Editors' Choice

CASE REPORT

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Myelodysplastic syndrome with trisomy 8 presenting periodic fever and multiple *MEFV* gene variants outside exon 10: a case report

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ABSTRACT

Myelodysplastic syndrome is associated with the development of autoinflammatory conditions, such as recurrent fever, polymyalgia, arthralgia, and erythema. Trisomy 8 is a common chromosomal abnormality in patients with myelodysplastic syndrome. Myelodysplastic syndrome with trisomy 8 involves autoinflammatory conditions, especially Behçet's disease-like symptoms with intestinal mucosal damage. *MEFV* variants, particularly those in exon 10, are pathogenic in familial Mediterranean fever, the most common autoinflammatory disease, presenting typical symptoms such as periodic fever and pleuritis/pericarditis/peritonitis. *MEFV* variants outside exon 10 are common in Japanese patients with familial Mediterranean fever and are associated with atypical symptoms, including myalgia and erythema. *MEFV* variants in myelodysplastic syndrome with trisomy 8 have rarely been investigated, although myelodysplastic syndrome with trisomy 8 might develop autoinflammatory conditions similar to those in familial Mediterranean fever. We encountered a 67-year-old man who had myelodysplastic syndrome with trisomy 8 and multiple *MEFV* variants outside exon 10. He presented with periodic fever, as well as chest/abdominal pain, myalgia, and erythema, although the symptoms did not fulfill the diagnostic criteria of familial Mediterranean fever. We discussed the possibility that these symptoms are modified by *MEFV* variants outside exon 10 in myelodysplastic syndrome with trisomy 8.

Keywords: autoinflammatory disease, myelodysplastic syndrome, trisomy 8, *MEFV* gene

Abbreviations:
FMF: familial Mediterranean fever

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MDS: myelodysplastic syndrome
NF-κB: nuclear factor k-light-chain-enhancer of activated B cells

INTRODUCTION

Studies have shown that cellular genetic abnormalities (eg, chromosomal abnormalities and somatic variants) in patients with myelodysplastic syndrome (MDS) are associated with autoinflammatory disease.[1,2] Autoinflammatory disease is characterized by the dysregulation of innate immunity, in which myeloid lineage cells (ie, neutrophils) and monocyte lineage cells (ie, macrophages) are important cellular players.[1,2] The discovery of a novel adult-onset autoinflammatory disease associated with MDS has indicated the importance of characterizing the autoinflammatory disease in MDS cases.[2,3] Among 134 patients with MDS, 61 (46.3%) had an autoinflammatory condition, including recurrent fever, polymyalgia, arthralgia, arthritis, erythema, and pleural effusion.[1] Trisomy 8 is a common chromosomal abnormality in patients with MDS, occurring in approximately 10% of cases.[4] Trisomy 8 in patients with MDS causes autoinflammatory conditions, especially Behçet's disease-like symptoms (eg, fever, abdominal pain, and ulcerative intestinal lesions).[5-9] Only a few other inflammatory conditions are related to MDS trisomy 8: pyoderma gangrenosum, Sweet's syndrome, pulmonary alveolar proteinosis, and inflammatory arthritis.[10] Although some reports have suggested that trisomy 8 in patients with MDS leads to periodic fever and erythema nodosum without intestinal mucosal damage, these cases are currently recognized as being within the category of Behçet's disease-like symptoms.[8,9]

Gain-of-function variants in pyrin, a product of the *MEFV* gene, cause familial Mediterranean fever (FMF).[11] FMF is the most common autoinflammatory disease, affecting 120,000 people worldwide.[11] The Tel-Hashomer criteria described by Livneh et al are widely used to diagnose FMF.[12] They include five major criteria and four minor criteria. The five major criteria are: 1) peritonitis; 2) pleuritis or pericarditis; 3) monoarthritis; 4) fever alone; and 5) incomplete abdominal attacks differing from the typical attacks. The four minor criteria are: 1) and 2) incomplete attacks differing from the typical attacks, involving the chest or joints, respectively; 3) exertional leg pain; and 4) favorable response to colchicine. To diagnose FMF, one or more major criteria or two or more minor criteria should be met. Typical symptoms of FMF, including pleuritis and peritonitis, are related to variants in exon 10 of the *MEFV* gene.[13,14] Conversely, other *MEFV* variants (outside exon 10), which are more common in Japanese individuals, produce atypical symptoms, including myalgia and erythema.[13-15] Tanaka et al reported a patient with MDS who had trisomy 8 and an *MEFV* variant (outside exon 10) that manifested as periodic fevers and intestinal Behçet's disease-like symptoms.[16] However, to the best of our knowledge, no reports have been published describing MDS trisomy 8 presenting with periodic fever involving multiple *MEFV* variants (outside exon 10) with a suspicion of autoinflammatory conditions other than Behçet's disease-like symptoms. Here, we describe a patient with MDS and trisomy 8 exhibiting multiple *MEFV* variants outside exon 10, although his symptoms such as periodic fever, as well as chest/abdominal pain, myalgia, and erythema, did not fulfill the diagnostic criteria of FMF.

CASE PRESENTATION

Our patient, a 67-year-old Japanese man with no family history of periodic fever, presented to our hospital. At the age of 61 years, he had begun to experience fever "attacks" of 40°C at

intervals of approximately 4 weeks; the duration of each attack was approximately 5–7 days. Symptoms were right anterior chest pain, left posterior back pain, abdominal pain, upper- and lower-extremity myalgia, and bilateral leg erythema. He did not experience oral aphtha/uveitis/genital ulcers. During each fever attack, thrombocytopenia and macrocytic anemia appeared (platelets 13.5×10^4/μL; hemoglobin 7.7 g/dL at admission), along with an elevated inflammatory response (C-reactive protein of 22.34 mg/dL at admission); however, his symptoms consistently resolved spontaneously (Table 1). Bone marrow examination revealed orthomorphic to partially

Table 1 Laboratory data upon hospital admission and serum cytokine analysis in a febrile period

Laboratory data on admission					
Complete blood count		Biochemistry		Immunologic test (continues)	
WBC	7700/μL	Total protein	7.9 g/dL	IgG	1,833 mg/dL
Neutrophils	78.5%	Albumin	3.3 g/dL	IgA	287 mg/dL
Lymphocytes	14.4%	Glucose	118 mg/dL	IgM	98 mg/dL
Atypical lymphocytes	1.0%	BUN	40.9 mg/dL	Genetic analysis	
Blasts	0%	Creatinine	1.54 mg/dL	Chromosomal analysis (G-band)	47, XY, +8 [18 cells/ 20 cells]
RBC	208×10^4/μL	Na	134 mEq/L	WT1 mRNA	170 copy/μg RNA
Hemoglobin	7.7 g/dL	K	3.9 mEq/L	HLA	A24, B7, B52, DR1, DR15
Hematocrit	23.9%	Cl	94 mEq/L	*MEFV* gene	E148Q (exon 2), heterozygous
MCV	114.9 fL	AST	33 U/L		R202Q (exon 2), heterozygous
Platelets	13.5×10^4/μL	ALT	16 U/L		S503C (exon 5), heterozygous
Coagulation		LDH	362 U/L	Serum cytokine (febrile)	
PT-INR	1.01	γ-GTP	20 U/L	TNF-α	3.46 pg/mL (NR 0.75–1.66 pg/mL)
APTT	30.3 seconds	CK	516 U/L	IL-1β	194 pg/mL (NR <10 pg/mL)
Fibrinogen	637 mg/dL	CRP	22.34 mg/dL	IL-6	35.5 pg/mL (NR <4.0 pg/mL)
D-dimer	0.67 μg/mL	Ferritin	2,318 ng/mL	IL-18	720 pg/mL (No suggested NR)
Endocrine		Vitamin B12	776 pg/mL		
TSH	1.6078 μU/mL	Folic acid	10.0 ng/mL		
Free T3	2.03 pg/mL	sIL-2R	842.0 U/mL		
Free T4	1.57 ng/dL	MMP-3	89.8 ng/mL		
Urine		HTLV-1 Ab	0.1 C.O.I		
U-glucose	(–)	Immunologic test			
U-protein	(–)	Anti-Tg Ab	22.4 IU/mL		
U-occult blood	(–)	Anti-TPO Ab	33 IU/mL		
		ANA	<×40		
		PR3-ANCA	<1.0 U/mL		
		MPO-ANCA	<1.0 U/mL		

ALT: alanine aminotransferase
ANA: anti-nucleolar antigen
Anti-Tg Ab: anti-thyroglobulin antibody
Anti-TPO Ab: anti-thyroid peroxidase antibody
APTT: activated partial thromboplastin time
AST: aspartate aminotransferase
BUN: blood urea nitrogen

CK: creatine kinase
Cl: chlorine
CRP: C-reactive protein
γ-GTP: γ-glutamyl transpeptidase
HLA: human leukocyte antigen
HTLV-1 Ab: human T-lymphotropic virus type 1 antibody
Ig: immunoglobulin
IL: interleukin
K: potassium
LDH: lactate dehydrogenase
MCV: mean corpuscular volume
MMP-3: matrix metalloprotease 3
MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibodies
Na: sodium
NR: normal range
PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibodies
PT-INR: prothrombin time-international normalized ratio
RBC: red blood cell
sIL-2R: serum interleukin-2 receptor
TNF-α: tumor necrosis factor-α
TSH: thyroid-stimulating hormone
WBC: white blood cell
WT1 mRNA: Wilms' tumor 1 gene mRNA

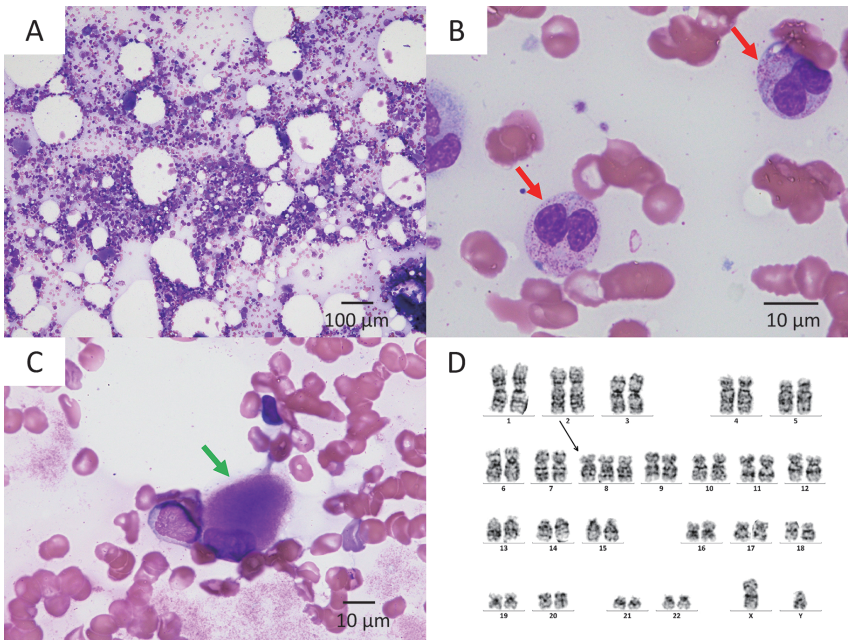

Fig. 1 Bone marrow smear images
Low-power field shows orthomorphic to partially hyperplastic bone marrow with increased megakaryocytes (Panel A; scale bar = 100 μm). High-power fields show specific morphological abnormalities indicative of myelodysplastic syndrome with hypo-segmented mature neutrophils (red arrows) (Panel B; scale bar = 10 μm) and micro-megakaryocytes (green arrow) (Panel C; scale bar = 10 μm). Panels A–C depict Giemsa staining results. Black arrows indicate trisomy 8 (Panel D).

hyperplastic bone marrow with increased megakaryocytes and specific morphological abnormalities with hypo-segmented mature neutrophils and micro-megakaryocytes. Chromosomal analysis (G-band) revealed 47,XY,+8 in 18/20 cells. The patient was thus diagnosed with MDS-refractory cytopenia with multi-lineage dysplasia (ie, MDS-RCMD) and trisomy 8 (Fig. 1). Two sets of blood cultures were negative. Contrast-enhanced computed tomography and gallium-67 citrate scintigraphy showed no obvious findings regarding the origin of the fever. Upper and lower gastrointestinal endoscopy showed no malignant findings/ulcerative lesions. Enteroscopy was not performed because bloody/black stools never appeared. Skin biopsies of erythema and purpura on both legs showed no obvious vasculitis/neutrophilic infiltration. The patient exhibited gait disturbance as well as dysarthria, which became worse. The patient's general condition improved during afebrile periods, although neurological symptoms, including impaired gait and dysarthria, remained. There was muscle weakness in distal muscles but not in proximal muscles (eg, deltoid, iliopsoas, and quadriceps). Needle electromyography showed no obvious myogenic findings; there were no fibrillation potentials, positive sharp waves, or myogenic changes of motor unit potentials in proximal muscles (tested in deltoid, biceps, and quadriceps). Elevated creatinine kinase at admission was normalized without specific therapy. Head magnetic resonance imaging showed chronic cerebral ischemic changes, and spine magnetic resonance imaging showed osteoarthritis, as well as cervical and lumbar spinal canal stenosis (C3/4-6/7, L3/4, L4/5). The patient did not exhibit findings suggestive of meningitis on cerebrospinal fluid examination.

At the time of determining the therapeutic plan, no evidence suggested the cause of the periodic fever, such as bacterial infection, solid malignancy, myositis, meningitis, vasculitis, Sweet's syndrome, Behçet's disease, or tumor necrosis factor receptor-associated periodic syndrome (ie, TRAPS), except for MDS with trisomy 8. The symptoms of periodic fever, chest/abdominal/left

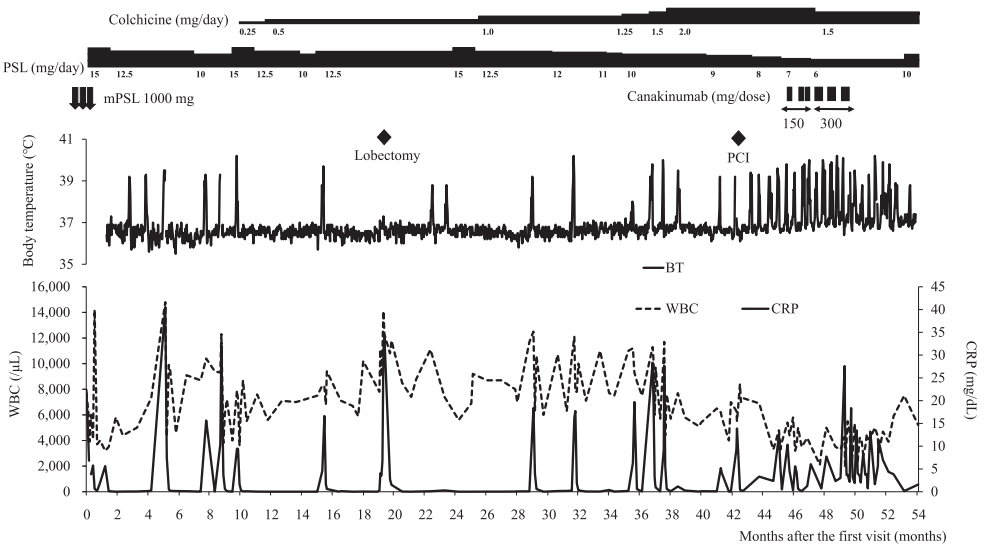

Fig. 2 Clinical course of this patient

BT: body temperature
CRP: C-reactive protein
mPSL: methylprednisolone
PCI: percutaneous coronary intervention
PSL: prednisolone
WBC: white blood cell

posterior back pain, upper- and lower-extremity myalgia, and bilateral leg erythema resembled FMF. We investigated only all 10 exons of the *MEFV* gene in the affected patient, based on reports of known variants according to the Infevers database (http://fmf.igh.cnrs.fr/ISSAID/infevers/).[17] These investigations revealed the heterozygotic variants E148Q (exon 2), R202Q (exon 2), and S503C (exon 5) in the *MEFV* gene.

The patient began 15 mg of prednisolone daily followed by pulse treatment (1 g of methylprednisolone per day for 3 consecutive days) considering the inflammatory condition in relation to MDS with trisomy 8, but his periodic fever did not disappear (Fig. 2). Then, we considered the possibility that the symptoms were related to FMF. Colchicine was initiated and corticosteroid treatment was gradually reduced, but the interval between the fever attacks shortened to approximately once every 2 weeks. Canakinumab treatment did not help to resolve the fever attacks and was therefore discontinued after 4 months. Currently, the patient continues to experience periodic fever at intervals of 1–3 months, despite the oral administration of 10 mg of prednisolone daily. The patient underwent lung lobectomy of the upper right lobe for adenocarcinoma and percutaneous coronary intervention for acute myocardial infarction during the follow-up period (at 19 and 42 months after the first visit to our hospital, respectively).

DISCUSSION

Our patient exhibited MDS with trisomy 8 and periodic fever complicated by chest/abdominal pain, myalgia, and erythema, although there were no specific findings, including pleuritis, peritonitis, arthritis, and vasculitis. Our patient was diagnosed with MDS-refractory cytopenia with multi-lineage dysplasia at the time of diagnosis in accordance with the 2008 World Health Organization criteria.[18] The symptoms of our patient resembled FMF, despite not fulfilling the criteria for this condition. Our patient exhibited typical FMF symptoms such as chest pain and exertional leg pain, which are compatible with the Tel-Hashomer criteria. However, a period of 5–7 febrile days was longer than that of typical attacks (lasting between 12 hours and 3 days in the criteria), and he did not exhibit typical FMF findings (eg, pleuritis, peritonitis, and monoarthritis) during periods of fever. Furthermore, a reduction in the frequency of fever attacks was finally achieved not by colchicine, but by corticosteroid. The Tel-Hashomer criteria do not strictly define a good response to colchicine, but the administration of this treatment is expected to reduce fever attack frequency and symptom severity.[11,12]

The patient had multiple *MEFV* variants in exons 2 and 5. *MEFV* variants have been associated with diseases other than FMF, such as vasculitis including IgA vasculitis, polyarteritis nodosa, Behçet's disease, and juvenile rheumatoid arthritis, although the exon sites were not reported.[19-21] *MEFV* variants in MDS were previously reported in Sweet's disease and patients with intestinal Behçet's disease-like symptoms.[16,22] These diseases were potential differential diagnoses of our patient. Although small bowel inflammation was not completely ruled out, none of these diseases sufficiently explained the periodic fever condition and clinical findings of the patient.

MDS, trisomy 8, and multiple *MEFV* gene variants can be etiologically associated with the activation of innate immunity. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is an important component of the innate immune response, and is also important in the pathogenesis of autoinflammation.[23,24] In MDS, the pathway through Toll-like receptors (TLRs), which activate NF-κB, is overactive.[25] Trisomy 8 has the possibility of being involved in the activation of NF-κB. A report suggests that trisomy 8 causes duplication of the IkB kinase β gene.[26] IkB kinase β is a protein that promotes apoptosis-resistant, proinflammatory, and proliferative pathways through NF-κB.[23,27] Pyrin, encoded by the *MEFV* gene, binds to and

deregulates IkBα, which originally functions to inactivate the NF-κB pathway, and results in the activation of NF-κB.[23,28]

The pathogenic significance of each *MEFV* variant in patients who have MDS with trisomy 8 is unclear because *MEFV* variants in MDS with trisomy 8 are rarely investigated in affected patients. Among the *MEFV* variants in FMF, E148Q and R202Q in exon 2 and S503C in exon 5 are assumed to have unknown or no pathogenicity.[29,30] However, E148Q in exon 2, in combination with non-exon 10 variants, may cause clinical manifestations of FMF (eg, periodic fevers, abdominal pain, and arthralgia).[31] The coexistence of E148Q and R202Q variants in exon 2 was also reported as a disease modifier in chronic myelogenous leukemia-associated Sweet's disease.[32] Multiple reports have suggested a pathogenic role for S503C in exon 5.[33-35] Therefore, although it is still controversial whether *MEFV* variants are involved in its pathogenesis, they may have a disease-modifying effect on the autoinflammatory pathology of MDS with trisomy 8.

This case report had several limitations. First, it was not determined whether the *MEFV* variants that occurred in this patient were germinal or somatic. In FMF, *MEFV* gene variants occur in the germline.[2,11] Therefore, it is natural that the patient was born with multiple *MEFV* variants but was asymptomatic and developed MDS trisomy 8 later in life. Conversely, Watad et al reported that somatic variants in MDS are a risk factor for autoinflammatory diseases.[1] A report also suggests that acquired *MEFV* variants occurred in patients with polycythemia myelofibrosis.[36] Thus, it is notable that the *MEFV* variants were caused by MDS along with trisomy 8 in our reported case. Second, the cause of our patient's neurological symptoms was unclear. Gait disturbance and dysarthria might be explained as neurological symptoms, which occur in approximately 14% of autoinflammatory diseases associated with MDS.[1] Because our patient exhibited thyroid autoantibodies, his neurological symptoms may also have been related to an autoimmune mechanism associated with MDS.[37] Furthermore, his chronic cerebral ischemia, as well as his cervical and lumbar spinal canal stenosis, may have led to a worse overall condition during periods of fever.

CONCLUSION

We encountered a patient who had MDS with trisomy 8 and exhibited multiple *MEFV* variants outside exon 10. However, the symptoms of the patient did not fulfill the Tel-Hashomer criteria for diagnosing FMF. The findings in this case suggest that MDS with trisomy 8 may be complicated by *MEFV* variants, which are related to the autoinflammatory pathogenesis.

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ETHICAL STATEMENT

This case report was approved by the university ethics review committee (approval number: 2018-0445), of which the first author was a former member. Written informed consent was obtained from the patient for the publication of this report.

CONFLICTS OF INTEREST STATEMENT

NT reports that his current affiliated institution was established by donations from Aichi Prefecture and Nagoya City, Japan, and that he has received grants and personal fees from Novartis Pharma KK outside the submitted work.

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Nothing to disclose.

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