An Unusual Presentation of Familial Mediterranean Fever with Pericardial Tamponade: Report of Two Cases

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Abstract

Familial Mediterranean fever (FMF) is a hereditary autosomal recessive, auto inflammatory disease characterized by recurrent, self-limited short duration episodes of fever accompanied by inflammation of peritoneum, synovium and pleura. Pericardial involvement is a rare but well-known feature of the disease. However, pericardial effusion as an initial manifestation of FMF is very rare and few cases of pericardial tamponade were reported in the literature. Here we report two patients that presented initially with pericarditis and pericardial tamponade and diagnosed to have FMF based on clinical and laboratory findings and past history. They were started on colchicine therapy and their attacks disappeared. In conclusion, we suggest that FMF should also be considered in the differential diagnosis of patients with pericardial effusion especially in certain ethnic groups.

Key words: Familial mediterranean fever, pericarditis, tamponade

Introduction

Familial Mediterranean Fever (FMF) is a autosomal recessive, autoinflammatory disease characterized by recurrent, self-limited, short duration episodes of fever and serositis [1]. It is the most frequent periodic febrile syndrome; about 100,000 subjects are affected world-wide [2]. It affects predominantly Turks, non-Askenazi Jews, Armenians and Arabs. Recent studies have expanded the list of the populations affected by FMF to include Italians [3]. In the past, it was called ‘benign recurrent polyserositis’ and ‘familial paroxysmal polyserositis’ [4]. The Mediterranean Fever gene (MEFV) was isolated in 1997 and its encoded product Pyrin/Marenastrin was identified [5]. Mutated pyrin is associated with the loss of delicate control of the inflammatory pathways, which results in inflammation that predisposes FMF patients and carriers of the MEFV mutation to a pro-inflammatory state. This increased inflammation might lead to susceptibility to vascular co-morbidities in FMF patients. The frequent occurrence of Polyarteritis nodosa (PAN) with FMF has been reported and prevalence of PAN in FMF disease was shown [6]. Additionally, MEFV mutations are more frequent in HSP than in the general popula-
ation [7]. Colchicine is the single effective therapy; able to improve the quality of life by reduction or abolition of FMF attacks [8].

Pericardial effusion as an initial manifestation of FMF is very rare. Here, we report two patients with FMF presenting with acute pericarditis and pericardial tamponade as the initial symptom and diagnosed to have FMF during the follow-up period.

**Case 1**

A 5-year-old boy was admitted to the hospital with the complaints of abdominal and chest pain, dyspnea, and fever for a week. On the physical examination, his fever was 38˚C; tachycardia, tachypnea, distant heart sounds, suprasternal retractions, and hepatomegaly were detected.

On laboratory examination, hemoglobin 9.7 g/dl, white blood cell count (WBC) 30.100/mm³, platelets 487,000/mm³. The examination of acute phase reactants showed elevated erythrocyte sedimentation rate (ESR) (71 mm/h) and C-reactive protein (CRP) (135 mg/dl) (N:<8 mg/dl). Renal and liver function tests and urinalysis were normal. Chest X-ray revealed cardiomegaly and Pleural effusion (Figure 1). Low voltage of the QRS complexes and typical ST-T changes were detected on the electrocardiogram. Echocardiogram showed a large amount of pericardial effusion with right ventricular collapse, indicative of cardiac tamponade. Consequently, 250 ml exudative pericardial effusion was aspirated by pericardiocentesis. After pericardiocentesis, clinical findings were dramatically improved. Pericardial fluid examination revealed 90% neutrophil leukocytes, but not microorganism on gram stain. Pericardial fluid and blood glucose levels were 69 mg/dl and 109 mg/dl respectively, and pericardial fluid protein at undetermined high level. He was considered as purulent pericarditis and given intravenous antibiotics. On the 3rd day of the therapy, his body temperature was 39˚C, and increased pericardial effusion was detected on echocardiogram. His antibiotics were changed and 110 cc pericardial fluids was drained again. On the 5th day of the treatment, although he had still high fever and acute phase reactants, pericardial fluid cultures were found to be negative. Computerized tomography (CT) of thorax revealed bilateral pleural effusion and pericardial empyema. On the 15th day, echocardiogram showed unremarkable amount of pericardial effusion, and ESR and CRP turned to normal levels. However, his fever was still very high (41˚C) and purpuric eruptions developed on bilateral ankles. The patient was thought to have vasculitis. Serum C3 and C4 complement fractions were normal, antinuclear antibodies (ANA), anti-double stranded DNA antibodies, p and c-antineutrophilic cytoplasmic antibodies (ANCA) and anticardiolipin (ACL) IgM and IgG antibodies were negative. When his past medical history was re-evaluated, he had recurrent short term episodes of abdominal pain with fever and a brother having the same complaints. He was diagnosed as probable FMF and given colchicine at a dose of daily 2 tablets. His abdominal ultrasound showed bilateral enlarged kidneys, and hyperechogenic infarct or ischemic areas on the left (25x15mm) and right kidneys (27x15mm). Dimercaptosuccinic acid (DMSA) renal scan revealed bilateral heterogeneity but not any scar. Abdominal CT showed bilateral enlargement of kidneys consisting of numerous low contrast agent adsorbent hypodense areas (Figure 2). Since he was thought to have vasculitis associated with FMF, CT-renal angiography was performed but no vasculitic sign was detected. Renal biopsy was performed from hyperechogenic areas under the guideline of ultrasound and showed glomerular congestion, mesangial cell proliferation and interstitial neutrophil infiltration without immunofluorescent deposition,

![Figure 1. Cardiomegaly and bilateral pleural effusion](https://www.aprjournal.org/DOI: 10.5455/apr.070220121533)
vessel walls slightly thickened but didn’t show significant inflammation or necrotizing arteritis signs. He was given intravenous pulse methylprednisolone (30mg/kg/day, 3 days) and his clinical findings improved dramatically. He was discharged from the hospital with low dose oral prednisolone and colchicine. One month later, he had no complaints with normal laboratory findings. FMF gene analysis showed M694V heterozygous mutation. Three months later, his renal ultrasound and DMSA scan were completely normal and steroid treatment was gradually ended. The patient remained free of attacks with colchicine in the follow-up period of 26 months.

Case 2

A 15-year-old girl was referred to our hospital with the complaints of dyspnea, orthopnea, cough, chest pain and fever for five days. She had fever 39.5 °C, tachycardia and tachypnea. Physical examination showed distant heart sounds, suprasternal retractions with inspiration and hepatomegaly. Laboratory examination showed mild degree anemia and acute phase reactants showed elevated ESR, CRP and fibrinogen. Renal and liver function tests and urinalysis were normal. Chest X-ray revealed cardiomegaly and pleural effusion (Figure 3). A large pericardial effusion with the collapse of the right ventricle was noted on the transthoracic echocardiography. She was diagnosed as pericardial tamponade, and 450 ml exudative pericardial fluid was drained with a pericardial catheter. Pericardial fluid examination revealed 70% neutrophil leukocytes without any microorganisms on gram stain. Pericardial fluid and blood glucose levels were 71 mg/dl and 108 mg/dl respectively, and pericardial fluid protein level was very high (5.4 g/dl). Because of the possibility of purulent pericarditis, she was started on wide-spectrum antibiotic therapy. On the 4th day, all clinical findings and acute phase reactants returned to normal, pericardial effusion disappeared and pericardial catheter was removed. Pericardial fluid cultures were negative. She was discharged from the hospital after completing the treatment. One month later, she was readmitted with the complaints of fever, chest pain and dyspnea. Physical examination showed fever, tachycardia and tachypnea. Chest X-ray showed bilaterally pleural effusion. Echocardiogram revealed moderate pericardial effusion. On laboratory examination, WBC, ESR, CRP and fibrinogen were found very high. Transudative 300 ml pleural fluid was drained with thoracentesis. Two days later, she didn’t have any complaints, acute phase reactants returned to normal. When her past medical history was reevaluated, her parents were relatives, and she had recurrent abdominal pain and fever attacks. She was thought to have FMF and started on colchicine treatment (2 tablets daily). During the follow-up period of next two months, she came two more times with complaints of fever, shoulder pain and skin eruptions and had elevated acute phase reactants each time. FMF gene analysis showed R761H heterozygous mutation. Echocardiogram showed pericardial thickness without pericardial effusion. The dose of colchicine was increased to 3 tablets daily and she remained free of attacks.
attacks during the following 32 months.

**Discussion**

FMF is the most common autosomal recessive periodic disease. The onset of FMF usually occurs during childhood, with 60% of patients showing first symptoms before the age of 10 years [9]. Attacks usually last for 1-3 days, and a prominent feature in addition to fever is serositis and arthritis [10]. The disease is caused by mutations in the MEFV gene, which codes for the protein called pyrin. Although genotype analysis might support the diagnostic work-up, the identification of FMF remains essentially clinical, based on the history of self-limiting recurrent fever and serositis attacks that can be prevented by colchicine treatment [11]. Currently, 51 gene variants grouped in two hot spots of the MEFV gene are known [12]. Actually, about 75% of patients show single or no mutation [13].

The association of vasculitis as Henoch Schönlein purpura and polyarteritis nodosa (PAN) with FMF is well described. The prevalence of PAN is reported 6/100,000 for the general population but 9/1000 for FMF patients [14]. The pathogenesis of vasculitis in patients with FMF is unknown. The occurrence of circulating immune complexes, complement dysregulation and uncontrolled release of tumor necrosis factor might explain the immune-related mechanism.

A large proportion of FMF patients in the world live in Turkey. The estimated prevalence of FMF in Turkey is 1:1000, and the carrier rate is 1:5. The widest study about FMF was reported by the Turkish FMF Study Group [14]. In this study, 60 patients (2,4%) had at least one attack of pericarditis: 34 had definite (positive clinical and laboratory findings) and 26 probable pericarditis (diagnosis based on only clinical findings). Recurrent pericarditis was the initial and only manifestation of FMF in 2 patients in whom the diagnosis was supported by genetic analysis. The pericardial attacks resolved spontaneously in all patients except two. Urgent pericardiocentesis because of pericardial tamponade in one patient, and pericardectomy for the treatment of constrictive pericarditis in another patient were required. Zimand et al. [15] also reported a 16-year-old girl, presenting initially with pericarditis and life threatening pericardial tamponade, and developing characteristic clinical episodes of FMF few months later.

Our first case presented with prolonged fever and life-threatening pericardial effusion. Since analysis of pericardial fluid was compatible with exudate, he was given antimicrobial treatment. Because of fever lasting for 15 days, development of purpuric eruptions on the bilateral ankles together with renal ischemic areas on DMSA renal scan and abdominal CT, we considered that he might have vasculitis associated with FMF. Unfortunately, we couldn’t show any clue about vasculitis especially the polyarteritis nodosa. We found the p and c- anca antibodies negative and renal CT-angiography normal and biopsy findings didn’t support this diagnosis. He responded to iv pulse methylprednisolon therapy very well, and renal ischemic findings disappeared on control DMSA renal scan. Therefore, we thought that this patient had a vascular inflammation.

The second case had four pericardial effusion attacks during the follow-up period of 6 months. Unlike the first case, her attacks continued for at least 4 days, leading to the diagnosis of FMF more easily.

On FMF related serositis, the analysis of aspirated serosal fluid may show different variants from transudate to exudate, even septic-like pictures, but cultures for bacteria are always negative [16]. Pericardial tamponade as an initial manifestation of FMF is very rare and interesting. In the literature, only two cases were reported [14,15]. Additionally, contrary to expectations, both of two difficult patients had heterozygous mutation for FMF disease. We think that, this article supports a suggestion that clinical manifestations are superior to genotype analysis for identification of FMF.

In conclusion, although FMF is a well described disease, in some cases, the diagnosis may be difficult. In this case report, we suggest that pericardial effusion and more rarely pericardial tamponade might be the initial manifestation of FMF and the possibility of this disease asan etiology should be considered in these patients, especially in certain ethnic groups.

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