

[CASE REPORT]

Familial Mediterranean Fever Is Important in the Differential Diagnosis of Recurrent Aseptic Meningitis in Japan

Takahiro Hosoi¹, Kazuhiro Ishii², Naoki Tozaka², Dai Kishida³,
Yoshiki Sekijima³ and Akira Tamaoka²

Abstract:

Familial Mediterranean fever (FMF) is an autoinflammatory disease characterized by a recurrent fever and multiple serositis. In the present report, we discuss the case of a 42-year-old man diagnosed with FMF accompanied by recurrent aseptic meningitis (RAM). The patient experienced RAM at intervals of several years without any serositis or synovitis. We detected Mediterranean fever (*MEFV*) gene mutations (E148Q homozygotes) and diagnosed FMF in perfect accordance with clinical diagnostic criteria. FMF, in which RAM is a major symptom, has also been described in previous reports. Therefore, FMF should be considered in the differential diagnosis of causative diseases for RAM.

Key words: Familial Mediterranean fever, recurrent aseptic meningitis, *MEFV* gene, colchicine

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Introduction

Familial Mediterranean fever (FMF) is an autoinflammatory disorder characterized by a relapsing fever associated with multiple serositis (1). A mutation in the Mediterranean fever (*MEFV*) gene is the underlying cause of FMF, resulting in dysfunction of the inflammation control protein pyrin. Pyrin negatively regulates the activation of inflammasomes that modulate interleukin-1 β (IL-1 β) activity, and dysfunction of pyrin readily induces autoinflammation. Typical symptoms of FMF include a periodic fever lasting approximately one to three days, abdominal or chest pain due to serositis, and arthralgia due to synovitis. However, patients may be asymptomatic for two to four weeks (2). Furthermore, FMF has been associated with central nervous system involvement, with some patients exhibiting demyelinating lesions, posterior reversible encephalopathy syndrome, pseudotumor cerebri, optic neuritis, cerebral vasculitis, seizure, cerebral venous sinus thrombosis, and aseptic meningi-

tis (3-5).

Aseptic meningitis due to FMF is a very rare condition. One previous report indicated that only 7 of 12,000 adult patients with FMF experienced a single episode of aseptic meningitis, while none experiencing recurrent attacks over a 12-year follow-up period (3). In the present report, we discuss the case of a patient with a homozygous *MEFV* point mutation who experienced recurrent aseptic meningitis at intervals of several years.

Case Report

A 43-year-old man experienced recurrent episodes of a fever and neck pain. He did not report experiencing repeated episodes of infection during childhood and had no family history of neurologic disease or consanguineous marriage. At 20, 28, 32, and 37 years of age, he visited a local hospital due to a fever, headache, neck pain, and back pain, at which time he was diagnosed with aseptic meningitis by lumbar puncture. Five years later, he again developed a fe-

¹Department of General Medicine, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, Japan, ²Department of Neurology, Division of Clinical Medicine, Faculty of Medicine, University of Tsukuba, Japan and ³Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Japan

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Correspondence to Dr. Kazuhiro Ishii, kazishii@md.tsukuba.ac.jp

ver and neck pain, and a lumbar puncture was performed by his primary care physician. The cell counts in the cerebrospinal fluid (CSF) were increased, and he was again diagnosed with aseptic meningitis. Many of his symptoms naturally subsided within a few days, although his joint pain, fever, and headache reappeared several days later. He was admitted to the General Internal Medicine Department of our hospital for a further examination.

Upon admission, his vital signs were normal. A physical examination revealed tenderness in both elbows and the bilateral knee joints without apparent swelling. A neurological examination revealed no abnormalities, except for nuchal rigidity. Marked tenderness was observed in the left inner thigh and bilateral gastrocnemius muscles. An ophthalmologic examination revealed no abnormalities, such as uveitis. A peripheral blood examination revealed a white blood cell count of 4,100/ μ L, a C-reactive protein level of 1.50 mg/dL, and an erythrocyte sedimentation rate of 18 mm/h. Levels of serum Amyloid A protein (SAA) were elevated (991 μ g/mL). Laboratory tests revealed no signs of liver/renal dysfunction or glucose intolerance. Autoantibody results were as follows: anti-dsDNA IgG: 1.5 IU/mL (reference range: < 12.0 IU/mL); antinuclear antibody: 1:40; rheumatoid factor: 2 U/mL; anti-SS-A/B antibody: negative; anti-ribonucleoprotein antibodies: 9.8 U/mL (reference range: < 10.0 U/mL); anti-cyclic citrullinated peptide antibody: 0.6 U/mL (reference range: < 4.5 U/mL); proteinase-3-antineutrophil cytoplasmic antibody (PR3-ANCA): <1.0 (reference range: 0.0-3.40); and myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA): <1.0 (reference range: 0.0-3.40). Systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, and ANCA-associated vasculitis were excluded based on diagnostic criteria. A CSF examination revealed a cell count of 36 cells/ μ L with all lymphocytes and a protein concentration of 49 mg/dL. Varicella-zoster virus/herpes simplex virus (VZV/HSV) polymerase chain reaction results were negative. Radiological examinations, including brain magnetic resonance imaging (MRI), revealed no lesions. Upper and lower gastrointestinal endoscopies revealed no abnormalities, and duodenal and rectal biopsies showed no evidence of amyloidosis.

Our patient's symptoms and physical findings disappeared within one week after admission. We suspected FMF due to his recurrent fever and headaches. Genetic analyses revealed a homozygous *MEFV* mutation (p: E148Q). Laboratory tests at the time of symptom resolution indicated no inflammatory response. Our patient's fever and arthritis were in accordance with the diagnostic criteria for FMF, which also include meningitis and an elevated inflammatory response during attacks. Based on these additional symptoms, we excluded other diseases such as HSV-1 and HSV-2 infection, collagen disease, and classical causes of recurrent aseptic meningitis (RAM), including drug-induced RAM and cystic diseases of the brain. He was finally diagnosed with recurrent aseptic meningitis due to FMF (6-9). After confirming the diagnosis, treatment was initiated with colchicine at 0.5

mg/day, and no recurrence of symptoms was noted.

Discussion

RAM, or Mollaret meningitis, is characterized by repeated episodes of a fever and meningitis lasting two to five days, with most patients experiencing spontaneous recovery (8). Known causes of RAM include viral infections, such as HSV-1 or HSV-2; fungal meningitis; autoimmune diseases, such as SLE or Sjögren's syndrome; uveo-meningeal syndrome (Harada's disease); tumors, such as epidermoid cysts or craniopharyngiomas; and drug-induced and autoinflammatory diseases, such as FMF or Behçet's disease (8). Capton et al. proposed diagnostic criteria for recurrent meningitis related to FMF, as follows: (a) Episodes of RAM due to FMF should be accompanied by other clinical or biological features of FMF attacks; (b) colchicine should prevent or lessen episodes; and (c) other classical causes of RAM should be excluded (9). In a systematic review investigating the association between FMF and RAM, there were only five confirmed cases of FMF and RAM (including the present case), although the differential diagnosis mentioned above was incomplete in three cases (10-13) (Table). In previous case reports, the authors failed to sufficiently exclude or describe the exclusion of other diseases (11, 13). Despite the relatively short observation period following colchicine treatment in the present case, our patient has experienced no recurrence to date.

In most cases, the interval between episodes ranges from two to four weeks. However, intervals may be relatively long in patients with aseptic meningitis. The asymptomatic period in our patient lasted approximately four years, making a diagnosis difficult. Symptoms are reported to be mild and exacerbated less frequently when accompanied by mutations in exon 2 (E148Q, E148Q/L110P) (14). In addition, previous studies have indicated that the atypical progression of FMF is accompanied by mutations of exons 1, 2, 3, and 5. Atypical symptoms, which were also observed in our case, include the following: (a) a fever typically lasting more than four days; (b) often unrecognized attacks of serositis; (c) arthralgia and myalgia (15). Recent reports have demonstrated that cases associated with low-penetrance gene mutations (exons 2 and 3, etc.) are milder than those associated with high-penetrance gene abnormalities (exon 10), with genetic mutations also exhibiting a "dose effect" (16). In addition, researchers have speculated that the FMF onset may be due to the presence of mutations in genes other than *MEFV*, as well as environmental factors. In a nationwide survey of FMF in Japan conducted between 2009 and 2015, the rate of E148Q appearance was 39.1%, with homozygous E148Q accounting for 13.9% of this rate. This rate was significantly higher than that reported for healthy controls (17). In cases of RAM, especially in areas where there are many reports of exon 2 mutations, such as Japan, investigating *MEFV* mutations may aid in the diagnosis of FMF even when the asymptomatic period occurs yearly.

Table. Diagnostic Evidence in Previous Cases of Recurrent Meningitis Associated with Familial Mediterranean Fever (FMF).

First author (ref)	Age/sex	Age at onset (years)	Duration of symptoms/asymptomatic interval	CSF analysis Cell (μL) Mono ¹ (%), Pro ² (mg/dL) Glu ³ (mg/dL) IL-6 (pg/mL)	Neurological findings associated meningitis	Major criteria for FMF diagnosis	Minor criteria for FMF diagnosis	Exclusion of other systemic diseases	Exclusion of brain lesions and drug-induced meningitis	MRI findings	MEFV mutation
(10)	66 F	46	10 days/ 2 months	Cell 35 μL , 83% Pro 77 mg/dL, Glu 54 mg/dL IL-6 767pg/mL	Headache	Fever	Response to colchicine	Yes	Yes	HIA ⁵ of the cerebral white matter	E148Q/ E148Q
(11)	13 M	13	5 days/ 3 months	Cell 47 μL , 97% Pro 27 mg/dL Glu 80 mg/dL	Meningeal sign	Fever	Response to colchicine	No	Yes	N/A	E148Q/ E148Q
(12)	48 F	45	3 days/ unknown	Cell 12 μL , Pro 154mg/dL Glu 79mg/dL	Unconscious and nuchal rigidity	Fever	Atypical arthritis, Response to colchicine	No	Yes	No lesions	L110P/ E148Q
(13)	38 M	5	4 weeks/ unknown	Cell 79 μL , 60%, Pro N/A, Glu N/A	Headache and nuchal rigidity	Fever, abdominal pain	Response to colchicine	No	Yes	No lesions	E148Q/ S503C
Present case	41 M	20	Days to 2 weeks/ several years	Cell 36 μL , 97% Pro 49mg/dL, Glu 57 mg/dL IL-6 3.5pg/mL	nuchal rigidity	Fever, typical arthritis	Atypical arthritis, exertional leg pain, response to colchicine	Yes	Yes	No lesions	E148Q/ E148Q

Mono¹: monocyte, Pro²: protein concentration, Glu³: glucose concentration, IL-6⁴: interleukin 6, N/A: not available, HIA⁵: High intensity area. Other diagnoses were sufficiently excluded in the present case only.

In conclusion, we discussed the case of a patient with FMF who presented with RAM and exhibited *MEFV* gene mutations (p: E148Q). As the interval between FMF episodes may last several years, FMF should be considered in the differential diagnosis of recurrent meningitis in areas where there are many reports of E148Q mutations, such as Japan.

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

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