with FMF include infection, trauma, stress, and (in women) menstruation (5). Colchicine may also be effective in preventing the development of amyloidosis (6), the most serious complication of FMF.

MEFV is currently the only gene known to be associated with the development of FMF. However, cases of patients clinically diagnosed with FMF but harboring only one typical pathological variant of the MEFV gene have been reported, as have cases in which no variant was identified (7). Cases involving patients presenting with a variety of symptoms, including those without a fever (8) but with headache (9) and meningitis (10), have been reported in Japan.

The Coronavirus disease 2019 (COVID-19) pandemic that first emerged in China in December 2019 has had a significant impact worldwide (11). The causative virus is severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), which is diagnosed by polymerase chain reaction (PCR) and antigen testing of nasopharyngeal swabs and saliva (12). The primary symptoms of COVID-19 include respiratory symptoms, such as a fever, nasal discharge, and cough, and some
patients complain of abnormalities in taste and smell (13). It is also not uncommon to experience symptoms such as headaches, thrombosis, and diarrhea. Most COVID-19 patients have only a minor illness, but some may progress to serious conditions that include respiratory failure, heart failure, sepsis, and septic shock. Antiviral and anti-inflammatory drugs are used to treat COVID-19, and vaccination is now available in many countries.

A fever is a major symptom for the differentiation of COVID-19. Therefore, in cases of febrile illnesses, such as FMF, differentiating the diagnosis is a critical task for physicians. The differential diagnosis enables the elimination of unnecessary viral nucleic acid testing and reduces the physical and economic burden on patients with febrile illnesses, such as FMF.

We herein report two cases of FMF diagnosed by an MEFV gene analysis during the COVID-19 pandemic.

Case Report

Case 1

In March 2020, a man in his 40s presented with a fever of 38.0 °C. Subsequently, he continued to have a fever in the 37-°C range, so he visited the Department of Respiratory Medicine at our hospital in April 2020. His body temperature was 37.8 °C when he presented at the hospital, and he was referred to the outpatient clinic for a fever. In the COVID-19-related questionnaire, he reported no history of international travel, no history of close contact or cohabitation with a person infected with SARS-CoV-2, no diarrhea, no malaise, no abnormal sense of taste or smell, mild respiratory distress, and mild headache. Therefore, PCR testing for SARS-CoV-2 was conducted, and the results were negative.

One year later, the patient visited a hospital near our facility with a chief complaint of a fever. However, he had no symptoms, such as a cough, phlegm, pharyngeal discomfort, or taste/smell disorder, and there was no history of overseas travel or close contact with overseas travelers. Therefore, in March 2021, the attending physician at a hospital near our facility suspected FMF and requested genetic testing. Genetic testing for the MEFV gene was performed in our hospital with the consent of the patient for the diagnosis of FMF.

Blood samples were collected at our hospital and sent to Kazusa DNA Research Institute (Chiba, Japan). SARS-CoV-2 PCR testing was also performed, and the result was negative. Since the date of genetic testing, the patient has been taking 0.5-mg colchicine tablets. However, he continues to develop a fever approximately once every 3 months. The pattern of the fever varies, with low-grade fevers that last for 2 weeks and high-grade fevers in the 38-°C range that resolve in a day.

- Personal history: tonsillitis (5 years old), ventricular tachycardia (35 years old), inflammation of the lacrimal sac (43 years old), right hemopneumothorax (44 years old)
- Physical examination findings at the first visit: height, 170 cm; body weight, 70 kg; serum C-reactive protein (CRP) level, 10.55 mg/dL
- Family history: No family history of patients suspected of having FMF other than proband. (Figure)
- MEFV gene analysis results: c.250G>A (p.Glu84Lys, rs150819742), c.1105C>T (p.Pro369Ser, rs11466023)

Case 2

A woman in her 40s presented with a high fever of 38-39 °C, and her temperature fluctuated for approximately 1.5 months in 2012. Because of suspicion of malignant lymphoma by a physician at a nearby hospital, the patient was referred to the hematology department of our hospital and admitted for a detailed examination. Kikuchi disease (neocrotizing histiocytic lymphadenitis) and FMF were suggested as possible differential diagnoses; however, no defini-
tive diagnosis was made.

Subsequently, the patient started to develop a fever approximately once a month. The fever was characterized by a duration of one day and relief the next day. In 2016, she developed pneumonia triggered by cold symptoms and visited the Department of Respiratory Medicine at our hospital; after that visit, she started visiting the outpatient clinic regularly.

In May 2020, oral administration of 0.5-mg colchicine tablets was started because FMF was suspected. The patient’s fever, abdominal pain, and chest pain improved with colchicine. After temporarily stopping colchicine, she began to experience back, abdominal, and chest pain in the spring of 2021. In June 2021, genetic testing for the MEFV gene was performed with the consent of the patient for the diagnosis of FMF.

Blood samples were collected at our hospital and sent to Kazusa DNA Research Institute (Chiba, Japan). SARS-CoV-2 PCR testing performed in our hospital was negative.

- Personal history: appendicitis (10 years old), asthma (35 years old)
- Physical examination findings at the first visit: height, 161 cm; body weight, 50 kg; serum CRP level, 28.54 mg/dL
- Family history: No family history of patients suspected of having FMF other than proband (Figure)
- MEFV gene analysis results: c.1105C>T (p.Pro369Ser, rs11466023), c.1223G>A (p.Arg408Gln, rs11466024)

### Discussion

In our experience, the onset of the fever in case 1 coincided with the onset of the second COVID-19 wave in Japan (July to August 2020), and approximately one year elapsed between the patient’s first visit to the physician and the diagnosis of FMF. In order to prevent the spread of COVID-19 during this period, it was important to discriminate the fevers induced by SARS-CoV-2 infection from fevers associated with other diseases. During this period, many medical institutions in Japan were busy treating COVID-19 patients, and a so-called “medical collapse” appeared imminent. As the patient in case 1 tested negative for COVID-19 by PCR and did not present with life-threatening symptoms, suspicion of FMF would have been unlikely given the circumstances facing the medical system at that time.

Previous reports have shown that COVID-19 and FMF are similar in terms of clinical symptoms and laboratory findings (14), and both diseases are characterized by a fever, abdominal pain, chest pain, elevated CRP levels, and leukocytosis (15). Among these potential symptoms, a fever and elevated CRP level appeared in case 1, whereas a fever, abdominal pain, and chest pain appeared in case 2.

The diagnosis of FMF is based on Livneh’s Tel-Hashomer diagnostic criteria (16), the new Eurofever/PRINTO classification criteria (17), and the diagnostic criteria specified in Japan’s own guidelines for the treatment of autoinflammatory diseases (18). The Tel-Hashomer diagnostic criteria focus on clinical symptoms, whereas the Eurofever/PRINTO and Japanese criteria combine clinical symptoms with the results of MEFV genetic testing. The diagnosis of FMF is often made based on clinical findings, and the fact that our two cases had symptoms common with COVID-19 highlights the difficulty of making a differential diagnosis. As COVID-19 is an important infectious disease, the differential diagnosis of FMF with a fever is important in order to eliminate unnecessary tests, not only for patients but also medical staff.

According to Migita et al. (19), the average time between the FMF onset and its diagnosis in Japanese patients is nine years, which places patients at risk of developing amyloidosis. In case 2, approximately eight years had elapsed from the time the patient first became aware of the symptoms of FMF in 2013 to the time of the definitive diagnosis. Fortunately, this patient did not develop amyloidosis during this time, but we will need to continue closely monitoring her progress. The rarity of FMF in Japan may be one reason for the delay between the onset and diagnosis, and FMF may also be diagnosed as another disease with similar symptoms, such as COVID-19. A survey of Japanese patients with a fever of unknown origin found that approximately 30% were diagnosed with FMF by an MEFV gene analysis (20), clearly demonstrating that an MEFV gene analysis can aid in the diagnosis of FMF. However, it is suspected that there are many patients affected by FMF who remain undiagnosed because they have not undergone genetic testing. This disease needs to be diagnosed as early as possible, as continuous colchicine treatment can both alleviate symptoms and prevent the development of amyloidosis.

Since the emergence and spread of COVID-19 in Japan, discrimination and prejudice against those infected with or suspected of being infected with SARS-CoV-2 and their families has become a social problem in Japan. In February 2021, the “Act on Partial Revision of the Act on Special Measures against Pandemic Influenza, etc.” was enacted, and provisions were made to prevent prejudice and discrimination against persons affected by COVID-19 and their families. Some patients who had not been properly diagnosed with FMF may have experienced overreaction from others in their community due to the similarity of their symptoms to those of COVID-19. Although ideally there should be no discrimination or prejudice against anyone with a particular disease, from the perspective of the COVID-19 pandemic, patients may be able to avoid such mistreatment if FMF is properly diagnosed.

The results of the MEFV gene analysis in the two present cases did not involve the exon 10 variant, which is common in FMF patients in the Mediterranean region, but instead involved the exon 1 (p.Glu84Lys) and exon 3 (p.Arg369Ser, p.Arg408Gln) variants. The features of clinical symptoms and MEFV genotypes reportedly vary between FMF patients from the Mediterranean region and Japanese FMF patients (21). It has also been reported that patients compound
### Table. Differences between Familial Mediterranean Fever (FMF) and Coronavirus Disease 2019 (COVID-19).

<table>
<thead>
<tr>
<th></th>
<th>Familial Mediterranean fever</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Symptom</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Duration</td>
<td>High fever 38.0°C or higher</td>
<td>Fever, 37.5°C or higher</td>
</tr>
<tr>
<td>b) Interval</td>
<td>Lasts from half a day to three days.</td>
<td>Lasts from two day or more. Generally no interval. There are large individual differences.</td>
</tr>
<tr>
<td>2. Accompanying symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe abdominal pain and chest and back pain due to serositis. The inflammatory attacks such as fever, peritonitis, pleurisy, and arthritis are observed. Chest pain causes shallow breathing. Arthritis and erysipelas-like eruptions.</td>
<td>Cough, fatigue, loss of taste or smell, sore throat. Basic diseases are listed as a risk factor.</td>
<td></td>
</tr>
<tr>
<td><strong>II. Laboratory data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (CRP) and serum amyloid A (SAA) levels are markedly elevated during fever. They disappear during the interictal period.</td>
<td>CRP and ferritin levels are elevated. Lymph cell counts are decreased.</td>
<td></td>
</tr>
<tr>
<td><strong>III. Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A fever of 38°C or higher that lasts 12 to 72 hours and recurs 3 or more times.</td>
<td>Requirements for suspected patients as follows.</td>
<td></td>
</tr>
<tr>
<td>1. Any of the following symptoms are recognized as concomitant symptoms of fever. a) Abdominal pain due to non-localized peritonitis. b) Chest and back pain due to pleurisy. c) Arthritis. d) Pernicarditis. e) Testicular serositis. f) Headache attributed to meningitis.</td>
<td>1. Persons who have fever or respiratory symptoms (including mild cases) and who are infected with COVID-19. Persons who have a history of close contact with a person who has been confirmed to have COVID-19.</td>
<td></td>
</tr>
<tr>
<td>2. Seizures disappear or are alleviated by oral prophylaxis with colchicine.</td>
<td>2. Patients who have traveled to or lived in an area with COVID-19 outbreak within 14 days before the onset of symptoms.</td>
<td></td>
</tr>
<tr>
<td>Genetic testing is indicated for definitive diagnosis. Typical FMF showed the exon 10 mutations (Met694Ile, Met680Ile, Met694Val, Val726Ala) in MEFV gene. On the other hand, atypical FMF showed the other than Exon 10 (Glu54Lys, Glu148Gln, Leu110Pro-Glu148Gln, Pro369Ser-Arg408Gln, Arg202Gln, Gly304Arg, Ser503Cys) in MEFV gene.</td>
<td>Antigen test, nucleic acid testing (polymerase chain reaction [PCR], loop-mediated isothermal amplification [LAMP], Transcription Mediated Amplification [TMA] etc.) are required for a diagnosis. Nucleic acid testing, especially PCR for SARS coronavirus Tor2 is indicated for definitive diagnosis.</td>
<td></td>
</tr>
<tr>
<td><strong>V. Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Colchicine is effective for the inflammatory attacks in 90% of cases.</td>
<td>1. Antiviral drugs Remdesivir (RNA synthetase inhibitor), Molnupiravir (RNA synthetase inhibitor) and Nirmatrelvir/ritonavir (protease inhibitors).</td>
<td></td>
</tr>
<tr>
<td>2. Interleukin (IL)-1 therapy (canakinumab), tumor necrosis factor (TNF) α inhibitors (infliximab, etanercept), thalidomide, etc. are effective in patients who do not respond to colchicine.</td>
<td>2. Neutralizing antibody drug Sotrovimab, Casirivimab/ imdevimab</td>
<td></td>
</tr>
<tr>
<td>There is no definitive treatment; corticosteroids are ineffective.</td>
<td>3. Immunosuppressants and immune modulators Tocilizumab (anti-IL-6 receptor antibody) Dexamethasone (steroid drug), Baricitinib (Janus kinase inhibitor), Tocilizumab (anti-IL-6 receptor antibody)</td>
<td></td>
</tr>
</tbody>
</table>

heterozygous for p.Pro369Ser and p.Arg408Gln present with varied clinical symptoms and responded poorly to oral colchicine (22). The patient in case 2 harbored this variant and experienced more-pronounced side effects than the patient in case 1, although the fever, abdominal pain, and chest pain improved with colchicine treatment. Patients who are compound heterozygous for this variant may need to be followed more carefully than others in order to monitor them for side effects as well as for the efficacy of colchicine.

**Conclusion**

We reported two cases of FMF involving MEFV variants. For these patients, it was important to discriminate FMF from COVID-19. Patients with a confirmed diagnosis of FMF benefit not only from reducing their risk of developing amyloidosis through colchicine treatment but also from medical subsidies. For patients with a fever in whom SARS-CoV-2 infection has been ruled out, FMF should be considered as a differential diagnosis, and MEFV genetic testing should be conducted (Table).

**Author’s disclosure of potential Conflicts of Interest (COI).**
Tomohiro Nakayama: Advisory role, Health Sciences Research Institute, Inc.
Acknowledgement

The authors would like to thank all the medical staff involved in the care of these patients.

The patients provided their informed consent for publication.

References


The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/ by-nc-nd/4.0/).