Familial Mediterranean Fever with Psychiatric Disorder which Have not Been Diagnosed over 30 Years: A Case Report

Kanata TONOSAKI[*1,2], Kazumichi YONENAGA[*1,2], Shunsuke ITAI[*1], Takashi MIZUNO[*1] and Shigeto OYAMA[*1]

[*1]*Department of General Medicine, Towada City Hospital*
[*2]*Department of Eat-Loss Medicine, Graduate School of Medicine, The University of Tokyo*

(Received August 12, 2021; Accepted October 11, 2021)

Familial Mediterranean fever (FMF) is an inherited autoimmune disease characterized by periodic fevers and serositis. Most cases have been diagnosed within 10 years or less; however, there have been no reports of cases in which diagnosis was delayed for several decades. In this study, we encountered a case of FMF in which the patient had recurrent unexplained fevers since childhood, but diagnosis was delayed for more than 30 years due to a psychiatric disorder. Our findings showed that a possible reasons for this delay are possibility of neglect or parenting skills issues, little knowledge of FMF in Japan and the lack of social connections due to the patient's underlying mental illness. We suggest that it is important to conduct a thorough medical interview to identify FMF, as it may go undiagnosed, especially when the patient has few social ties.

Key words: Familial Mediterranean fever, autoimmune disease, psychiatric disorder, schizophrenia, fever

INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited autoimmune disease characterized by periodic fever and serositis [1]. Fever is the most common symptom, and it is characterized by spontaneous resolution after 1–3 days. During fever, there is an increase in acute-phase proteins, such as C-reactive protein (CRP) and serum amyloid A (SAA). Associated symptoms may include serositis, mainly pleurisy and peritonitis, and synovitis symptoms in the knee and ankle joints. In about 300 FMF patients in Japan, fever, pleurisy, peritonitis, and arthritis were reported in 95.5%, 35.8%, 62.7%, and 31.3% of them, respectively [2]. The prevalence of FMF is high in the Mediterranean region, and the Mediterranean fever (MEFV) gene has been identified as the causative gene [3]. The diagnosis of FMF is mainly based on the Tel-Hashomer criteria proposed by Livneh *et al*. [4], and most cases have been diagnosed in less than 10 years [2, 5–7]; however, cases in which diagnoses was delayed for decades have not been reported.

In this report, we describe a case of FMF in which the patient had recurrent unexplained fevers since childhood, but due to psychiatric disorders, the patient did not seek medical attention, and diagnosis was delayed for over 30 years.

CASE REPORT

Case: A 43-year-old man

Chief complaints: Fever and mobility difficulty

Medical history: clipping of unruptured cerebral aneurysm

Oral prescription: None

Life history: The patient had trouble with human relationships, has had suicidal thoughts for over 20 years, and has been a recluse.

Present Illness: The patient had a fever of 39.3°C and had difficulty moving. Since he was 10 years old, he had been suffering from a fever of unknown origin, followed by mild recovery within 2–3 days, once every 3 months.

Medical examination: Consciousness level on Glasgow coma scale, 15 points (E4V5M6); blood pressure, 148/96 mmHg; pulse rate, 118 times/min (regular); body temperature, 39.2°C. He had been experiencing recurrent thoughts of death for more than 20 years, and he has been experiencing worsening auditory hallucinations and delusions for several months. At the time of examination, there were no obvious physical findings that could have been the cause of the fever.

Laboratory findings at admission: Blood tests revealed increased inflammatory response; white blood cell (WBC) count, 13000/μL; CRP, 0.21 mg/dL; and SAA, 292.3 μg/mL. Consolidation was not observed on chest X-ray, and computed tomography (CT) revealed no abnormal findings.

Clinical course: The clinical course is presented in Fig. 1. Based on these findings, fever of unknown origin and schizophrenia were diagnosed, and meropenem (MEPM) was initiated. On day 2, his fever reduced, and his condition improved. On day 5, considering that the antibiotics had little effect, MEPM was completed, and the patient was discharged on the 7th day. On day 19, a blood test was performed at the time of

Kazumichi YONENAGA, Department of Eat-loss Medicine, Graduate School of Medicine, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan Tel: +81-3-5800-8669 Fax: +81-3-5800-6832 E-mail: yonenaga-tky@umin.ac.jp

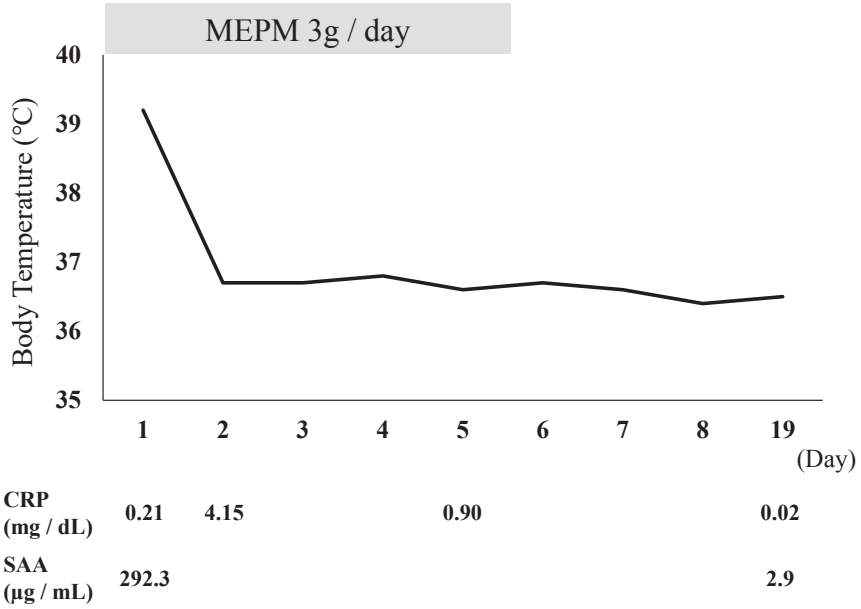

Fig. 1 Clinical Course

fever resolution and showed WBC of 3700 /μL, CRP of 0.02 mg/dL, and SAA of 2.9 μg/ml, which were negative inflammatory findings. We suspected FMF and administered colchicine (0.5 mg). After 6 months without symptoms including fever, he showed periodic fever and elevated amyloid A levels during fevers, and the seizures disappeared with prophylactic colchicine use, leading to a definitive diagnosis of FMF. A genetic search was performed, but no MEFV gene mutation was found, nor was there any obvious family history. In addition, amyloidosis was not suspected. Regarding the psychiatric symptoms, the patient was discharged from our hospital and consulted a psychiatrist, who diagnosed the patient with schizophrenia and prescribed antipsychotic medication.

DISCUSSION

FMF is an autoinflammatory disease characterized by periodic fevers of 1–3 days duration, with spontaneous resolution and serositis. Although symptoms of serositis include peritonitis, pleurisy, and monoarthritis, these symptoms were not observed in the case presented in this study, as the only symptom was a fever of 38°C or higher, which improved within 12 h to 3 days. In addition, the patient responded well to colchicine and met the Ted-Hashomer criteria, one major and one minor, thus confirming the diagnosis of FMF.

It has been reported that MEFV gene mutations occur in 53.2% of FMF cases, and the frequency of serositis complications is high [2]. In the case presented in our study, no mutation was found, and no complication of serositis was observed, which is in accordance with previous reports [2]. Furthermore, Kiyoshi *et al.* reported 134 cases of FMF in Japanese with an average age at onset of 19.6 ± 15.3 years, age at diagnosis of 28.7 ± 18.5 years, and delay duration of 9.1 ± 9.3 years from onset to diagnosis. In particular, 20.1 ± 4.5 years elapsed in cases of amyloidosis, suggesting that the longer the time to diagnosis, the more likely amyloidosis is to occur [2]. However, there were no findings suggestive of amyloidosis in our case report. The age at onset, age at diagnosis, and time from onset to diagnosis, including data from overseas, are summarized in Table 1. In this case, the age at onset was approximately 10 years, and that at diagnosis was 43 years, which was similar to data from other countries [5, 9, 10]. However, in other reports, the time from onset to diagnosis was generally approximately 10 years, and there have been no reports of cases in which diagnosis was delayed for 30 years, suggesting that the time from onset to diagnosis reported in this study may be the longest ever.

The delay by at least 30 years in the diagnosis will be discussed in two categories: the period between the onset of FMF and mental illness, and time after the onset of mental illness. In the former period, the parents may not have anticipated any abnormality in the child's condition that could receive clinical attention. When the diagnosis of a chronic disease is delayed, as in this case, neglect and parenting skills issues need to be considered. We also searched PubMed for "Familial Mediterranean fever" and retrieved reports from 1981 to 2020, pertinent reports by Japanese (Fig. 2). The disease may have affected the patient during the 1980s and 1990s, when cases of FMF were extremely rarely reported, especially in Japan. As those few reports had suggested, there was little knowledge of FMF, which might have prevented its diagnosis. In the latter period, one possible reason is the lack of social connections due to the patient's underlying mental illness, which may have prevented him from visiting a medical institution for fever-related symptoms, or may have resulted in a one-time visit. Another reason is because he lived with his parents for a long time, had little contact with them at home, and shut himself indoors at home. The fact that the fever, which is a characteristic of FMF, lasted only a few days and that no one suggested that he saw a doctor was thought to be a reason why the diagnosis was not made.

In the case of fever in patients with psychiatric disorders such as schizophrenia, malignant syndromes and malignant catatonia should be considered in

Table 1 Summary of the patient's clinical characteristics

Characteristics	Age at onset (year ± SD)	Age at diagnosis (year ± SD)	Delay to diagnosis (year ± SD)
This case	about 10	43	> 30
Japanese [7] (n = 26)	27.3	38.9	11.5
Japanese [2] (n = 134)	19.6 ± 15.3	28.7 ± 18.5	9.1 ± 9.3
Turkish [5] (n = 2838)	9.6 ± 8.55	16.4 ± 11.57	6.9 ± 7.65
Chinese [8] (n = 11)	29.4 ± 18.2	37.7 ± 13.2	8.31 ± 7.08
Ashkenazi [9] (n = 57)	21.6 ± 13.6	34.3 + 15.9	12.8 ± 12.1
Iraqi [9] (n = 62)	25.4 ± 14.9	34.9 ± 13.3	9.8 ± 10.9
North African [9] (n = 61)	9.6 ± 9.1	16.6 ± 12.2	7.0 ± 8.8

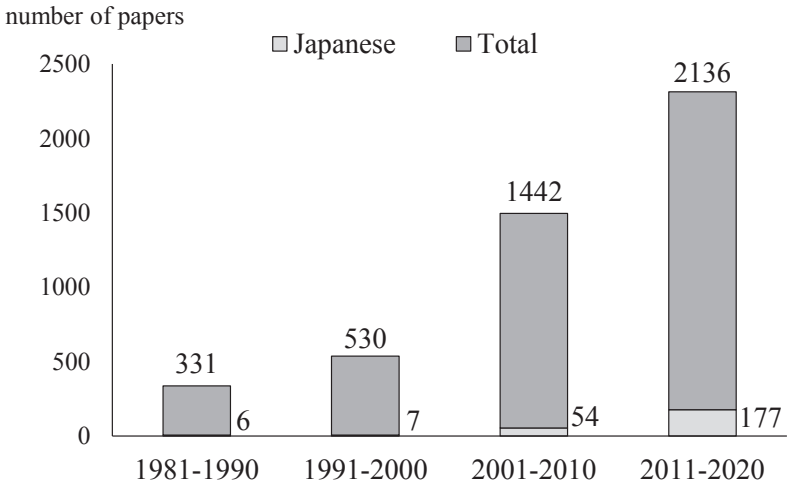

Fig. 2 Number of reports on "Familial Mediterranean fever" in PubMed from 1981 to 2020

addition to general medical disorders, and more differentiation is required than in patients who visit general internal medicine outpatient clinics. FMF has a good prognosis if it is not associated with amyloidosis and if it does not present with consciousness disorder, and it should be considered when the patient has periodic symptoms including fever for a short period. However, it is believed that some patients with latent fever do not receive medical attention or follow-up services due to mental illness, in addition to the fact that their symptoms improve within a short period and do not require a thorough examination.

It has been reported that patients with schizophrenia are at risk of severe acute coronavirus 2 (SARS-CoV-2) infection and mortality [10, 11]. Mental illness has also been reported as a risk factor for other diseases. Nemani *et al.* discussed the possible involvement of impaired pro-inflammatory cytokine signaling in patients with schizophrenia, in addition to causing delayed treatment in SARS-CoV-2 infection. Hence, the possibility that schizophrenia itself is related to FMF cannot be ruled out.

In this study, we were able to differentiate fevers and diagnose FMF by carefully interviewing the patient. Since colchicine prevents fever and amyloidosis, it is important to start treatment early. As this is the first report worldwide of an FMF patient with psychiatric disorders, more cases are required to clarify whether there is a relationship.

In conclusion, considering that FMF may go undiagnosed in patients who also have schizophrenia and other psychiatric disorders, with little social connection, it is important to conduct a thorough medical interview to identify FMF.

CONFLICT OF INTEREST

The authors have no conflicts of interest in association with this report.

REFERENCES

1) Onen F. Familial Mediterranean fever. Rheumatol Int 2006; 26: 489–96.
2) Kiyoshi M, Kazunaga A. Clinical aspects of Familial Mediterranean fever. Jpn J Clin Immunol 2011; 34: 355–60.
3) The International FMF Consortium. Ancient Missense Mutations in a New Member of the RoRet Gene Family Are Likely to Cause Familial Mediterranean Fever. Cell 1997; 90: 797–807.
4) Livneh, A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, *et al.* Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997; 40: 1879–85.
5) Turkish FMF Study Group. Familial Mediterranean fever (FMF)

in Turkey. Results of a nationwide multicenter study. Medicine 2005; 84: 1–11.
6) Duşunsel, R., Dursun I, Gündüz Z, Poyrazoğlu MH, Gürgöze MK, Dundar M. Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. Pediatr Int 2008; 50: 208–12.
7) Kunimatsu J, Maeda J, Watanabe R, Kato O, Kishida D, Yazaki M, *et al*. Fever of unknown origin in the outpatient setting: A retrospective analysis of 30 cases of familial Mediterranean fever. Jpn J Clin Immunol 2016; 39: 130–9.
8) Wu D, Shen M, Zeng X. Familial Mediterranean fever in Chinese adult patients. Rheumatology 2018; 57: 2140–4.
9) Lidar M, Kedem R, Berkun Y, Langevitz P, Livneh AV. Familial Mediterranean fever in Ashkenazi Jews: the mild end of the clinical spectrum. J Rheumatol 2010; 37: 4225.
10) Nemani K, Li C, Olfson M, Blessing EM, Razavian N, Chen J, *et al*. Association of Psychiatric Disorders With Mortality Among Patients With COVID-19. JAMA Psychiatr 2021; 78: 380–6.
11) Wang Q, Xu R, Volkow ND. Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World Psychiatr 2020; 20: 124–30.