

CASE REPORT

Atypical type of familial Mediterranean fever: An underdiagnosed cause of chronic aseptic meningitis

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Key words

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Abstract

We report an atypical case of familial Mediterranean fever (FMF) concomitant with chronic aseptic meningitis. The patient experienced fever, abdominal and back pain because of serositis, and headache because of aseptic meningitis for 4 weeks. Blood examinations revealed increased white blood cells and serum amyloid A level. Medications, including steroids, did not improve his symptoms. However, the patient experienced immediate relief after the administration of colchicine. We diagnosed him as having atypical FMF based on the symptoms, especially positive response to colchicine, and heterozygous mutations on exon 2 and 5 (E148Q/S503C) in *MEFV* gene. Unlike typical FMF, a cause of recurrent aseptic meningitis, atypical FMF might be an underdiagnosed cause of chronic aseptic meningitis.

Introduction

Familial Mediterranean fever (FMF), a genetic disorder, is caused by mutations in the *MEFV* gene coding pyrin.¹ Patients with FMF have acute inflammatory reactions caused by the gain-of-function mutations in pyrin, as well as have transient inflammation with elevated white blood cells (WBCs), erythrocyte sedimentation rate (ESR), and serum amyloid A (SAA).²

Familial Mediterranean fever can be categorized as being “typical” and “atypical”.³ The clinical features of typical FMF are self-limited bouts of fever lasting 12 h to 3 days, with symptoms of serositis, pleuritis, arthritis,¹ and recurrent aseptic meningitis.⁴ In contrast, atypical FMF has different features.

We herein report an atypical case of FMF concomitant with chronic aseptic meningitis improved by colchicine.

Case report

A 38-year-old man developed lower abdominal and back pain, headache experienced as his head is being tightened, and fever 2 weeks before admission. His familial history was not specific. His past history revealed a few events of self-limited fever and abdominal pain, and the first event was reported at age 5. Although his urinary tests were negative, he was diagnosed as having urinary tract infection by his personal physician and was therefore prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), steroids (prednisolone, total dose: > 200 mg for 2 weeks), and antibiotics (Quinolone, dose: 500 mg/day for 7 days). However, his

symptoms were not improved, and he was admitted to our hospital.

He was alert, and his symptoms were not alarming, except for the following: body temperature: 38.5 °C, peritoneal irritation on lower abdomen, bilateral costovertebral angle tenderness, and neck stiffness. No skin and mucosal lesions were observed throughout his clinical course. Peripheral blood examinations yielded the following results: WBC: 16 000/µL with 90% neutrophils, SAA: 13.5 µg/mL (reference range: < 8.0), and ESR: 45 mm/h. His cerebrospinal fluid (CSF) was sterile, with a cell count of 79 cells/µL (monocytes: 60%). Radiological examinations showed no lesions. NSAIDs and acyclovir (dose: 1500 mg for 7 days) did not improve his symptoms and were discontinued due to drug-induced liver injury. Subsequently, we prescribed colchicine (1.0 mg daily) on day 11 of admission. Three days later, he was afebrile, and blood and CSF examinations showed improvement. An analysis of the *MEFV* gene (Fig. 1a) showed heterozygous mutations on exon 2 (E148Q) and 5 (S503C), and we diagnosed him as having atypical FMF concomitant with chronic aseptic meningitis. Colchicine was continued for 1 year, and he had no recurrence to date (Fig. 1b).

Discussion

The present case of atypical FMF concomitant with chronic aseptic meningitis for 4 weeks indicated favorable responses to colchicine. Our case fulfilled not essential but supportive criteria of the diagnostic tool for FMF proposed by the Ministry of Health, Japan.² In addition, based on *MEFV* genetic analysis, we diagnosed the patient as having atypical

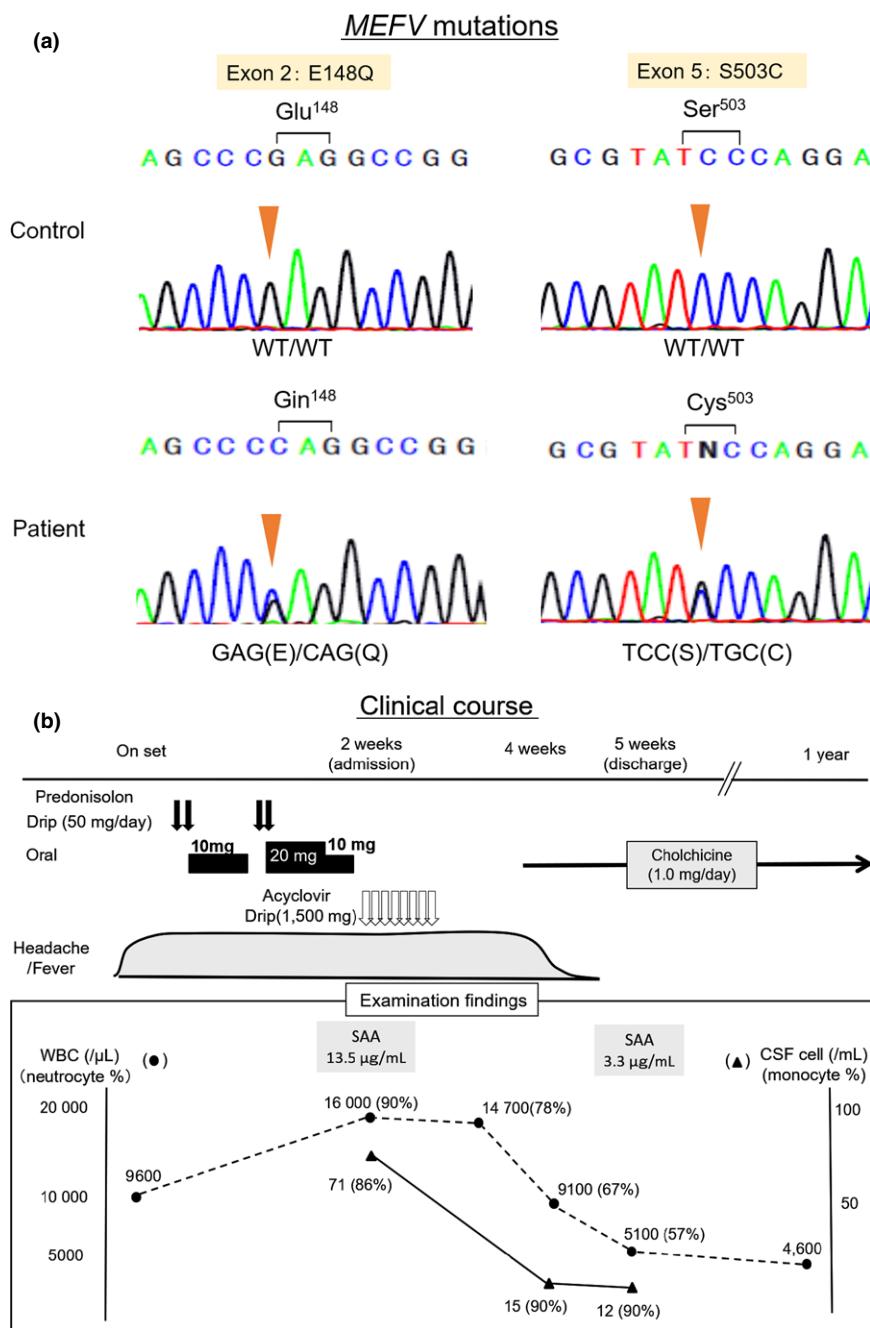


Figure 1 (a) The genetic analysis of *MEFV* showed the heterozygous mutations in exon 2 (E148Q) and 5 (S503C). (b) The Clinical course. SAA, Serum amyloid A; CSF, Cerebrospinal fluid.

FMF. There was a possibility of a NSAIDs-related meningitis; however, he had no recurrence of meningitis despite administration of them.

A study reported that 43% cases of Japanese FMF were of the atypical type.³ Atypical FMF, unlike typical FMF, has the following features: clinical course of less than 12 h or more than 3 days, over 14 days in some cases, localized abdominal signs, or atypical distribution of arthritis.¹ Colchicine is also effective.³ The present case developed fever, lower abdominal and back pain because of serositis, and

headache because of chronic meningitis. These symptoms improved only after the administration of colchicine.

The *MEFV* exon 10 mutations, the low frequency of high-penetrance in the FMF population, are a cornerstone for dividing into 2 phenotypes.^{1,3} Some of the FMF patients without exon 10 and with especially exon 3 mutations presented with an atypical FMF symptoms.³ Our patient, however, had heterozygous mutations on exon 2 and 5 (E148Q/S503C) of the *MEFV* gene. The E148Q mutation, the high frequency of low-penetrance mutation, found frequently in Japanese patients.^{3,4} This

mutation, including heterozygous mutation, attributes to manifestation of FMF symptoms^{2,3}; meanwhile, the genetic role of S503C mutation is not known.^{1,3} These mutations are detected only in atypical FMF.³ Therefore, we considered he had the phenotypic and genotypic features of an atypical FMF.

Recurrence of aseptic meningitis, including Mollaret's meningitis, is suggested as a complication of typical FMF.⁴ In contrast, based on the present case, we indicate a hypothesis that chronic aseptic meningitis may be a complication of atypical FMF. It was recognized that no cause determined in one-third of chronic and recurrent aseptic meningitis cases.⁵ Therefore, atypical FMF may be an underdiagnosed cause of chronic aseptic meningitis, but typical FMF may a cause be of recurrent aseptic meningitis.

In summary, we report an atypical case of FMF accompanied with chronic aseptic meningitis showing a good response to colchicine. Clinicians should consider the possibility of atypical FMF, as well as typical FMF, in the differential diagnosis of agnogenic aseptic meningitis.

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