

[ CASE REPORT ]

## Transient and Recurrent Pulmonary Infiltrations Associated with Familial Mediterranean Fever

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### Abstract:

Chest symptoms and pleural effusion due to serositis in familial Mediterranean fever (FMF) are occasionally misdiagnosed as acute pneumonia. However, the actual pulmonary involvement of FMF is extremely rare. A 67-year-old man was referred to our hospital due to repeated and transient anterior chest pain. Chest images revealed a moderate amount of pericardial fluid, slight bilateral pleural effusion, and infiltrations in both lower lung lobes. Colchicine treatment without antibiotics rapidly improved these symptoms and findings. Pericarditis, pleurisy and the response to colchicine indicated FMF. FMF should be considered as a causative disease of pulmonary infiltrations, especially if it occurs repeatedly.

**Key words:** familial Mediterranean fever, pulmonary infiltrations, colchicine treatment, cryptogenic organizing pneumonia

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### Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease in which certain symptoms, such as a fever, arthralgia, and abdominal and chest pain due to serositis, recur and resolve spontaneously (1). Autoinflammatory diseases result from overproduction of proinflammatory cytokines induced by genetic mutations that encode key regulatory molecules of the innate immune system, and autoantibodies and autoreactive T cells are usually not identified.

The FMF disease-related gene is *MEFV* (Mediterranean Fever gene); regional differences in clinical symptoms, the *MEFV* mutation detection rate, and the genotype have also been reported (2, 3). Tsuchiya-Suzuki et al. reported that 36% of Japanese patients experienced their first attack after 20 years old, and the average time from the onset to the diagnosis was 13.2±11 years (3). In addition, many cases are mild and lack abdominal attack and arthritis (3). FMF has been recognized as an important disease in the differential

diagnosis of a fever of unknown origin, but the diagnosis is often difficult for atypical cases. Therefore, many undiagnosed cases are assumed to be present in Japan.

We herein report an atypical adult case of FMF in which bilateral lung infiltrations were observed during an attack of pericarditis and pleuritis but quickly disappeared with the introduction of colchicine treatment.

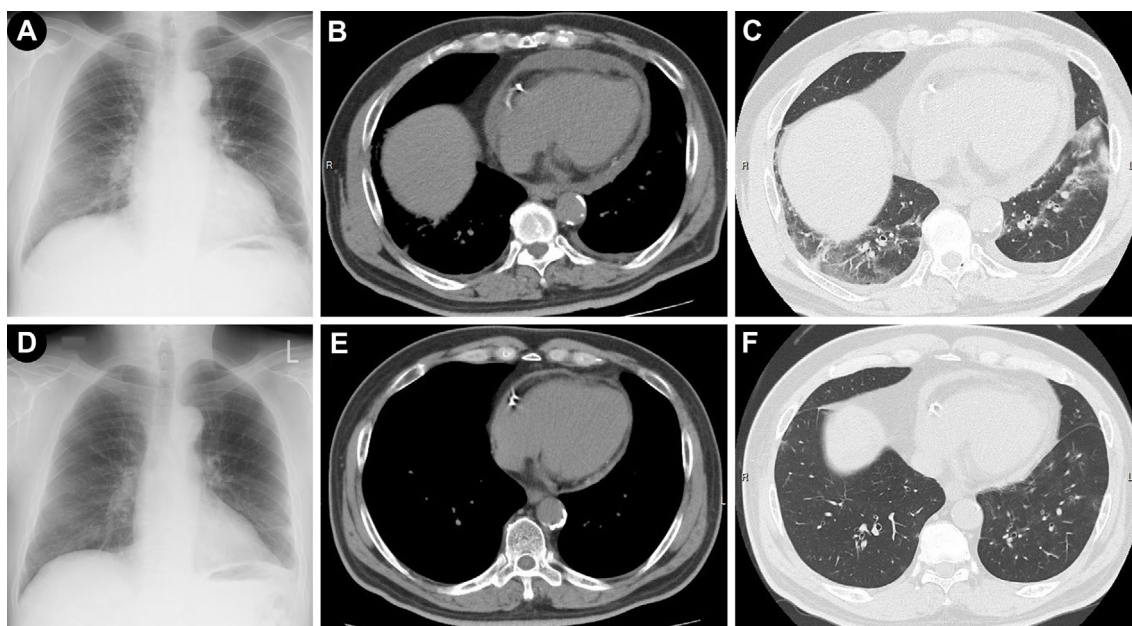
### Case Report

A 67-year-old man was referred to our hospital due to repeated and transient anterior chest pain lasting several years. The duration of the pain was less than 72 hours, and the frequency was at most once every 10 days. There were no other subjective symptoms suggestive of peritonitis, synovitis, testicular serositis, or meningitis. He was dealing with the pain using loxoprofen tablets but did not take them regularly. He had been treated for pneumonia with antibiotics (tazobactam/piperacillin and azithromycin) alone for four days at another hospital three years earlier. At that time, he experienced chest pain, fatigue, dyspnea, and low-grade fe-

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**Figure 1.** Time course of chest X-ray (A, D) and computed tomography (CT) (B, E: mediastinal window, C, F: lung parenchyma window) images (A-C: on admission, D: three days later, E, F: 12 days later). (A-C) An enlarged heart shadow, moderate amount of pericardial fluid, very slight bilateral pleural effusion, and infiltrations in both lower lung lobes. (D-F) Improvement in the enlarged heart shadow, pericardial fluid, pleural effusion, and lung infiltrations.

ver, but these symptoms disappeared within three days. On a physical examination at our hospital, his temperature was 37.3°C, pulse 100/min, blood pressure 120/72 mmHg and oxygen saturation 95%. Chest auscultation revealed no abnormalities.

Chest images on the first visit to our hospital revealed an enlarged heart shadow, moderate amount of pericardial fluid, slight bilateral pleural effusion, and infiltrations in both lower lung lobes (Fig. 1A-C). Pulmonary lesions mainly presented as ground-glass opacities partially accompanied by consolidation, and their distribution was non-segmental, not suggestive of a bacterial infection. The details of the distribution within the secondary lobules were unclear.

Initial laboratory data were as follows: red blood cell count  $469 \times 10^4/\mu\text{L}$ ; hemoglobin 14.7 g/dL; platelet count  $28.9 \times 10^4/\mu\text{L}$ ; white blood cell count 9,400/ $\mu\text{L}$  (neutrophils 78.6%; lymphocytes 10.7%; eosinophils 2.0%; monocytes 8.2%; basophils, 0.3%); creatine phosphokinase 46 IU/L; lactate dehydrogenase 143 IU/L; C-reactive protein (CRP) 16.7 (<0.3) mg/dL; brain natriuretic peptide 30.6 pg/mL; serum amyloid A (SAA) 1,030 (<8.0)  $\mu\text{g}/\text{mL}$ ; Krebs von den Lungen (KL) -6 296 U/mL (Table). Rheumatoid factor, anti-nuclear antibodies, anti-aminoacyl-transfer RNA synthetase antibodies, anti-DNA antibodies, anti-Smith antibodies, anti-topoisomerase I antibody antibodies, anti-ribonucleoprotein antibodies, anti-neutrophil cytoplasmic antibodies and anti-Sjögren's syndrome type A/B antibodies were negative (Table). Loop-mediated isothermal amplification for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using a nasopharyngeal swab and an interferon gamma release assay (T-SPOT) were also negative (Table).

Although echocardiography showed mild left ventricular dysfunction, he had no symptoms of heart failure or respiratory infection. The amount of pericardial fluid was not sufficient to perform the puncture safely. The patient did not have a recurrent (>3) fever ( $\geq 38^\circ\text{C}$ ) lasting a short period (between 12 hours and 3 days), which is required for complete attack as defined by the Tel-Hashomer criteria for the diagnosis of FMF. However, the presence of recurrent chest attacks likely due to pericarditis and pleurisy without a fever was consistent with incomplete attack defined by the criteria (4). The cause of the pulmonary infiltrations was unclear, but a bronchoscopic examination was not performed because physical stress during the procedure in a patient with pericardial effusion can induce heart failure. At this point, the diagnostic criteria had not been met, so FMF diagnostic treatment with colchicine but without antibiotics was started.

The patient's chest pain and enlarged heart shadow improved after 3 days, and computed tomography (CT) performed 12 days later showed that the pericardial fluid, pleural effusion, and lung infiltrations had almost disappeared (Fig. 1D-F). Bacterial or tuberculous infection and malignant diseases were considered unlikely as causes of pericarditis, since the clinical symptoms improved in a short time without chemotherapy. Good disease control was maintained with colchicine treatment. The levels of CRP and SAA while the patient was stable were 0.59 mg/dL and 12.1  $\mu\text{g}/\text{mL}$ , respectively. Serositis is generally a poor prognostic factor of autoimmune diseases, and the positive rate of autoantibodies in autoimmune diseases with serositis, including elderly cases, is high (5-9). However, in our patient, no autoantibodies suggesting systemic lupus erythematosus,

**Table. Clinical Laboratory Results.**

<u>Blood test</u>					
RBC	469×10 <sup>4</sup> /μL	CRP	16.7 mg/dL	Anti-adenovirus antibodies (CFT)	Negative
Hb	14.7 g/dL	BNP	30.6 pg/mL	Anti-mumps IgM antibodies (EIA)	Negative
WBC	9,400 /μL	SAA	1,030 μg/mL		
Neutrophils	78.6 %	KL-6	296 U/mL	T-SPOT	Negative
Lymphocytes	10.7 %				
Eosinophils	2.0 %	Rheumatoid factor	1 U/mL	<i>MEFV</i> mutation	Negative
Monocytes	8.2 %	ANA	×40		
Basophils	0.3 %	Anti-ARS Ab	Negative		
Plt	28.9×10 <sup>4</sup> /μL	Anti-DNA Ab	<2.0 IU/mL	<u>Urinary test</u>	
		Anti-Sm Ab	<1.0 U/mL	Qualitative analysis	
Albumin	3.5 g/dL	Anti-Topo I Ab	<1.0 U/mL	Gravity	1.036
AST	31 IU/L	Anti-RMP Ab	<2.0 U/mL	pH	5.5
ALT	30 IU/L	PR3-ANCA	<1.0 IU/mL	Protein	(1+)
LDH	143 IU/L	MPO-ANCA	<1.0 IU/mL	Glucose	(-)
CPK	46 IU/L	Anti-SSA Ab	<1.0 U/mL	Urobilinogen	(+/-)
CPK-MB	9 U/L	Anti-SSB Ab	<1.0 U/mL	Bilirubin	(-)
Troponin I	2.2 pg/mL			Ketones	(-)
BUN	15.9 mg/dL	IgG	1,587 mg/dL		
Creatinine	0.91 mg/dL	IgG4	89.6 mg/dL		
Na	138.1 mEq/L			<u>Nasopharyngeal swab</u>	
K	4.17 mEq/L			LAMP for SARS-CoV-2	Negative

RBC: red blood cell, Hb: hemoglobin, WBC: white blood cell, Plt: platelet, AST: aspartate amino transferase, ALT: alanine amino transferase, LDH: lactate dehydrogenase, CPK: creatine phosphokinase, CPK-MB: CPK-myocardial band, BUN: blood urea nitrogen, Na: sodium, K: potassium, Cl: chloride, CRP: C-reactive protein, BNP: brain natriuretic peptide, SAA: serum amyloid A, ANA: anti-nuclear antibodies, anti-ARS Ab: anti-aminoacyl-transfer RNA synthetase antibodies, Anti-DNA Ab: Anti-DNA antibodies, Anti-Sm Ab: Anti-Smith antibody, Anti-Topo I Ab: anti-topoisomerase I antibody, Anti-RNP Ab: anti-ribonucleoprotein antibodies, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibodies, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibodies, Anti-SSA Ab: anti-Sjögren's syndrome type A antibodies, Anti-SSB Ab: anti-Sjögren's syndrome type B antibodies, CFT: complement-fixation test, EIA: enzyme immunoassay, LAMP: Loop-mediated isothermal amplification

rheumatoid arthritis, systemic sclerosis, or mixed connective tissue disease that might lead to pleurisy were detected. In addition, the diagnostic criteria for these diseases were not met.

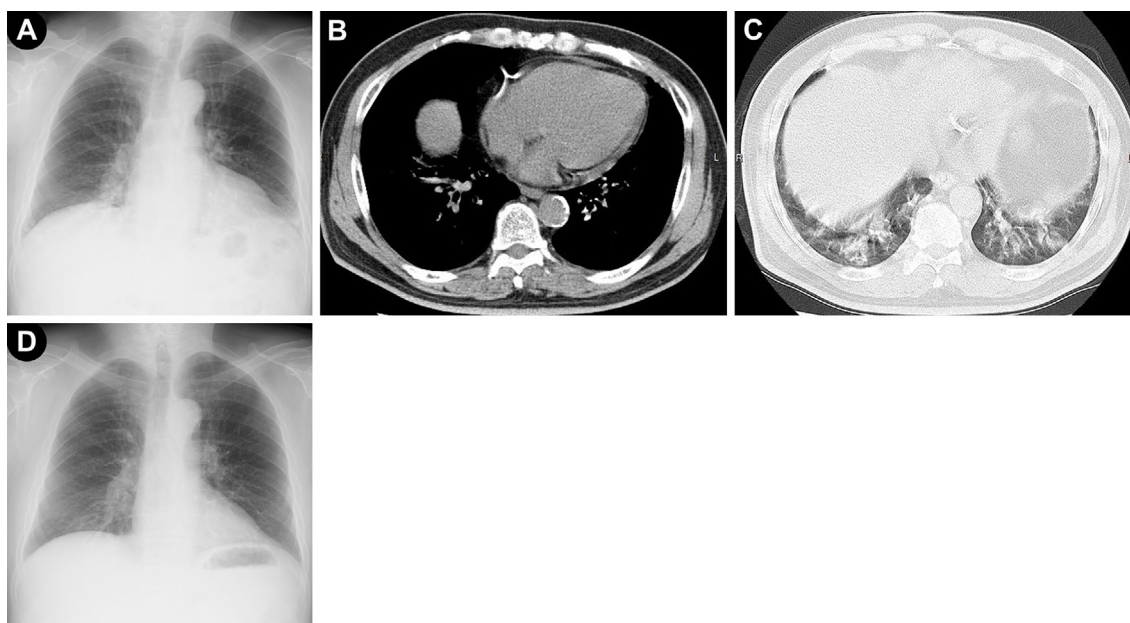
However, our patient did meet the Tel-Hashomer criteria, as he had two minor candidate criteria: incomplete chest attacks and a good response to colchicine (4). Chest images taken at another hospital at the onset of pneumonia, which were able to be reviewed after the start of colchicine treatment, showed a small amount of pericardial fluid. The pulmonary lesions at that time were similar to those on admission. The enlarged heart shadow improved after three days. A second CT procedure was not performed (Fig. 2A-D). This clinical course supported our diagnosis of FMF and suggested that pulmonary infiltrations recurred during the chest attacks. Later, an *MEFV* genotype analysis at Kazusa DNA Research Institute (Kisarazu, Japan) did not detect any known disease-associated mutations, such as *M694I*, *M680I*, *M694V*, or *V726A* in exon 10 or *E84K*, *E148Q*, *L110P*, *P369S*, *R408Q*, *R202Q*, *G304R*, or *S503C* in other exons. No low-frequency variants below 1% were detected (databases: gnomAD v3.1.1, iJGVD 8.3KJPN, ClinVar 20201031 and HDMG 2021.1).

## Discussion

In FMF, structural changes in pyrin due to mutations in the *MEFV* gene that encodes the protein induce the activation of associated inflammasome, leading to serositis attacks (10). However, 10-20% of patients with FMF have no identifiable mutations, and such cases are presumed to be associated with genetic abnormalities in *MEFV*-related metabolic pathways (11).

Laboratory data usually show a non-specific increase in inflammatory markers such as neutrophils, CRP, and SAA (1). In addition, thoracoscopic or laparoscopic examinations during an attack, including a biopsy of the serosal membranes, do not generally produce any specific findings. Therefore, a detailed understanding of the clinical course is important for the diagnosis. The evaluation of diagnostic treatment with colchicine, which is thought to suppress the polymerization of microtubules required for activation of pyrin inflammasome, is also needed (1, 4, 10). An early diagnosis is critical, as amyloidosis develops in patients with FMF who have been untreated for a long time, which can lead to renal failure (1).

Our patient met the Tel-Hashomer criteria because he had two minor candidate criteria: incomplete chest attacks (pericarditis and pleurisy without a fever) and a good response to



**Figure 2.** Chest X-ray (A, D) and computed tomography (CT) (B: mediastinal window, C: lung parenchyma window) images (A-C: on admission, D: three days later) three years earlier. (A-C) An enlarged heart shadow, small amount of pericardial fluid, and infiltrations in both lower lung lobes. (D) Improvement in the enlarged heart shadow.

colchicine (4). In monogenic autoinflammatory disease, where the association between genetic abnormalities and pathological conditions is clear, nonsteroidal anti-inflammatory drugs (NSAIDs) or steroids are generally effective, but not colchicine. Exceptionally, however, colchicine is effective against FMF, while NSAIDs/steroids are not (12). Second- and third-line therapeutic options for colchicine-resistant FMF are interleukin-1 (IL-1) inhibitors and tumor necrosis factor- $\alpha$  inhibitors (or immunosuppressive agents), respectively (12). In Japan, human anti-IL-1 $\beta$  monoclonal neutralizing antibody (canakinumab) is covered by health insurance for such patients (13). According to the Eurofever/the Paediatric Rheumatology International Trials Organisation (PRINTO) criteria, the three-day duration of episodes and absence of aphthous stomatitis, urticarial and maculopapular rash, and painful lymph nodes in our patient supported the diagnosis (14).

Respiratory involvement in FMF is mostly limited to pleurisy. Although direct pulmonary lesions due to secondary amyloidosis are rarely confirmed, a hypercoagulable state in the nephrotic phase of amyloid nephropathy may induce the development of pulmonary thromboembolism (15). A recent cohort study identified 3 cases of cryptogenic organizing pneumonia (COP) (0.3%) that seemed to be associated with FMF. However, the individual clinical course, including the time series of FMF attacks and COP, and actual chest images were not shown (16). In addition, one case of pulmonary necrotizing granuloma in a patient with FMF was reported. In the pulmonary lesion, pyrin-domain-containing protein-1 (NALP1)-positive inflammatory cell infiltration was observed, suggesting pulmonary involvement of FMF (17). FMF has been reported to be associated with

a wide spectrum of inflammatory disorders, such as inflammatory skin disease, glomerulonephritis, vasculitic condition, and inflammatory rheumatic disease (16). Various vasculitis complications in FMF are not rare, but there are few reports of lung lesions with vasculitis (15). FMF complicated with autoimmune disease is difficult to diagnose, but a case of FMF in a patient with polymyositis who had interstitial pneumonia was reported. In that case, lung lesions were observed during the FMF attack but disappeared quickly, suggesting FMF pulmonary involvement, although the details of any pathological changes are unknown.

Chest symptoms and pleural effusion in FMF, with secondary atelectasis in some cases, are occasionally misdiagnosed as acute pneumonia. In addition, FMF, as well as COP and eosinophilic pneumonia (EP), should be considered as causative diseases of pulmonary infiltrations, especially if they occur repeatedly.

The present study has several limitations. First, this case is classified as an atypical case according to the Japanese standard criteria of FMF by the research group of Ministry of Health, Labour and Welfare, as the patient did not present with complete attack or an *MEFV* mutation (18). Although the frequency of febrile attacks has been reported to be lower in patients with atypical FMF than in typical cases in Japan, the *MEFV* mutation was usually found in previously reported FMF cases without a fever (19-21). Second, since lung lesion tissue was not obtained, rare pathological conditions other than FMF, COP, and EP, which can resolve spontaneously without the use of colchicine, cannot be ruled out. For example, the possibility of mycoplasma and viral (other than SARS-CoV-2) infections, which can occasionally induce pericarditis, was not fully investigated. Alveolar hemor-

rhaging and hypersensitivity pneumonia may also be included in the differential diagnosis.

Further studies utilizing biopsy specimens from lung lesions at the time of the attack are appropriate, although the clinical settings in which such biopsies can be performed may be extremely rare.

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

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