INTERNAL MEDICINE

□ CASE REPORT □

Familial Mediterranean Fever with Onset at 66 Years of Age

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Abstract

The patient was a 68-year-old woman who had experienced recurrent febrile episodes since 66 years of age. Despite various examinations and treatments, the etiology remained unclear. Further examinations following another referral failed to uncover the cause. Therefore, despite her age, it was presumed that she had familial Mediterranean fever. An analysis of the familial Mediterranean fever (MEFV) gene detected heterozygous L110P, E148Q, and R202Q mutations. No further febrile episodes occurred after colchicine treatment was initiated. Familial Mediterranean fever presenting in patients in their sixties is extremely rare.

Key words: abdominal pain, familial Mediterranean fever, febrile episodes, MEFV gene

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Introduction

Familial Mediterranean fever (FMF) is the most common, genetic, autoinflammatory disease, with a predominantly autosomal recessive pattern of inheritance. It is characterized by periodic fever and symptoms of serositis, such as abdominal pain, chest pain, and joint pain, and occurs mostly at a young age. The case of a patient who presented with FMF for the first time at 66 years of age is herein reported. An investigation of the association between genetic mutations and the age of onset reported in the Japanese literature is also presented.

Case Report

A 68-year-old woman was referred to our department for further evaluation and treatment with a 2-year history of febrile episodes ranging from 37℃ to 40℃, which lasted for a few days. The febrile episodes occurred with a cycle of between one and three months. Initially, the patient was treated with antibiotics at another hospital, although the etiology of the fever was unclear despite various examinations. She was subsequently treated with non-steroidal anti-inflammatory drugs (NSAIDs) alone after it was found that her fever subsided without antibiotic therapy. She was admitted to our department for further evaluation and treatment.

The physical examination on admission showed evidence of severe anemia in the palpebral conjunctiva, a mild systolic murmur on chest auscultation, and vague abdominal tenderness. She had no abnormal neurological findings. There were no signs of a skin eruption, swelling of the lymph nodes and tonsils, or swelling or deformity of the joints. She had no joint pain even during febrile attacks. There was no pain on percussion of the spine or costovertebral angles.

At that point, the differential diagnosis of her febrile attacks included infection, malignancy, collagen disease such as seronegative rheumatoid arthritis, seronegative spondyloarthropathy or vasculitis, and arthritis from gout or calcium pyrophosphate deposition (CPPD).

Laboratory tests during febrile episodes showed evidence of increased inflammation, such as an elevated level of C-

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Table 1. Laboratory Findings during a Febrile Episode

[Peripheral blood]			[Biochemistry]			[Serological tests]			[Tumor markers]		
WBC	10200	/μL	T-Bil	0.3	mg/dL	CRP	12.6	mg/dL	CEA	1.1	ng/mL
seg	83	%	AST	14	IU/L	ESR	169	mm/hr	sIL-2R	761	U/mL
lym	12	%	ALT	15	IU/L				SCC antigen	0.9	ng/mL
mono	4	%	LDH	103	IU/L	RF	<9.4	IU/mL			
RBC	229x10⁴	/μL	ALP	314	IU/L	ANA	<20		[Urinalysis]		
Hb	6.1	g/dL	γGTP	87	IU/L	C3	132	mg/dL	occult blood	-	
Hct	20.3	%	Amy	63	IU/L	C4	27.5	mg/dL	protein	-	
Plt	58.8x10⁴	/μL	CK	19	IU/L	CH50	71.4	U/mL	glucose	-	
			UA	4.9	mg/dL	IgG	1840	mg/dL			
			TP	7.2	g/dL	IgM	126	mg/dL			
			Alb	2.9	g/dL	IgA	278	mg/dL			
			BUN	20	mg/dL	ferritin	462	ng/mL			
			Cr	1.17	mg/dL	FT3	1.66	pg/mL			
						FT4	1.14	ng/mL			
						TSH	1.31	IU/mL			

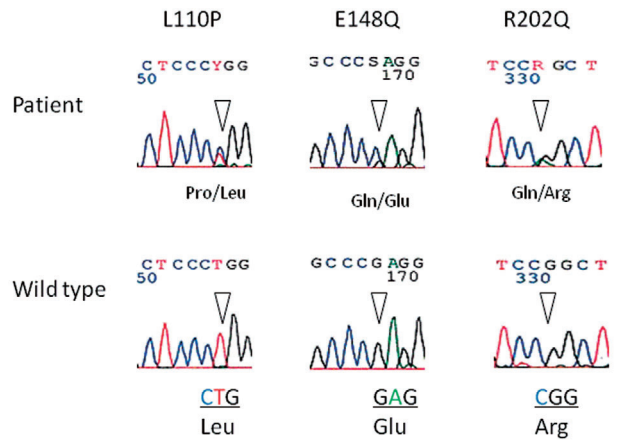

Figure 1. DNA sequencing demonstrating the L110P, E148Q, and R202Q mutations in the patient and a healthy control.

reactive protein (C-reactive protein (CRP); 6.94-28.11 mg/dL), leukocytosis (9,300-31,600/μL, segmented neutrophils 73-95%), and an increased erythrocyte sedimentation rate (ESR; 160 mm/hr). In contrast, during the fever-free period, her inflammatory markers were normal or slightly increased: CRP 0.09-9.47 mg/dL; leukocyte count 3,600-16,000/μL, segmented neutrophils 39-82%; and ESR 66-159 mm/hr (Table 1). The tumor marker levels were within the normal limits, except for the fact that the ferritin level and soluble interleukin 2 receptor level were slightly increased. The plasma uric acid level was not increased. No immunological abnormalities were found. The urinalysis was normal and the fecal occult blood test was negative. X-ray examinations of the chest and abdomen, a computed tomography (CT) scan from the head to the pelvis, ultrasound evaluations of the heart and abdomen, upper and lower gastrointestinal endoscopy, and laryngoscopy were all negative. In addition, positron emission tomography/computed tomography (PET/CT) and bone-marrow aspiration were performed, but they revealed no abnormalities. Repeated blood, urine, and fecal cultures were all negative. Considering the findings of the physical examination, laboratory tests, and imaging, she did not appear to have any infection, malignancy, or arthritis from gout or CPPD.

Treatment with a glucocorticoid (prednisolone 40 mg) was initiated on the assumption that she had had some sort of collagen disease, such as seronegative rheumatoid arthritis, seronegative spondyloarthropathy, or adult Still's disease, because the frequency of febrile episodes increased during hospitalization. However, this did not alleviate her fever, and treatment was stopped. At the same time, a sample specimen was obtained to analyze the familial Mediterranean fever (MEFV) gene to determine whether she had FMF. Exons 1, 2, 3, and 10 of the MEFV gene, where mutations of FMF are often confirmed, were analyzed, and heterozygous L110P, E148Q, and R202Q mutations were identified in exon 2 (Fig. 1). Since FMF is sometimes complicated by AA-type amyloidosis, endoscopic duodenal mucous membrane biopsies were performed, and the serum amyloid A protein (SAA) levels were measured. Amyloid was not detected in the biopsy specimens. The SAA protein level was increased during the febrile episodes, but it did not increase during the fever-free period (Fig. 2).

Colchicine at a dose of 0.5 mg once a day was started. This was insufficient to suppress the febrile episodes, so the dose of colchicine was increased to 1.5 mg three times a day. Therapy was discontinued several times because of abdominal pain, nausea, and diarrhea, which were probably side effects of colchicine or FMF peritonitis. Low-dose colchicine at 0.25 mg once a day was eventually used after one of these discontinuations, followed by an increase to 0.5 mg twice a day. The white blood cell (WBC), CRP, ESR, and SAA protein levels decreased to within the normal limits, and the patient had no further febrile episodes. As of this time, 6 months have passed since her last febrile episode. Her blood inflammatory markers still remain within the normal limits.

Retrospectively, her symptom of vague abdominal pain tended to be seen more frequently during febrile attacks than during the fever-free period. Although there were no apparent physical signs of peritonitis, the pain could have indicated peritonitis. However, this would not be surprising since there are no apparent physical signs of peritonitis in the elderly. The amyloidosis, favorable response to colchicine treatment, and recurrent febrile episodes satisfied the Tel Hashomer criteria for the diagnosis of FMF, which take into account the clinical symptoms and the efficacy of colchicine (Table 2). Therefore, the MEFV gene mutation, the patient's clinical symptoms, and the favorable response to colchicine treatment led to a diagnosis of FMF, though the age at onset of 66 years was very unusual.

Discussion

A case of FMF with an age at onset of 66 years is herein described. FMF is the most common, inherited, autoinflammatory disease. It is inherited in an autosomal recessive pattern, and it is characterized by periodic attacks of fever, aseptic serositis, and synovitis. The Tel Hashomer criteria for FMF have previously relied on clinical signs alone, so it

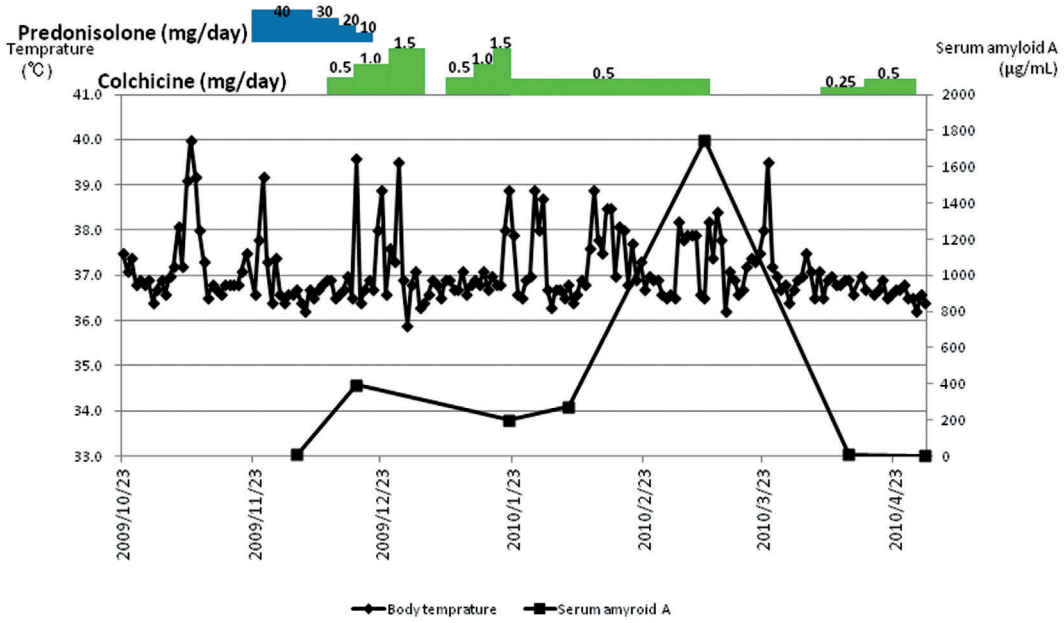

Figure 2. The patient's clinical course.

Table 2. Tel Hashomer Criteria for the Diagnosis of FMF

Major criteria
1. Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis.
2. Amyloidosis of the AA-type without predisposing disease.
3. Favorable response to continuous colchicine treatment.
Minor criteria
1. Recurrent febrile episodes.
2. Erysipelas-like erythema.
3. FMF in a first-degree relative.
Definitive diagnosis: 2 major or 1 major and 2 minor.
Probable diagnosis: 1 major and 1 minor.

Table 3. 53 Cases of FMF in the Japanese Literature

Sex	Male 26 Female 27	
Age of onset (y)	19.7 ± 12.8 y (1-66 y) 0-10 y: 9(16%) 11-20 y: 29(56%) 21-30: 7(13%) 31-40y: 4(8%) 41-50y: 2(3%) 51-60y: 1(2%) 61y-: 1(2%)	
MEFV mutations (cases)	M694I/E148Q	20
	M694I	11
	M694I/E148Q/L110P	4
	M694I(homo)	3
	E148Q	2
	E148Q(homo)	2
	E148Q/P369S	2
	E148Q/L110P/R202Q	1
	E148Q/R408Q/P369S	1
	E148Q/R202Q	1
	E148Q/S503C	1
	R408Q/P369S	1
	E148Q/L110P	1
	Uncertain	3

was difficult to make a correct diagnosis in patients with mild or atypical symptoms. In 1997, the MEFV gene, which is responsible for the development of FMF, was cloned. It is located on the short arm of chromosome 16 (1). The detection rate of MEFV gene mutations in FMF patients remains low, at only approximately 60% (2). Nevertheless, analyzing the MEFV gene is used as an adjunct diagnostic examination, especially when the clinical features are not distinctive, or when there is no family history of FMF.

The MEFV gene encodes a protein called pyrin, which suppress cryopyrin, which is involved in the induction of an inflammatory reaction. MEFV gene mutations depress pyrin function, which increases the inflammatory reaction. MEFV mutations are found mostly on exons 2 and 10. L110P and E148Q on exon 2 and M680I, M694I, M694V, and V726A on exon 10 are the most common mutations. In the present patient, there was no evidence of a mutation on exon 10, such as M694I, which is the most common mutation related to MEFV in Japan. However, there were heterozygous L110P, E148Q, and R202Q mutations on exon 2. In addition to the MEFV gene mutations, the characteristic clinical symptoms and the efficacy of colchicine, which met the Tel-Hashomer criteria, led to the diagnosis of FMF.

It is well known that FMF usually occurs at a young age. The majority of patients develop FMF before 20 years of age (3). According to Sohar et al. (4), the age at onset of FMF in 755 patients was 0-10 years in 65.5%, 11-20 years in 24%, 21-30 years in 8.2%, 31-40 years in 1.5%, 41-50 years in 0.3%, and unknown in 36 patients. As of October 2010, only 53 cases of FMF have been reported in Japan, including the present case (5-18). Of these, the age at onset was 0-10 years in 9 patients (16%), 11-20 years in 29 patients (56%), 21-30 years in 7 patients (13%), 31-40 years in 4 patients (8%), 41-50 in 2 patients (3%), 51-60 years in 1 patient (2%), and 61 years (2%) in 1 patient (Table 3). The present case had the latest age at onset of FMF in Japan.

The reason why FMF develops in the elderly needs to be considered. The E148Q mutation is considered to be the mildest mutation and to result in a milder form of

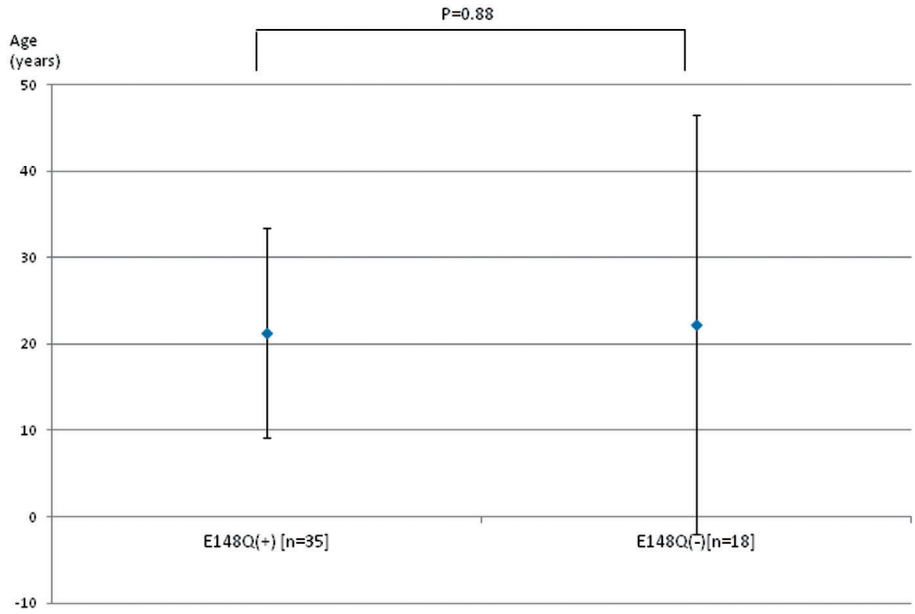

Figure 3. **Age of onset of FMF in the Japanese literature with or without E148Q mutation.**

FMF (19). It has also been reported that patients with homozygosity for the pyrin variant E148Q mutation have less severe symptoms and fewer attacks than those with heterozygosity for the pyrin variant E148Q/M694I mutation (15, 16). The patient in the present case was found to have a heterozygous E148Q mutation. According to our analysis of all cases reported in the Japanese literature (n=53), the age at onset of FMF with the E148Q mutation was 21.31±12.11 years (n=35), while that without the E148Q mutation was 22.23±24.28 years (n=18). There is apparently no significant difference in the age at onset of FMF based on the E148Q mutation (Student's *t*-test, p=0.86) (Fig. 3).

With respect to the R202Q mutation, Giaglis et al. (20) reported that, in 152 Greek FMF patients and 140 Greek healthy controls, homozygosity for the R202Q mutation was detected in 14/152 (9.2%) FMF patients and in 1/140 (0.7%) healthy controls (p=0.001, diagnostic odds ratio = 14.1, 95% CI 2.33-84.72). Heterozygosity of the R202Q mutation was detected in 48/152 (31.6%) FMF patients and in 47/140 (33.6%) healthy controls (p=0.717, diagnostic odds ratio =0.913, 95% CI 0.560-1.49). Yamaguchi et al. (21) reported that R202Q heterozygotes were observed in 7/170 (4.1%) of randomly selected healthy Japanese subjects. They and their families had no episodes of periodic fever similar to FMF. R202Q homozygotes were not observed. In our analysis of all cases of FMF reported in the Japanese literature (n=53), R202Q heterozygotes were observed in 2/53 (3.8%) FMF patients. The rates of R202Q mutation differ between Greek and Japanese, but there is little difference between FMF patients and healthy controls in the rate of heterozygosity of R202Q. It is thus, thought that the heterozygosity of the R202Q mutation does not play a significant role in FMF. On the other hand, homozygosity of the R202Q mutation is strongly associated with FMF. However, few reports have so far analyzed the impact of the L110P mutation.

Therefore, the reasons why FMF develops in the elderly remain unclear. More analysis of the association between the mutations of MEFV, the onset of FMF, and the frequency of febrile episodes is needed. However, the present case suggests that FMF should be considered in cases of unknown fever regardless of the patient's age.

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

References

1. Bernot A, da Silva C, Petit J-L, et al. Non founder mutations in the *MEFV* gene establish this gene as the cause of familial Mediterranean fever (FMF). Hum Mol Genet **7**: 1317-1325, 1998.
2. Lidar M, Pras M, Langvitz P, Livneh A. Thoracic and lung involvement in familial Mediterranean fever (FMF). Clin Chest Med **23**: 505-511, 2002.
3. Ben-Chetrit E, Levy M. Familial Mediterranean fever. Lancet **351**: 659-664, 1998.
4. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever: A survey of 470 cases and review of the literature. Am J Med **43**: 227-253, 1967.
5. Kawabata H, Murakami M, Nishikomori R, et al. A Japanese case of familial Mediterranean fever with MEFV gene mutation. Hokkaido Igaku Zasshi **84**: 419-422, 2009 (in Japanese, Abstract in English).
6. Sasaki K, Tahara T, Mitani K. Presentation of familial Mediterranean fever in heterozygous MEFV mutation triggered by immunosuppressive therapy for myelodysplastic syndrome. Int J Hematol **90**: 91-93, 2009.
7. Fukui N, Mukoyama M, Saito Y, et al. Systemic AA amyloidosis caused by familial Mediterranean fever and response to colchicines. Nippon Naika Gakkai Zasshi **97**: 3046-3048, 2008 (in Japanese).
8. Araki H, Onogi F, Ibuka T, Moriwaki H. A Japanese family with adult-onset familial Mediterranean fever and periodic episodes of high fever and abdominal pain. Nippon Shokakibyou Gakkai Zasshi **107**: 427-431, 2010 (in Japanese).

9. Sugiura T, Kawaguchi Y, Fujikawa S, et al. Familial Mediterranean fever in three Japanese patients, and a comparison of the frequency of MEFV gene mutations in Japanese and Mediterranean populations. Mod Rheumatol **18**: 57-59, 2008.
10. Nakamura A, Matsuda M, Tazawa K, Shimojima Y, Ikeda S. Successful treatment with infliximab and low-dose methotrexate in a Japanese patient with familial Mediterranean fever. Intern Med **46**: 1247-1249, 2007.
11. Kim S, Ikusaka M, Mikasa G, et al. Clinical study of 7 cases of familial Mediterranean fever with MEFV gene mutation. Intern Med **46**: 221-225, 2007.
12. Yamane T, Uchiyama K, Hata D, et al. A Japanese case of familial Mediterranean fever with onset in the fifties. Intern Med **45**: 515-517, 2006.
13. Suzuki T, Nakamura A, Yazaki M, Ikeda S. A Japanese case of familial Mediterranean fever with homozygosity for the pyrin E148 Q mutation. Intern Med **44**: 765-766, 2005.
14. Kotone-Miyahara Y, Takaori-Kondo A, Fukunaga K, et al. E148Q/M694I mutation in 3 Japanese patients with familial Mediterranean fever. Int J Hemaol **79**: 235-237, 2004.
15. Nakamura A, Yazaki M, Tokuda T, Hattori T, Ikeda S. A Japanese patient with familial Mediterranean fever associated with compound heterozygosity for pyrin variant E148Q/M694I. Intern Med **44**: 261-265, 2005.
16. Matsuda M, Nakamura A, Tsuchiya S, Yoshida T, Horie S, Ikeda S. Coexistence of familial Mediterranean fever and Behcet disease in a Japanese patient. Intern Med **45**: 799-800, 2006.
17. Masahide Y. Familial Mediterranean fever. Shinsyuishi **55**: 173-180, 2007.
18. Migita K, Koga T, Izumi Y, Miyashita T, Ishibashi H. Autoinflammatory disease: clinical and genetic aspects of familial Mediterranean fever. IRYO **63**: 363-369, 2009.
19. Cazeneuve C, Ajapetyan H, Papin S, et al. Identification of MEFV-independent modifying genetic factors for familial Mediterranean fever. Am J Hum Genet **67**: 1136-1143, 2000.
20. Giaglis S, Papadopoulos V, Kambas K, et al. MEFV alterations and population genetics analysis in a large cohort of Greek patients with familial Mediterranean fever. Clin Genet **71**: 458-467, 2007.
21. Yamaguchi K, Ikeda K, Ihara K, Takada H, Kusuhara K, Hara T. Lack of association between E148Q MEFV variant and Kawasaki disease. Hum Immunol **70**: 468-471, 2009.