

Familial Mediterranean Fever with Rheumatoid Arthritis Complicated by Pulmonary Paragonimiasis

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Abstract

A 42-year-old woman presented with an intermittent fever and chest and back pain, and an abnormal chest shadow was detected. She was diagnosed with paragonimiasis caused by *Paragonimus westermani*. Praziquantel therapy improved the abnormal chest shadow, but did not relieve her symptoms. She was also diagnosed with familial Mediterranean fever (FMF), and colchicine therapy resolved her symptoms. She subsequently developed arthralgia and morning stiffness in her hands. We also diagnosed the patient with rheumatoid arthritis (RA), and corticosteroid and salazosulfapyridine therapy improved her symptoms. The existence of paragonimiasis complicated the diagnosis of FMF. The coexistence of FMF and RA is very rare, but does exist.

Key words: familial Mediterranean fever, paragonimiasis, rheumatoid arthritis

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Introduction

Familial Mediterranean fever (FMF) is a hereditary periodic fever syndrome characterized by acute episodes of fever and painful manifestations (1, 2). Chest pain attacks are initially misdiagnosed as recurrent pneumonia in many patients with FMF. Pulmonary paragonimiasis is a food-borne parasitic disease characterized by cough, sputum, hemoptysis, and chest pain (3). The coexistence of FMF and rheumatoid arthritis (RA) is very rare (4-7).

We herein present a rare case of coexisting FMF and RA complicated by pulmonary paragonimiasis. Our patient presented with an intermittent fever and chest and back pain, and an abnormal chest shadow was detected. We diagnosed her with pulmonary paragonimiasis. Praziquantel therapy resolved the abnormal chest shadow on computed tomography (CT) and reduced the serum anti-*Paragonimus westermani* IgG antibody level. Her symptoms reappeared, however, after the completion of praziquantel therapy. The patient was also diagnosed with FMF according to recurrent symptoms

and a mutation analysis of the *MEFV* gene. Colchicine therapy resolved her recurrent serositis attacks. Three months after the start of colchicine therapy, her hands began to show signs of arthritis and her serum rheumatoid factor (RF) level was elevated. She was thus diagnosed with RA and corticosteroid and salazosulfapyridine therapy resolved her symptoms of arthritis.

Case Report

In June 2010, a 42-year-old woman was admitted to our hospital for a recurrent fever, chest and back pain, and an abnormal chest shadow on an X-ray. She had a past medical history of retinal detachment and tonsillectomy for a persistent tonsil infection. She occasionally cooked wild boar and deer and ate small amounts of wild boar and deer meat raw. She experienced a recurrent fever and chest and back pain continuing for several days every several months for the previous 2 years. She was treated with antibiotics according to a diagnosis of pleuritis each time her symptoms appeared. She was admitted to our hospital for a more detailed exami-

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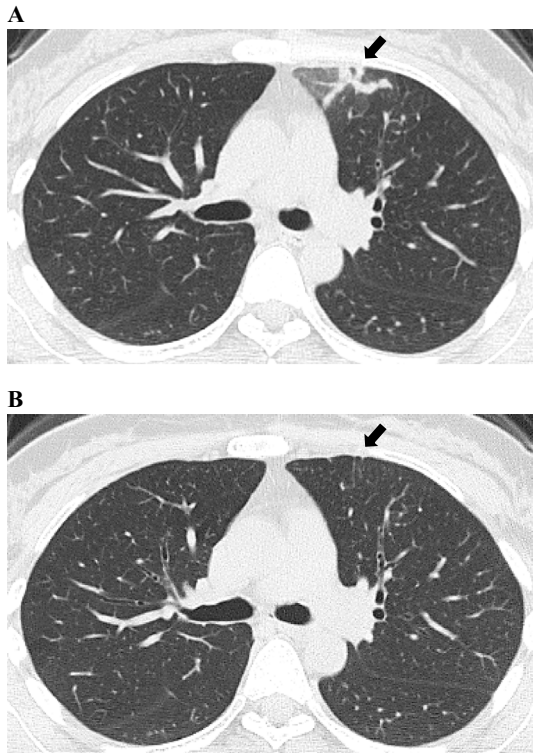


Figure. A: Chest computed tomography on admission showed a bundle shadow with a ground-glass opacity in the anterior segment of the left upper lobe (arrow). B: Four months after praziquantel therapy, the abnormal chest shadows were markedly diminished (arrow).

nation. On admission, her temperature was 36.3°C, pulse rate 69 beats/min, and respiratory rate 18 breaths/min. No crackles were heard in either lung field. Swelling of her hand joints was not observed. Laboratory data on admission included a white blood cell count of 3,950 cells/mm with 47.6% neutrophils, 39.5% lymphocytes, 6.6% eosinophils, 1.0% basophils, and a C-reactive protein level of 0.04 mg/dL. Her serum IgE level was elevated to 1,118 IU/mL. A chest CT scan detected a bundle shadow with a ground-glass opacity in the anterior segment of the left upper lobe (Figure A). A bronchoalveolar lavage (BAL) specimen revealed an elevated eosinophil ratio to 64.3%. A transbronchial lung biopsy showed slight infiltration of lymphocytes in a part of the alveolus. Her serum anti-*P. westermani* IgG antibody level was also elevated. According to these findings, we diagnosed her with pulmonary paragonimiasis and treated her with oral praziquantel therapy at a dose of 3,600 mg/day for 3 days. Four months after praziquantel therapy, her serum levels of IgE and anti-*P. westermani* IgG antibody were normal. A chest CT scan indicated an improvement of the bundle shadow with ground-glass opacity in the anterior segment of the left upper lobe (Figure B). Her symptoms also diminished. At 10 months, after completing praziquantel therapy, she again complained of a fever and chest and back pain. The anti-*P. westermani* IgG antibody titers remained normal at 12 months and 27 months after praziquantel therapy. The intermittent painful attacks appeared a total of five

times after praziquantel therapy. We suspected that the patient also had FMF with the manifestation of pleuritis. A mutation analysis of the *MEFV* gene revealed heterozygosity for the R314R allele in exon 3 and M694I in exon 10. We detected no mutation in *TNFRSF1A*. We diagnosed the patient with FMF according to the Tel-Hashomer criteria (8) and started her on a daily dose of oral colchicine therapy (0.5 mg/day) in August 2013. Thereafter, her fever and chest and back pain resolved. She complained of arthralgia and morning stiffness in her hands beginning in November 2013. Swelling was observed in both proximal interphalangeal joints, metacarpophalangeal joints, and wrists joints. Her serum RF level was elevated to 24 U/mL (cut-off value 10 U/mL). Treatment with oral prednisolone (15 mg/day) was initiated, and the dose was tapered over a short period. Her symptoms were relieved, but did not disappear. We restarted corticosteroid therapy with prednisolone at 10 mg/day and gradually tapered the dose to 1.0 mg/day. We diagnosed the patient with RA according to the ACR/EULAR 2010 classification criteria for RA, i.e., the involvement of 14 small joints (including proximal interphalangeal joints, metacarpophalangeal joints, and wrists joints), a high serum RF titer, and persistent arthritis (≥ 6 weeks) (9). We subsequently increased the dose of prednisolone to an alternate-day dosing of 10 mg and started salazosulfapyridine at a dose of 0.5 g/day, which was increased to 1.0 g/day. The current dose of prednisolone has been reduced to an alternate-day dosing of 5 mg and her symptoms have been relieved.

Discussion

FMF is a rare, inherited, autosomal recessive autoinflammatory disorder characterized by acute episodes of fever and painful manifestations, usually in the abdomen, chest, joint, skin, scrotum, and muscles (10). Approximately 40% of patients with FMF complain of pleuritic chest pain accompanied by a fever (1). Livneh et al. suggested that an erroneous diagnosis may postpone the diagnosis of FMF when chest attacks are the first manifestation of FMF (2). In many patients with FMF, chest pain attacks are misdiagnosed as pneumonia due to atelectasis accompanied by pleural inflammation (11-13). When non-FMF pulmonary disease coexists with FMF, it is not easy for clinicians to surmise the coexistence of both diseases at the initial diagnosis (14). Pulmonary paragonimiasis is a food-borne parasitic disease found in Southeast Asia. Most patients with pulmonary paragonimiasis caused by *P. westermani* present with respiratory symptoms, such as cough, sputum, hemoptysis, chest pain, dyspnea, and a fever (3). Because a fever and chest pain are common symptoms of both FMF and pulmonary paragonimiasis, it was difficult to conjecture the coexistence of these two diseases in our patient at the initial diagnosis.

Lung involvement in FMF, other than transient pleuritis, is extremely rare. Amyloidosis of the lung is rare and occurs in severe FMF cases associated with symptomatic amyloidosis of other organs (2). Vasculitis of the lung is possible in

Table. Clinical Characteristics of Patients with Coexistent Familial Mediterranean Fever and Rheumatoid Arthritis.

Reference No.	Onset age of FMF	Sex	Underlying disease	Symptoms of FMF	MEFV mutation	Therapy for FMF	Outcome of FMF
4	62	F	None	High fever, severe pain in the right hip for arthritis of right hip joints	Heterozygosis of E148Q in exon 2	Colchicine	Remission
5	42	F	IgA nephropathy	Recurrent high fever	Heterozygosis of E148Q/G304R in exon 2, P369S/R408Q in exon 3	Colchicine	Remission
6	45	M	None	Low-back pain for acute sacroiliitis	Heterozygosis of E148Q in exon 2 and A744S in exon 10	Colchicine	Remission
7	75	F	SLE	Chest pain, fever	Heterozygosis of E148Q in exon 2	Colchicine	Remission
7	52	F	None	Arthralgia, fever	Heterozygosis of E148Q/L110P in exon 2	Colchicine	Remission
Our case	40	F	Retinal hiatus, tonsillectomy for persistent tonsillitis	Fever, chest pain	Heterozygosis of R314R in exon 3, M694I in exon 10	Colchicine	Remission

FMF: familial mediterranean fever, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus

FMF due to the strong association of FMF with various vasculitides (15). Mesothelioma has been reported in relation to chronic or recurrent stimulation of the serous membrane (2). Additionally, cases of lung disease have been reported as the first manifestation of RA (16-19). Pulmonary necrobiotic rheumatoid nodules are a manifestation of the disease when they precede arthritis or the detection of circulating RF (16, 20, 21). The possibility of pulmonary involvement of FMF or RA preceded by lung disease had to be excluded in our case. FMF causes a massive influx of neutrophils and inflammation of the serosal membrane at the affected site (1, 2). Patients with RA had increased percentages of neutrophils and lymphocytes in the BAL fluid (22). *P. westermani* infection evokes eosinophilic inflammation in the affected organs (3). In our case, pulmonary lesions were likely due to pulmonary paragonimiasis, rather than pulmonary involvement of FMF or RA preceded by lung disease, because the ratio of eosinophils was elevated in the BAL fluid and the pulmonary lesions improved following praziquantel therapy.

The prevalence of FMF is extremely low in Japan (23). The coexistence of FMF and RA is very rare. Only five cases have been reported in the literature (4-7) (Table). As with our case, four of the five patients were Japanese (4, 5, 7). According to the Japanese national survey of FMF, the mean onset age of FMF in Japan was 19.6±15.9 years and 12.5% of patients were greater than or equal to 40

years of age (24). As in our case, the onset of FMF occurred at 40 years of age or older in all previous cases of coexistent FMF and RA (4-7). Older-age onset of FMF may be a specific characteristic of coexistent FMF and RA. It is unknown whether specific *MEFV* mutations could be the causative agent for coexistence of FMF and RA. Three studies reported that the *MEFV* mutation is related to the disease severity of RA (25-27). Rabinovich et al. suggested that carriers of the E148Q mutation alone had a significantly higher severity score of RA than non-carriers (27). All of the previous coexistent cases of FMF and RA had heterozygosity of E148Q in exon 2 in common (4-7). These results imply that E148Q might be related to the coexistence of FMF and RA. Unlike previously reported cases, our case had heterozygosity of R314R in exon 3 and M694I in exon 10. Only two cases of FMF patients with R314R have been reported in the literature (28). It is unknown whether R314R could be involved in the pathogenesis of RA because to date no study has examined the relationship between R314R and RA. M694I is one of the common *MEFV* mutations in Japanese patients with FMF (24, 29-31). Migita et al. reported that M694I was not observed among 126 Japanese RA patients and 76 Japanese controls (32).

We reported a case of coexistent FMF and RA complicated by pulmonary paragonimiasis. The patient was successfully treated with praziquantel therapy for pulmonary paragonimiasis and colchicine therapy for FMF. Thereafter,

arthritis of the hands developed as a symptom of RA and we initiated corticosteroid and salazosulfapyridine therapy. Our case provides two important lessons: ① the coexistence of infectious disease could create difficulty in the diagnosis of FMF due to common symptoms, and ② although the coexistence of FMF and RA is very rare, it does occur.

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

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