Acute Pericarditis as the First Manifestation of Familial Mediterranean Fever: A Possible Relationship with Idiopathic Recurrent Pericarditis

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Abstract

A 56-year-old man was admitted to our hospital due to periodic episodes of acute pericarditis. These episodes occurred monthly along with a high fever and elevation of the C-reactive protein (CRP) level. The patient became afebrile and his CRP level decreased following the administration of a non-steroidal anti-inflammatory drug. A mutation analysis revealed the heterozygote of the familial Mediterranean fever (FMF) gene (E84K, G304R). This finding confirmed our diagnosis, and we treated the patient with colchicine. He responded to treatment and has been visiting our hospital without disease recurrence. FMF should be included in the differential diagnosis of repeated episodes of pericarditis.

Key words: familial Mediterranean fever, recurrent pericarditis


Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder caused by a mutation of the Mediterranean fever gene (MEFV) (1). MEFV codes pyrin, a protein contained in neutrophils that inhibits the inflammatory response. Dysfunction of pyrin due to the mutation of MEFV results in the activation of neutrophils and acute onset of FMF. FMF is clinically characterized by recurrent episodes of fever associated with serositis. Although peritonitis is typically the first manifestation of FMF and is experienced by most patients during the course of the disease, the incidence of pericarditis is reported to be low (0.7-1.4%) in patients with FMF (2, 3). Furthermore, it is rare for recurrent pericarditis to be the first manifestation of FMF, with only two case reports of this symptomatology having been reported (4, 5).

Idiopathic recurrent pericarditis (IRP) is defined as repeated episodes of acute pericarditis of unknown etiology. The pathogenesis of IRP is controversial, and both autoimmune and autoinflammatory mechanisms have been proposed (6). Recently, it was demonstrated in a randomized trial that the administration of colchicine, which is effective for the treatment of FMF, reduces the recurrence rate after the initial attack of acute pericarditis (7). Therefore, controversy exists as to whether some patients with IRP may actually have FMF.

We herein report a case of genetically proven FMF in which the initial manifestation was recurrent pericarditis and discuss the relationship between FMF and IRP.

Case Report

A 56-year-old man was admitted to our hospital due to a high fever, chest pain and atopic dermatitis-like skin lesions. He had been in good health until three months before admission to our hospital, when he noticed a high fever (38-39°C) and chest pain that worsened in association with changes in position over seven days. He visited his family doctor. Laboratory results revealed marked elevation of the C-reactive protein (CRP) levels (26.56 mg/dL). Electrocardiogram (ECG) findings showed apparent ST-segment eleva-

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Figure 1. Electrocardiogram (ECG) showing apparent ST-segment elevation in the II, III, and aVF leads (A, B). The ECG findings normalized after therapy (C).

Electrocardiogram showing apparent ST-segment elevation in the II, III, and aVF leads (Fig. 1A). Meanwhile, echocardiography disclosed mild pericardial effusion, although the wall contraction was normal. Computed tomography (CT) of the chest showed mild pericardial effusion; however, no pleural effusion was detected. The patient was diagnosed with acute pericarditis and treated with a non-steroidal anti-inflammatory drug (NSAID). Glucocorticoid therapy was not administered during his hospital course. On the fifth hospital day, the patient became afebrile, and his chest pain was relieved. In addition, the CRP level decreased to 2.6 mg/dL. He was discharged on 28th hospital day without medications.

Three days after discharge, the patient’s fever and chest pain recurred, and he again visited his family doctor. The laboratory results revealed re-elevation of the CRP level (26.56 mg/dL). At this time, an antinuclear antibody (ANA) test was positive, with a titer of 1:80 (speckled pattern). He was treated as an outpatient with an NSAID. His fever and chest pain were subsequently relieved with a few days, and the CRP level decreased to 3.30 mg/dL. Treatment with aspirin (3.0 g daily) and colchicine (0.1 mg daily) was prescribed starting on 40 days after admission in order to prevent relapse. Because the patient’s remission continued for one month and his CRP level decreased to 0.8 mg/dL, both aspirin and colchicine were discontinued on 10 days before admission. However, six days later, the fever and chest pain recurred, and the CRP level increased to 24.35 mg/dL with moderate eosinophilia (14.5%). Treatment with aspirin and colchicine was again prescribed. The patient was referred to our hospital under suspicion of a diagnosis of collagen disease and admitted.

At the time of admission, the patient’s temperature was 38.2°C, his pulse rate was 125 beats/min and his blood pressure was 96/60 mmHg. His heart sounds were clear without audible murmurs or pericardial friction rub. His breath sounds were normal, and no crackles were detected. However, atopic dermatitis-like skin lesions were noted over the patient’s entire body. The remainder of the physical examination was unremarkable, and patient did not exhibit, erysipelas-like erythema, headaches, myalgia or abdominal pain due to peritonitis.

The laboratory results showed an elevated white blood cell count of 12,900/μL (71.5% neutrophils, 14.5% lymphocytes, 6.5% monocytes, 7.3% eosinophils, and 0.2% basophils), moderately elevated transaminase levels (aspartate aminotransferase 99 IU/L, alanine aminotransferase 65 IU/L): an elevated lactate dehydrogenase level 321 IU/L and a markedly elevated CRP level (26.56 mg/dL). In addition, serum protein electrophoresis revealed an increased γ globulin fraction (27.5%). ANA (1:1,280), rheumatoid factor (73 U/mL) and anti-SSA antibodies (240 U/mL) were positive. Complement, anti-double strand (ds) DNA antibodies, anti-SSB antibodies, anti-cyclic citrullinated peptide antibodies, proteinase 3-antineutrophil cytoplasmic antibodies, (ANCA), myeloperoxidase ANCA and antistreptolysin O (ASO) were all negative. An ECG revealed mild ST-segment elevation in the II, III and aVF leads (Fig. 1B), while CT of the chest showed mild pericardial effusion and mild left pleural effusion (Fig. 2A). Echocardiography revealed only mild pericardial effusion.

At the first visit, we considered the possibility of serositis due to a collagen disease such as SLE or Sjögren’s syndrome. Although ANA were positive, anti-ds DNA antibodies were negative and cytopenia was absent. In addition, while arthralgia was detected, the eruption was not specific for SLE, and no photosensitivity, oral ulcers, renal dysfunction or psychological disorders were detected. Therefore, the patient met only three criteria for the diagnosis of SLE. Furthermore, although anti-SSA antibodies were positive, symptoms of generalized dryness were lacking. In addition, a re-
A (before treatment)  

B (after treatment)  

**Figure 2.** Computed tomography of the chest showing mild pericardial effusion and mild left pleural effusion (A). The Pericardial and pleural effusion disappeared after therapy (B).

- **E84K (heterozygote)**  
- **G304R (heterozygote)**

*Figure 3.* The MEFV gene mutation analysis revealed the heterozygote of MEFV (E84K, G304R).

Markably elevated serum CRP level was noted, a finding not usually observed in these diseases. Most importantly, glucocorticoids are essential for the treatment of serositis due to SLE or Sjögren’s syndrome. Because the patient’s condition improved without glucocorticoid therapy, a diagnosis of SLE or Sjögren’s syndrome was unlikely as the cause of his pericarditis. In addition, a form of vasculitis, such as microscopic polyangiitis, was unlikely because, in the past, the patient’s condition improved without glucocorticoid treatment. A diagnosis of rheumatic fever was also unlikely because ASO was negative. The repeated episodes of pericarditis together with marked elevation of the CRP level led us to suspect the presence of FMF. We therefore continued treatment with colchicine without glucocorticoids. The next day, the patient became afebrile and his chest pain was gradually relieved.

The MEFV gene was assessed in order to confirm the diagnosis. A gene mutation analysis revealed the heterozygote of MEFV (E84K, G304R) (Fig. 3). Although these mutations are uncommon in FMF patients and their penetrance is low, they are considered to be disease-causing mutations. We thus confirmed the diagnosis of FMF (incomplete type) based on the Tel-Hashomer criteria. A differential diagnosis was performed in order to rule out the possibility of other autoinflammatory diseases. Hyper-IgD syndrome (HIDS) is characterized by periodic fevers, cervical lymphadenopathy, erythematous macules, abdominal pain, vomiting and arthralgia with persistent inflammation. TRAPS is characterized by periodic fevers, conjunctivitis, erythematous skin lesions, myalgia, arthralgia and abdominal pain, with the fever lasting over the long term. Based on patient’s features, the diagnosis of HIDS and TRAPS were ruled out clinically. Behcet’s disease was also ruled out based on the absence of oral ulcers, genital ulcers, erythema nodosum and uveitis. The colchicine treatment was continued, and the patient’s CRP level continued to decrease (Fig. 4). In addition, peri-
cardial and pleural effusion disappeared (Fig. 2B). The eosinophil count increased temporarily (19.4%), although it normalized (6.4%) after two weeks, and the atopic dermatitis-like skin lesions improved. Furthermore, the patient’s liver function subsequently normalized. He was discharged on 17th hospital day and has continued to visit our hospital as an outpatient while receiving colchicine treatment. During this time, his ECG findings normalized (Fig. 1C) and no disease recurrence has been detected.

**Discussion**

IRP is a challenging complication of acute pericarditis. The etiology of the first episode of acute pericarditis in most cases of IRP remains unknown, as microbiological examinations such as viral cultures of pericardial fluid, are usually not performed. Therefore, in most cases, the patient is diagnosed with idiopathic disease, although a viral infection is likely. It is speculated that the initial injury caused by the viral infection stimulates an immune reaction, causing IRP. Controversy exists as to whether the immune reaction is autoimmune or autoinflammatory in nature (6).

An autoimmune pathogenesis of IRP is suggested as autoantibodies including ANA (8) and anti-heart antibodies (9), are detected in 43.3% and 67.5% of subjects, respectively. However, the existence of an autoantibody does not necessarily mean that the autoantibody is pathogenic. In the present case, although the titer of ANA was initially low-positive (1:80), it increased to a high-titer (1:1,280) during the course of the disease. It is possible that activation of innate immune system may have induced these autoantibodies; that is, the autoantibodies may have simply been by-products of the disease. Furthermore, the patient exhibited moderate eosinophilia with atopic dermatitis-like skin lesions, which are not common features of FMF. However, these manifestations were ameliorated following the administration of colchicine, which inhibits the neutrophil function.

On the other hand, an autoinflammatory pathogenesis of IRP is also suggested as there are several similarities between IRP and FMF. First, colchicine is effective in treating both IRP and FMF. Second, although the incidence of pericarditis is thought to be low in patients with FMF, echocardiography has been reported to show pericardial involvement in up to 27% of subjects with FMF (10). Furthermore, pericarditis is the first and only manifestation of FMF in some patients. Therefore, it is natural to consider that at least some of the reported cases of IRP may have, in fact, been FMF. In the present case, pericarditis was the primary complication in our patient, and other frequently accompanied symptoms recognized in FMF were not observed. Presumably, the patient had a type of FMF in which pericarditis emerges at early stage. Recently, mutation analyses of MEFV have been proven useful in identifying patients with FMF (11). Although many mutations have been reported, the most frequent mutations are located in exon 10 (M694V, M680I, V726A and M694I) and exon 2 (E148Q) (12). Migita et al. reported that among 142 Japanese FMF patients, they found 12 carrying a heterozygous E84K mutation and four carrying a heterozygous G304 mutation who presented with a heterogeneous clinical phenotype (13). Meanwhile, Brucato et al. searched for MEFV mutations confined to exon 10 (using direct sequencing) and exon 2 (E148Q) (12). In contrast, some FMF patients, as in the present case (E84K, G304R), have neither E148Q mutations nor mutations in exon 10. Therefore, these patients may have in fact FMF, not IRP.

It has been reported that the difference in the prevalence of peritonitis and pleuritis is significant between FMF patients with exon 10 mutations and those without (13). Therefore, it is possible that there is a correlation between the phenotype and genotype. However, mutation analyses of two patients with FMF whose initial manifestation was recurrent pericarditis revealed heterozygote mutations of M694V/M680I (4) and E148Q/L695A (5), respectively. In addition,
the present patient had mutations of E84K and G304R. Meanwhile, 12 FMF patients with the E84K heterozygous mutation and four with G304 heterozygous mutation in Japan have been reported, without accompanying symptoms of pericarditis (15). To date, no specific mutations related to the onset of recurrent pericarditis in FMF patients have been found. However, further analyses of more cases are needed to clarify this issue.

Cantarini et al. reported that 6% of IRP patients have TNFRSF1A mutations (16). TNFRSF1A codes tumor necrosis factor (TNF) α, and the mutation of TNFRSF1A causes TRAPS, a common autoinflammatory disease. These observations suggest that the pathogenesis of IRP is autoinflammatory in nature, in at least a subset of patients. In the present case, if the mutation analysis had not been performed, the patient may have been diagnosed with IRP. Therefore, it is important to perform mutation analyses of MEFV in patients with IRP. Such analyses can be used to determine the proportion of patients with IRP who actually have FMF and identify differences in the prevalence of pericarditis according to differences in MEFV mutations.

In summary, we herein reported a case of FMF in which the initial manifestation was recurrent pericarditis. Mutation analyses of MEFV should be performed in patients with IRP in order to provide a proper diagnosis and treatment.

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

References


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