

## Case Report

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# A case of familial mediterranean fever in an elderly patient experiencing recurrent fever and weigh loss

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### Abstract

Familial Mediterranean Fever (FMF) is a rare hereditary autoinflammatory disease. In particular, the onset is rare in the elderly, and the symptoms are atypical, making diagnosis difficult. A 61-year-old man was referred to our hospital due to recurrent fever and weight loss 3 months ago. Prior to his visit, he had a temporomandibular disorder and right hip arthritis, in addition to a fever, and had visited several medical departments. Infection- and rheumatism-related examinations were performed for fever and systemic malignant diseases were examined for weight loss; however, the causes were unknown. FMF was suspected based on a 3-month fever pattern chart at the time of consultation. It is important to suspect FMF in patient with fever of unknown cause, even in atypical cases of elderly -onset (over 60 years of age).

**Keywords:** Familiar Mediterranean fever; Elderly patients; Atypical symptoms; Important of suspicion.

**Abbreviations:** CT: Computed tomography; FEMV gene: Familiar Mediterranean fever gene; FMF: Familiar Mediterranean fever.

### Introduction

Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disease characterized by periodic fever and aseptic arthritis. Its incidence is high in the Mediterranean region and its surrounding areas. Although it is a rare disease in Japan, the number of reports has increased in recent years owing to the sharing of disease information and advances in genetic testing. FMF has a juvenile onset, with approximately 90% of patients diagnosed before the age of 20. In 10% of adult-onset cases, atypical presentations are common, and diagnosis is often delayed, especially in older patients [1].

We report the case of a 61-year-old male patient with FMF who was referred for recurrent fever and weight loss. We inves-

tigated the reasons for this delay in diagnosis in elderly patients and reported on them.

### Case presentation

A 61-year-old Japanese man was referred to our department from a nearby general hospital with recurrent fever, hip arthritis, and weight loss. Approximately 3 months prior, he visited the internal medicine department at a nearby general hospital with a fever of unknown cause. Two and a half months ago, he visited the internal medicine department again because of a fever, and was unable to make a diagnosis based on whole-body computed tomography (CT), a negative anti-nuclear antibody, and two sets of blood cultures. Two months ago, he visited another hospital with right hip pain and was diagnosed with

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hip bursitis based on CT findings, CRP of 7 mg/dL, and WBC of 12,000/ $\mu$ L. At this time, he was suspected of having rheumatoid arthritis and visited the orthopedics department and the department of collagen disease at a nearby general hospital. At the time of presentation, his joint symptoms had disappeared and his inflammatory reaction was negative. He searched for malignancies during a weight-loss workup. Gastroscopy revealed esophageal *Candida*, a hiatal hernia, and fundic gland polyps. A colonoscopy revealed colonic polyps, and endoscopic mucosal resection was performed. Ga scintigraphy revealed uptake in the right hip joint but no abnormal uptake at other sites.

Since the cause of the recurrent fever and weight loss was unknown, he was referred to our department for examination 3 months after symptom onset. His weight loss was 9 kg over 3 months (range, 60–51 kg).

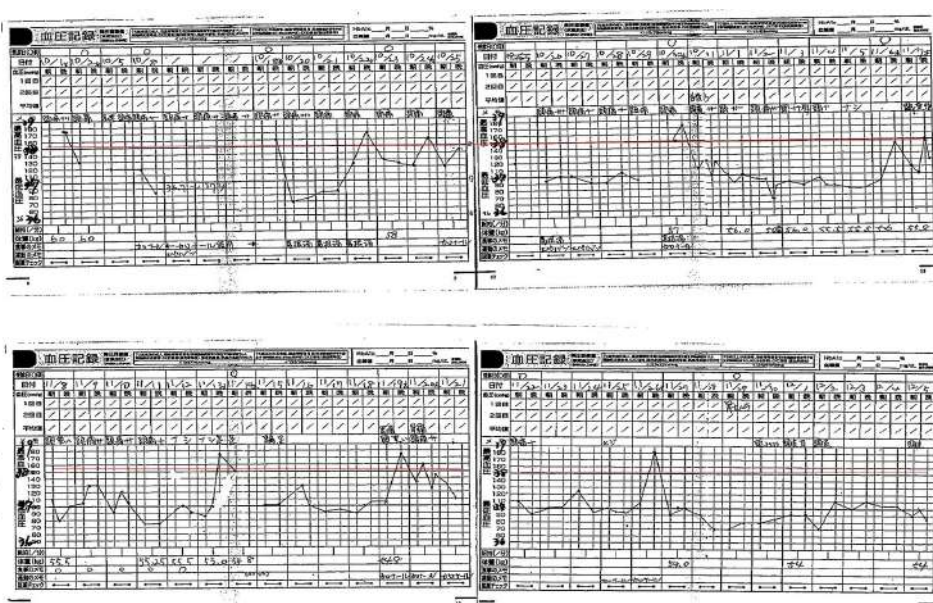
On the first day of the consultation, the patient had no fever or joint pain. The patient presented with a 3-month fever (Figures 1a, b). A fever of 38°C or higher lasted for 1-2 days, with an intermittent period of 6-7 days. He lost his appetite when he developed a fever, and he continued to feel malaise for 2-3 days after the fever subsided. Past medical history included appendicitis surgery at the age of 22 and no family history.

**Vital signs:** Blood pressure; 119/79 mmHg, pulse, 109 beats per minute; body temperature, 37.4°C; height, 165 cm; and weight, 51.7 kg. His chest, abdomen, and neurological findings were unremarkable. Blood tests showed no particular abnormality except for CRP at 0.25 mg/dL. Thyroid function was normal. Chest radiography showed no cardiomegaly, and electrocardiography showed sinus tachycardia (HR 101/min). Whole-body positron emission tomography/CT revealed no abnormalities. No malignancies that led to weight loss were observed.

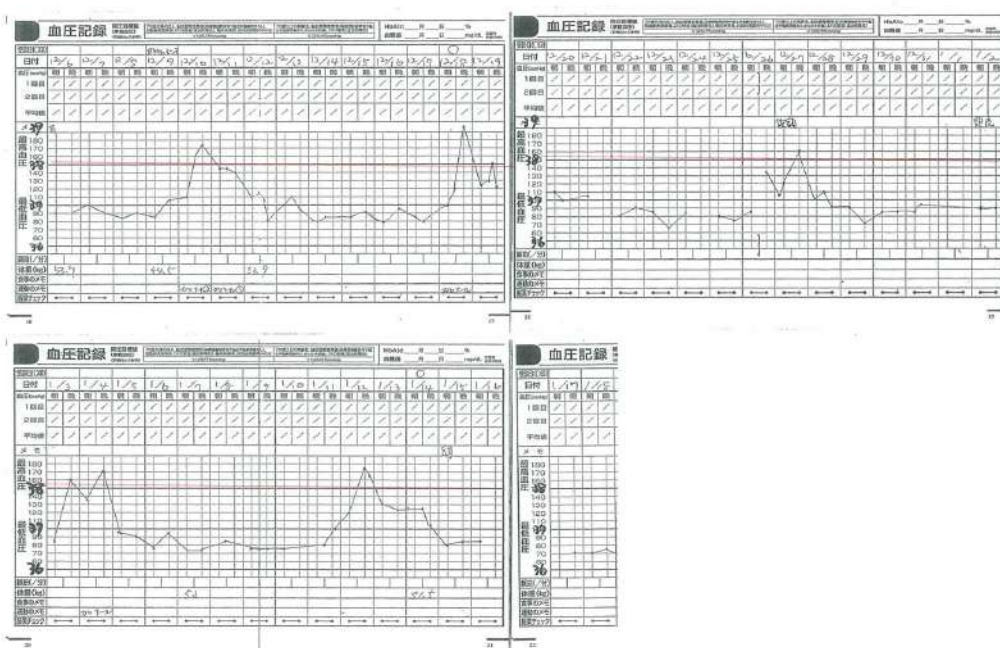
The FMF was suspected based on a history of recurrent fevers, arthritis (temporomandibular disorder and right hip arthritis), and regular periodic fever patterns. However, since we had never encountered a case of FMF, we decided to make the diagnosis based on an article by Kishida et al. [2]. There were two major criteria in the Livneh diagnostic criteria, and FMF was strongly suspected; therefore, we decided to observe the patient's response to colchicine. For genetic testing, we consulted a doctor in the Department of Clinical Genetics and obtained patient consent for Mediterranean fever (MEFV) gene testing. Treatment with colchicine (1 mg/day) was initiated. As for the response to colchicine, the frequency of a fever of 38°C or higher was once every 2 weeks, the duration was one day, and the general condition improved, showing a favorable response. Approximately 2 months later, MEFV genetic testing revealed a heterozygous Ser503Cys (TCC→TGC) mutation in exon 5 (Figure 2). FMF was confirmed based on patient history, colchicine response, and MEFV gene mutation. Subsequently, colchicine was increased to 1.5 mg/day. The frequency of fever decreased to once per month, and 8 months later, fever above 38°C was not observed. One year later, a fever of 37°C or higher disappeared.

### Discussion

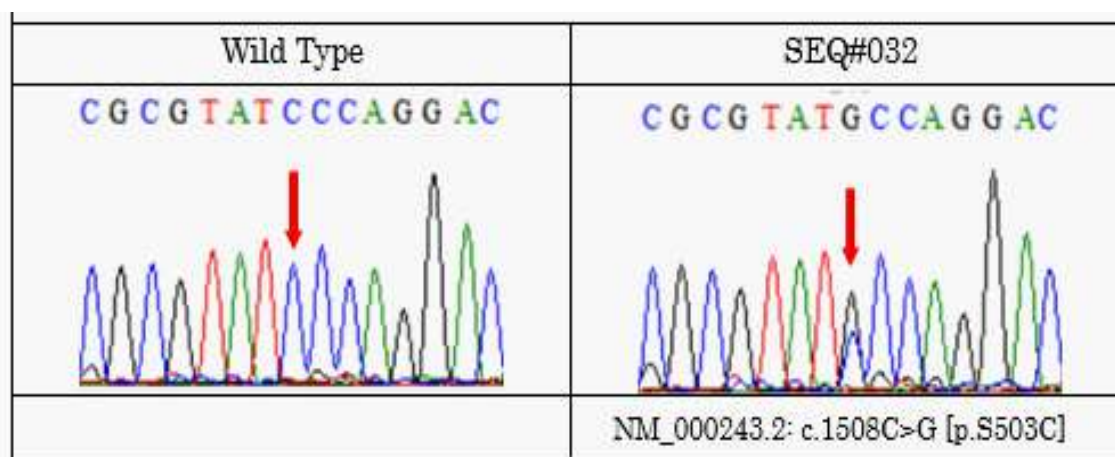
FMF is a rare hereditary autoinflammatory disease that causes recurrent fever, peritonitis, synovitis, and pleurisy and responds well to colchicine. Overall, 90% of patients have an onset before the age of 20 years and 65% before the age of 10 years [1]. Adult-onset is in 10% of patients, and elderly-onset (over 60 years of age) is extremely rare. Elderly patients present with atypical presentations, mild fevers, and coexisting illnesses that delay diagnosis [3,4]. Tanosaki et al. reported a case in which diagnosis took more than 30 years due to patients with psychiatric disorders and physicians' lack of knowledge of FMF, and other studies reported a delay from onset to diagnosis of



**Figure 1a:** Fever pattern sheet from Nov. 1 to Dec.5 (red line shows 38°C).



**Figure 1b:** Fever pattern sheet from Dec.6 to Jan.18 (red line shows 38°C).



**Figure 2:** A sequencing analysis of the MEFV gene. DNA sequencing shows a compound heterozygous mutation at S503C in exon 5 of the MEFV gene.

9.1–11.5 years [5-7]. Non-focal peritonitis is reported to be difficult to distinguish from pelvic inflammatory disease and Fitz-Hugh-Curtis syndrome in gynecology [7-9].

In this case, from onset to diagnosis, the patient initially visited an otolaryngologist and an oral surgeon for temporomandibular joint disorder and an orthopedic surgeon for hip joint pain. In addition, because of the weight loss, a full-body examination was performed; however, the cause was not investigated. The 3 month pattern of fever was a fever over 38 °C that lasted for 1-2 days about once a week, and the symptoms and inflammatory findings were relieved during the intermittent period, showing a typical periodic fever. Based on careful history-taking, we strongly suspected FMF.

As it is a rare disease, it was necessary to search the literature for its diagnosis. In addition, genetic testing requires advice from specialists. Applying the diagnostic criteria, colchicine was administered as a diagnostic treatment, and MEFV genetic testing was performed concurrently, leading to a diagnosis.

Autoinflammatory diseases are said to be the fourth most common fever of unknown origin after the three major fevers of unknown origin (infectious diseases, malignant diseases, and collagen diseases). Migita et al. reported a high frequency of FMF as a cause of unexplained fever and nonspecific rheumatic symptoms [10]. FMF is the most common autoinflammatory disease, and knowledge of its characteristics facilitates its diagnosis. MEFV genetic testing shows that the complete type has many mutations in exon 10, whereas the incomplete type has few mutations in exon 10 and is often associated with mutations in exons 1, 2, 3, and 5 [2]. Endo et al. reported that the late-onset group aged 40 years in Japan had fewer exon10 mutations and more arthritis and myalgia than those aged <40 years [11]. Our 61-year-old patient had an exon 5 mutation that was associated with a temporomandibular disorder and hip arthritis.

In Japan, MEFV genetic testing has been covered by insurance since 2020 and can be outsourced, making it easier to ge-

netically diagnose FMF as a rare disease. Therefore, suspicion should be based on the patient's medical history. In addition, early administration of colchicine is important to prevent amyloidosis, which can cause organ damage.

### Conclusion

FMF is a rare hereditary autoinflammatory disease. Diagnosis is more difficult in older patients; however, knowledge of their typical history and findings is the first step in managing atypical cases. As the genetic diagnosis of MEFV has become easier, early diagnosis and treatment have become increasingly important.

### Declarations

**Authors contributions:** SY reviewed the literature and drafted the manuscript. KK critically reviewed the manuscript. HN consulted for MEFV analysis and critically reviewed the manuscript.

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