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【 CASE REPORT 】

Coexistence of Mixed Connective Tissue Disease and Familial Mediterranean Fever in a Japanese Patient

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Abstract:
We herein report a Japanese patient with familial Mediterranean fever (FMF) who developed the clinical manifestations of mixed connective tissue disease (MCTD) and Sjögren's syndrome. The patient was a 36-year-old woman presenting with a periodic short-duration (2-3 days) fever and pleural pain. An Mediterranean fever *(MEFV)* gene analysis detected a complex allele mutation (P369S/R408Q) in exon 3 of the *MEFV* gene. Serological and clinical data showed the coexistence of MCTD and Sjögren's syndrome. Treatment with colchicine (1.0 mg/day) successfully eliminated febrile attack and pleuritis, leading to the diagnosis of FMF. Four months after the initiation of colchicine treatment, she presented with MCTD-related pulmonary artery hypertension. This is the first report of FMF coexisting with MCTD.

Key words: autoinflammatory disease, autoimmune disease, familial Mediterranean fever, mixed connective tissue disease, Sjögren's syndrome

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Introduction

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disease caused by *MEFV* gene mutations (1). FMF is characterized by short-duration (1-3 days) febrile attacks and polyserositis (2). Mixed connective tissue disease (MCTD) is an autoimmune disease that includes the clinical manifestations of systemic lupus erythematosus, scleroderma, and polymyositis along with high titers of anti-U1RNP antibodies (3). FMF and MCTD share rheumatic manifestations, such as a fever and pleural involvement.

Autoinflammatory and autoimmune diseases have been considered different disease spectra caused by the disruption of innate/adaptive immune homeostasis (4). MCTD and Sjögren's syndrome are both considered typical autoimmune diseases, whereas FMF is a prototypical autoinflammatory disease (1). Despite the different pathogenic mechanisms underlying MCTD and FMF, they share clinical manifestations, such as a fever, serositis, and muscle involvement. In the initial phase of the disease, MCTD remains subclinical, but the involvement of various organs, including in the form of serositis, myositis, and pulmonary artery hypertension (PAH), progressively develops (5).

In this case report, we describe a 36-year-old Japanese woman with FMF who presented with clinical manifestations of MCTD, such as serositis and PAH, shortly after the onset of FMF. This is the first case report describing a patient with FMF presenting with MCTD and Sjögren's syndrome; we also discuss this rare association.

Case Report

A 36-year-old Japanese woman who developed a periodic fever of more than 38℃ lasting 2-3 days, lymphadenopathy, and back pain was admitted to our department. The fever peaked at 40℃ but disappeared within 3 days. Febrile attack

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Table. Laboratory Findings and Cytokine/Chemokine Profile on Admission.

Peripheral blood		Serological tests	
Red blood cells	389×10⁴ /μL	C-reactive protein	10.42 mg/dL (<0.30)
Hemoglobin	12.2 g/dL	Erythrocyte sedimentation rate	53 mm/hr (<15)
Hematocrit	37.6 %	sIL-2R	721 U/mL (121-613)
Plt	24.4×10⁴ /μL	IgG	2,686 mg/dL (870-1,700)
White blood cells	3,600 /μL	IgA	232 mg/dL (110-410)
Neutriphil	71.0 %	IgM	57 mg/dL (35-220)
Eosinophil	0.0 %	Complement 3	103 mg/dL (65-135)
Monocyte	15.0 %	Complement 4	23 mg/dL (13-35)
Lymphocyte	14.0 %	ANA	×1,280 Speckled (<×40)
Baso	0.0 %	Anti-ds-DNA Ab	(-) (<9.9)
Blood chemistry		Anti-sm Ab	(-) (<6.9)
Total protein	8.0 g/dL	Anti-U1RNP Ab	142.0 U/mL (+) (<4.9)
Total bilirubin	0.5 mg/dL	Anti-SSA Ab	>240.0 U/mL (+) (<6.9)
Albumin	3.3 g/dL	Anti-SSB Ab	(-) (<6.9)
Glutamic-oxaloacetic transaminase	27 IU/L (13-33)	PR3-ANCA	(-) (<2.0 U/mL)
Glutamic-pyruvic transaminase	18 IU/L (8-42)	MPO-ANCA	(-) (<3.5 U/mL)
Lactate dehydrogenase	301 IU/L (119-260)	HBs Ag	(-)
Alkaline phosphatase	188 IU/L (80-250)	HCV Ab	(-)
Creatine Kinase	230 IU/L (62-287)	CMV antigenemia C10C11	(-)
Aldorase	11.2 U/mL	PVB19 IgM Ab	1.79 (+)
Blood urea nitrogen	19 mg/dL	PVB19 DNA	(-)
Cr	0.5 mg/dL		
Ferritin	209 ng/mL	Urinalysis	normal
Na	139 mEq/L		
K	4.2 mEq/L		
Cl	100 mEq/L		

sIL-2R: soluble interleukin-2 receptor, ANA: anti-nuclear antibody, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, HBsAg: hepatitis B virus surface antigen, HCV: hepatitis C virus, PVB 19 IgM Ab: Parvovirus B19 IgM antibody

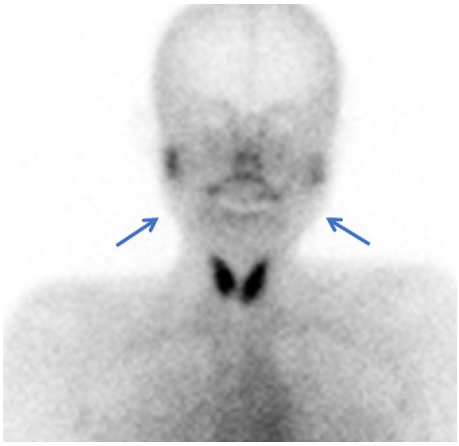

Figure 1. Salivary gland scintigraphy findings on admission. The uptake in the bilateral submandibular glands was delayed, and the concentration of the tracer was reduced (arrows), revealing a lack of salivary secretion.

was recognized at 34 years of age with a 3-month interval. Her medical history and family history were unremarkable.

On admission, her blood pressure was 163/110 mmHg, and her body temperature was 37.6℃. A physical examination revealed swollen hands, nailfold bleeding, and coarse crackles audible from the lower lung. The laboratory data were as follows (Table): white blood cells, 3,600/μL; platelets, 24.2×10⁴/μL; anti-nuclear antibody titer, 1,280 with a positive speckled pattern; and anti-UI-ribonucleoprotein (UI-RNP) antibody (index value, 142.0). Neither anti-dsDNA nor anti-Sm antibodies were detected. Normal levels of complement and high titers of anti-RNP antibodies were identified, consistent with a mixed picture of MCTD and Sjögren's syndrome. The diagnosis of MCTD was made based on the presence of a high titer of anti-RNP antibodies, swollen hands, and Raynaud's phenomenon (6). Sjögren's syndrome was suspected based on the presence of dry mouth and eyes. Saxon's test revealed saliva secretion of 0.74 g in 2 minutes. Scintigraphy of the salivary glands revealed a remarkably low accumulation (Fig. 1). Positivity for the antibody to SS-A/Ro was noted, with a high titer (Table). A diagnosis of Sjögren's syndrome was made because the patient met the revised Japanese criteria for this condition (7).

Chest radiography (Fig. 2A) and chest computed tomography (CT) (Fig. 3) on admission demonstrated fluctuating bilateral pleural effusions. However, the patient's symptoms began to spontaneously subside, and the pleural effusion disappeared within a week (Fig. 2B). A diagnosis of FMF was also suspected based on the presence of a periodic fever and pleuritis, so a genetic analysis of the *MEFV* gene

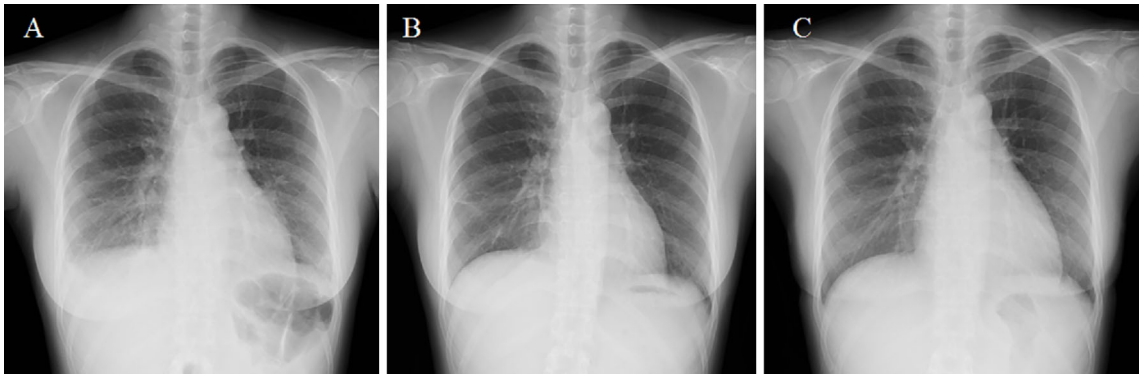

Figure 2. **Chronological changes in chest radiography. (A) Chest radiography findings on admission. There was pleural effusion in the right lung. (B) The pleural effusion disappeared eight days after admission. (C) Enlargement of the central pulmonary arteries and cardiomegaly four months after admission.**

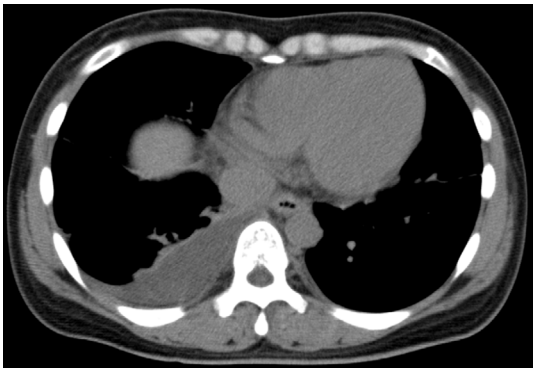

Figure 3. **Chest computed tomography (CT) findings on admission. There was pleural effusion in the lower lobe of the right lung.**

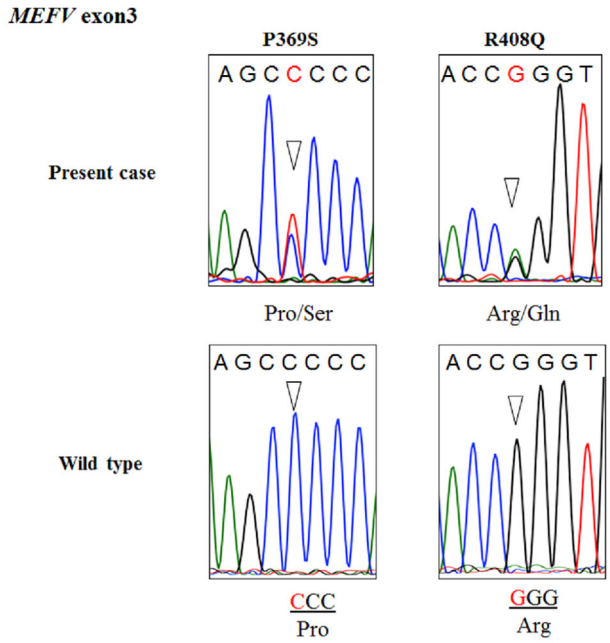

Figure 4. **The results of an *MEFV* gene analysis in a healthy control (wild type) and the present patient. In the patient, the C-to-T transition in codon 369 converted proline (P) to serine (S), and the G-to-A transition in codon 408 converted arginine (R) to glutamine (Q).**

was performed. This analysis showed a complex allele mutation (P369S/R408Q) in exon 3 of this gene (Fig. 4).

Against this background, we decided to treat her with colchicine. Shortly after starting the administration of colchicine at a dose of 0.5 mg/day, the patient's periodic fever abated and then disappeared. She was diagnosed with FMF in accordance with the diagnostic criteria of this condition (8). The elevated levels of C-reactive protein (CRP) and the erythrocyte sedimentation rate were also normalized after the colchicine therapy.

Four months later, the patient experienced progressive shortness of breath on physical effort. A second physical examination showed normotensive blood pressure (144/107 mmHg), slight tachycardia (118/min), and a low blood oxygen level [percutaneous oxygen saturation (SpO_2) 99%]. Neither jugular venous dilatation nor systemic edema was noted. Coarse crackles and low pulmonic valve closure sounds were detected. Laboratory examinations showed an elevated plasma brain natriuretic peptide (BNP) level (144.2 pg/mL) and slightly elevated levels of aspartate aminotransferase (AST) and alanine transaminase (ALT). Creatine kinase (CK) was elevated with a normal CK-MB level, indicating skeletal muscle injury. Magnetic resonance imaging (MRI; short T1 inversion recovery) showed a high intensity at the femoral muscles, indicating muscle inflammation (Fig. 5, arrows). Parvovirus B19 IgM antibody was positive; however, parvovirus B19 DNA was not detected by polymerase chain reaction (Table). Chest X-ray showed slightly enlarged pulmonary arteries and cardiomegaly (Fig. 2C). CT using intravenous contrast material showed subpleural reticulation in the lower lobe of the left lung. There was no evidence of pulmonary embolism. Electrocardiogram showed no apparent ST segment elevation or depression. Echocardiogram showed slight pericardial effusion and an ejection fraction of 66.3%, with an elevated digastric right ventricular pressure (39 mmHg). These clinical manifesta-

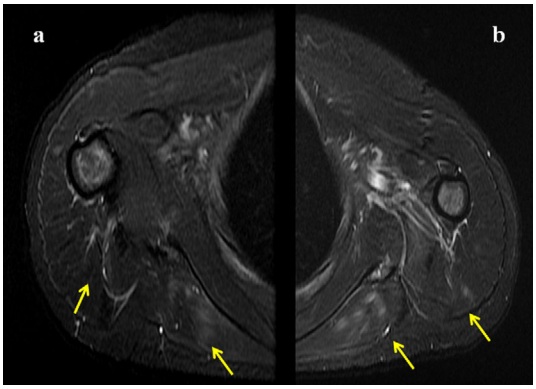

Figure 5. MRI findings on admission in the bilateral upper arms. Right upper arm (a) and left upper arm (b). T2-weighted STIR imaging showed hyperintensity in the muscle (arrows). MRI: magnetic resonance imaging, STIR: short-tau inversion recovery

tions were suggestive of MCTD-related pleuritis with inflammatory reaction and secondary PAH.

We considered performing right heart catheterization before treatment in order to diagnose PAH. Since the patient's condition was worsening, we decided that treatment should be started. Intravenous administration of methylprednisolone (1,000 mg/day) was performed for 3 days, after which the patient's symptoms quickly improved along with a decrease in the CRP level. After oral prednisolone was started at a dose of 30 mg/day, the clinical symptoms improved with the normalization of the laboratory data. The patient's dyspnea then ameliorated, and her plasma BNP level also declined after the initiation of steroid therapy. Right heart catheterization following steroid therapy demonstrated normal mPAP values (12 mmHg), with a normal pulmonary artery wedge pressure (5 mmHg), pulmonary vascular resistance (1.93 dyne.s.cm^3), and cardiac output (cardiac index 1.71 L/min/m^2). The digastric right ventricular pressure on echocardiogram was improved (20 mmHg).

On follow-up, her condition was found to have significantly improved and her creatinine kinase level had normalized, suggesting that the overlapping polymyositis had also subsided due to the steroid therapy.

Discussion

In this case report, we describe a Japanese patient with MCTD who carried a complex allele (P369S/R408Q) in exon 3 of the MEFV gene. Regarding the Tel Hashomer criteria (8), the patient met two major criteria (short-duration febrile attacks and pleuritis) and one minor criterion (response to colchicine), leading to a diagnosis of typical FMF. The complication of PAH was suspected because of the chest X-ray findings and the improvement of the right ventricular pressure on her echocardiogram. The P369S/R408Q mutation in exon 3 of the *MEFV* gene is mainly associated with an incomplete FMF phenotype and infrequently associated with the typical FMF phenotype (9), such as in the present case. The allele frequencies of P369S and R408Q were 1.8% and 1.8%, respectively, in typical FMF patients, compared to 14.7% and 14.7%, respectively, in incomplete FMF patients (10). Although this frequency is not very high, cases of typical FMF patients with this mutation have certainly been reported. In contrast, the respective allele frequencies of P369S and R408Q in healthy subjects are 4.0% and 3.3% (10), implying the low penetrance of exon 3 mutations (9). How this P369S/R408Q mutation is associated with the onset of FMF is unclear. Ryan et al. performed a functional analysis on P369S/R408Q (11). They noted that the B-box domain of pyrin encoded in exon 3 is necessary for the interaction with pyrin and proline serine threonine phosphatase interacting protein (PSTPIP1), but this mutation did not affect pyrin's interaction with PSTPIP1 (11). Since this mutation shows incomplete penetrance, other factors, including genetic factors and environmental factors, may influence the disease expression (12).

To our knowledge, no report has yet described the association between MCTD and exon 3. The coexistence of FMF and Sjögren's syndrome was previously reported (13). However, it is difficult to diagnose the concomitant association of FMF and MCTD, since such an association has not been previously reported. The major finding of this case report is that the possession of an *MEFV* mutation may modify the clinical course of MCTD, resulting in a proinflammatory phenotype, such as one characterized by pleuritis. The association of systemic lupus erythematosus (SLE) and FMF was previously reported (14, 15), with these reports suggesting that the *MEFV* mutation may modify the SLE disease phenotype, contributing to an excess of inflammatory manifestations, such as a fever and pleuritis (15). It is possible that MCTD-related serositis is precipitated in the affected organs, since the possession of an *MEFV* mutation modifies a variety of types of inflammation (16). Therefore, FMF overlap or an *MEFV* mutation in MCTD patients may modify the disease phenotype, introducing enhanced inflammatory episodes, including pleural and muscle manifestations (17).

Alternatively, the pleuritis and febrile episodes may be manifestations of FMF. The fever and serosal involvement in FMF usually disappear within 1-3 days (18) but are prolonged in MCTD. If a patient with a periodic fever or pleuritic pain responds to colchicine, the co-occurrence of both FMF and MCTD should be considered. If there is no response to a maintenance dose of colchicine for febrile attacks, we can rule out the coexistence of FMF (19). In the present case, the preceding febrile attacks were abolished by colchicine, whereas the clinical effectiveness of steroid was clear in the second episode of pulmonary involvement, and a high dose of steroid was needed to control the subsequently developing PAH. Serosal involvement is common in FMF. However, pulmonary conditions, including pleuritis and PAH, appear to represent the visceral involvement of MCTD (20), since these conditions develop during colchicine treatment. In the present case, these visceral mani-

festations may have been caused by MCTD dominancy and thus fall on the autoimmune spectrum of MCTD. Therefore, the development of pleuritis despite colchicine treatment suggests that these manifestations may be caused by MCTD, not FMF-related serositis.

In a retrospective study of PAH at the Mayo Clinic, a single FMF case with PAH was described (21); however, the direct association of FMF and PAH appears to be rare. The present findings suggested that pulmonary hypertension in FMF may result from pulmonary amyloidosis (21). Similarly, the development of PAH under colchicine treatment suggests that this manifestation may be caused by MCTD and is not representative of FMF-related involvement. Further reports of individuals with FMF and MCTD will be required to confirm this suspicion.

The present patient was positive for parvovirus B19 antibody on admission. The clinical manifestations of parvovirus B19 infection include erythema infectiosum arthralgia, fatal death, and transient aplastic crisis in patients with a shortened red blood cell survival and persistent infection in immunocompromised people. Parvovirus B19 infection sometimes resembles autoimmune diseases, such as SLE (a fever, rash, arthralgia, myalgia, lymphadenopathy, anemia, hepatitis, hypocomplementemia and production of antinuclear antibody) (22). The findings in the present case were insufficient to diagnose parvovirus B19 infection because the patient's symptoms promptly improved by immunosuppressive therapy with steroid therapy and her parvovirus B19 DNA was negative. Parvovirus B19 IgM is sometimes cross-reacted in Epstein-Barr virus-viral capsid antigen antibody IgM, cytomegalovirus IgM and rheumatoid factor IgM (23). Doyle et al. reported that 1% of the US blood donor population showed parvovirus B19 IgM positivity (24). Our findings concerning parvovirus B19 IgM need to be interpreted very carefully.

In summary, FMF is occasionally associated with autoimmune diseases and may modify their clinical manifestations. This case underscores the possibility that an *MEFV* mutation may contribute to the clinical manifestations of MCTD, including serositis, via the alteration of the pyrin inflammasome function (25). When we encounter an unusual clinical course in a patient with MCTD, we should consider the coexistence of FMF and MCTD, even in a Japanese patient.

Ethical approval for this study was provided by the Ethics Committee of Fukushima Medical University, and written informed consent for this case report and the genetic analysis was obtained from the patient.

Author's disclosure of potential Conflicts of Interest (COI).
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