【 CASE REPORT 】

Familial Mediterranean Fever Mutations in a Patient with Periodic Episodes of Systemic Pain Deriving from Cancer Bone Metastases

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Abstract:

Familial Mediterranean fever (FMF), the most common autoinflammatory disorder, is characterized by recurrent febrile attacks and polyserositis. FMF is caused by mutations in *MEFV*, which encodes pyrin. In this report, we present an atypical FMF case with E148Q/L110P mutations in *MEFV*. The patient experienced periodic episodes of systemic pain originating from prostate cancer bone metastases. The pain attacks were prevented by continuous prophylactic therapy with colchicine. In this case, the presence of atypical FMF may have modulated the clinical manifestations of cancer bone metastases. To our knowledge, this is the first report to demonstrate the potential modulatory effect of *MEFV* mutations on cancer manifestations.

Key words: cancer bone metastases, colchicine, familial Mediterranean fever, pain attack

Introduction

Familial Mediterranean fever (FMF), a recessively inherited inflammatory disorder, is characterized by recurrent episodes of a fever, peritonitis, pleuritis, rashes, and arthritis. FMF is most prevalent around the Mediterranean basin (1). However, an increasing number of FMF patients have been reported in countries of other ethnic roots, such as Japan (2).

FMF is caused by mutations in the *MEFV* gene, located on chromosome 16, which encodes pyrin, a regulator of inflammasomes (3). Among approximately 310 sequence variants in *MEFV* reported worldwide, the most common variant in Japanese FMF patients is E148Q in exon 2, followed by M694I in exon 10 and L110P in exon 2 (2, 4). In contrast, M694V, M680I, V726A, and M694I in exon 10 are frequently detected in the eastern Mediterranean regions (3). Pyrin regulates caspase 1 activation and subsequent interleukin (IL)-1β production, and mutated pyrin causes an exaggerated inflammatory response by secreting large amounts of IL-1β, suggesting that the mutations are probably gain-of-function mutations (3). The first-line treatment for FMF is colchicine, which is generally a safe and well-tolerated drug. Anti-IL-1 drugs seem to be a promising second-line treatment in refractory or intolerant patients (3).

We herein report an atypical FMF patient with periodic systemic pain that might have been triggered by bone metastases from prostate cancer.

Case Report

A 62-year-old man was referred to our hospital because of periodic episodes of severe systemic myalgia and arthralgia, particularly on the back, with a mild fever, fatigue, and body weight loss. The pain attack, which had occurred four times over the latest six months before his visit, usually persisted for several days and spontaneously remitted. Neither non-steroidal anti-inflammatory drugs nor pregabalin relieved his pain. He had no remarkable family history or personal history of diseases.

On his first visit to our hospital, he complained of severe systemic myalgia and arthralgia in the absence of a fever. A physical examination revealed anemic palpebral conjunctiva, without any other abnormalities. As shown in Table, the laboratory data indicated moderate anemia, immature

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Table.   Laboratory Findings.

Peripheral blood counts		Biochemistry			
WBC	4,670 /μL	TP	6.6 g/dL	UA	4.4 mg/dL
Neu	68.0 %	ALB	2.7 g/dL	TC	152 mg/dL
Ly	22.0 %	BUN	17 mg/dL	TG	54 mg/dL
Mono	6.0 %	Cre	0.63 mg/dL	Na	140 mEq/L
Eosino	1.0 %	T-bil	0.3 mg/dL	K	4.4 mEq/L
Baso	0.0 %	AST	80 U/L	Cl	104 mEq/L
Metamyelo	2.0 %	ALT	64 U/L	CRP	20.3 mg/dL
Myelo	1.0 %	LDH	385 U/L	RF	<8.0 U/mL
RBC	320×10⁴ /μL	ALP	741 U/L	ANA	<×40
Hb	8.6 g/dL	γ-GTP	55 U/L	PSA	2,224 ng/mL
Ht	26.4 %	AMY	38 U/L		
Plt	29.3×10⁴ /μL	CK	76 U/L		

WBC: white blood cell count, Neu: neutrophil, Ly: lymphocyte, Mono: monocyte, Eosino: eosinophil, Baso: basophil, Metamyelo: metamyelocyte, Myelo: myelocyte, RBC: red blood cell count, Hb: hemoglobin, Ht: hematocrit, Plt: platelets, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, T-bil: total bilirubin, AST: asparate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, AMY: amylase, CK: creatine kinase, UA: uric acid, TC: total cholesterol, TG: triglyceride, CRP: C-reactive protein, RF: rheumatoid factor, ANA: anti-nuclear antibody, PSA: prostate-specific antigen
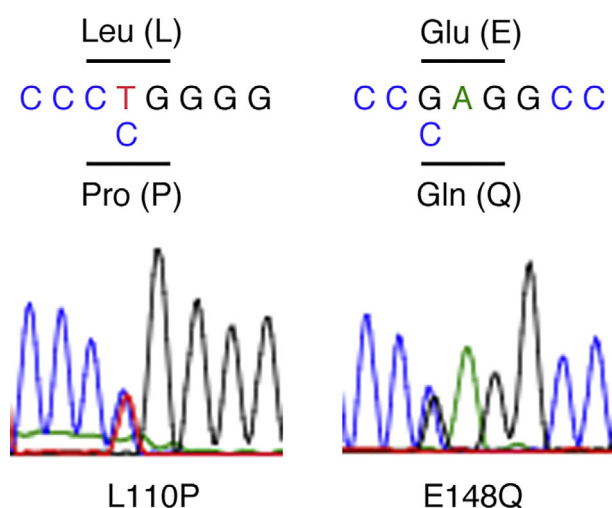

Figure 1.   *MEFV* mutations in exon 2. Heterozygous E148Q and L110P mutations were detected in the peripheral blood of the patient.

myeloid cells in the peripheral blood, and a strong inflammatory reaction irrespective of normal body temperature. The hematological abnormalities prompted us to perform a bone marrow biopsy, which revealed hypercellular marrow with fibrosis (MF-2 grade) but without obvious blast cells. The genetic test did not detect a Janus kinase 2 mutation V617F that leads to myeloproliferative neoplasms. Therefore, the bone marrow fibrosis observed was considered to be a secondary change associated with inflammation.

The recurrent episodes of pain were reminiscent of FMF. Indeed, the regular use of colchicine at a daily dose of 1 mg dramatically ameliorated the pain. Furthermore, the inflammatory reaction, as manifested by a high C-reactive protein

level, was completely suppressed by the treatment. Therefore, we performed a mutational analysis of *MEFV*. The patient provided his written informed consent for participation in an institutional review board-approved protocol at Kyoto University Hospital. The sequencing analysis revealed two heterozygous missense mutations, L110P and E148Q, in exon 2 of *MEFV*, in the genomic DNA extracted from the peripheral blood of the patient (Fig. 1).

The patient also underwent ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography (CT) imaging to determine the primary lesions causing the systemic pain. The FDG uptake was dramatically increased in almost all bones, reminiscent of metastatic bone cancer (Fig. 2). Given the high value of prostate-specific antigen (2,224 ng/mL) and malignant findings on prostate biopsy specimens, the patient was ultimately diagnosed with prostate cancer with systemic bone metastases. Since receiving hormone therapy for advanced prostate cancer, he has never experienced periodic pain attacks, suggesting that this symptom was associated with prostate cancer bone metastases.

Given these findings, we speculate that the clinical manifestations of prostate cancer with bone metastases might have been modified by the presence of atypical FMF in this case, thereby leading to the occurrence of periodic pain attacks. To our knowledge, this is the first report to describe the potential effects of *MEFV* mutations on cancer manifestations.

Discussion

In this report, we presented an atypical FMF case with *MEFV* mutations (E148Q/L110P) that might have modulated

Figure 2. **¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging. Note that almost all bones show an increased FDG uptake.**

the clinical manifestations of prostate cancer bone metastases. The presence of atypical FMF was further verified by the clinical finding that continuous prophylactic therapy with colchicine prevented the pain attacks.

The hallmarks of typical FMF are recurrent febrile attacks (>38℃) accompanied by polyserositis, lasting 1-3 days, and remitting spontaneously. The clinical symptoms observed in our case were periodic systemic myalgia and arthralgia in the absence of a high-grade fever. Thus, our case was unlikely to be a typical FMF case in the clinical setting. However, the mutational analysis of *MEFV* revealed E148Q/L110P mutations in exon 2 but no mutations in exon 10. Given the mutations in exon 2 and favorable responses to colchicine, the patient was ultimately diagnosed with atypical FMF according to the diagnostic criteria proposed by the Ministry of Health, Labor, and Welfare of Japan (Research on Measures for Intractable Diseases).

The mutations detected in our case were E148Q/L110P (exon 2) compound heterozygous mutations, which are prevalent in Japanese FMF patients, but not in Mediterranean patients. The E148Q mutation is the most common *MEFV* variant in Japan (2, 4). The L110P mutation, a frequent variant in Japan, is always associated with E148Q, and there are no marked differences in the clinical picture between E148Q/L110P and E148Q alone (4). The significance of the E148Q variant as a causative factor for FMF is still a matter of debate. The allele frequency of E148Q is high, even in healthy individuals; therefore, the E148Q variant is considered to be a benign polymorphism (5, 6). However, several studies have shown that patients with homozygous E148Q or compound heterozygous E148Q with other *MEFV* mutations exhibit an FMF-like phenotype, and their clinical course is relatively mild (7, 8). In Japan, FMF pa-

tients have a higher prevalence of E148Q than healthy individuals (2). Therefore, it is tempting to speculate that the E148Q mutation may be a disease-modifying factor, rather than a disease-causing factor. This idea may be supported by our patient, who developed periodic FMF-like symptoms at an older age (>60 years) and in combination with prostate cancer bone metastases.

The systemic pain in the present patient may have been attributable to two factors: prostate cancer bone metastases and inflammation by atypical FMF. This idea is substantiated by the fact that the systemic pain was efficiently suppressed by hormone therapy and colchicine administration. Recently, a large cohort study from Israel showed that FMF patients have a significantly lower incidence of cancer, including prostate cancer, than the general population of Israel, suggesting that the presence of FMF may not contribute to the development of cancer itself (9). In this light, the primary cause of systemic pain in our case would be prostate cancer bone metastases. Prostate cancer has a propensity to metastasize to the bones, and bone metastases are the primary cause of disability and a reduced quality of life. Notably, prostate cancer-induced bone pain is generally persistent, so the periodic pain attacks observed in our case are unusual (10). We therefore speculate that the presence of atypical FMF with E148Q/L110P mutations might have elicited an exaggerated inflammatory response, thereby periodically amplifying the systemic pain induced by prostate cancer bone metastases and resulting in severe periodic pain attacks.

This unique effect of *MEFV* mutations on cancer manifestations has not been reported elsewhere. A detailed analysis is required for a comprehensive understanding of how *MEFV* mutations modulate the symptoms caused by other organic diseases, such as cancers.

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

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