Familial Mediteranean fever with protein-losing enteropathy due to constrictive pericarditis

İbrahim Gökçe, Selim Gökçe, Ayhan Kılıç, Uğur Bozlar, Murat Kocaoğlu, Önder Öngürü, Faysal Gök

Ankara, Turkey

Background: **Constrictive pericarditis (CP) represents a rare cause of protein-losing enteropathy (PLE) resulting from intestinal lymphangiectasia (IL). In this report, we describe an 8-year-old Turkish boy with IL and PLE secondary to CP.**

Methods: **The boy was introduced to our clinic due to bilateral pretibial edema and swelling of the eyelids caused by hypoproteinemia. Physical examination revealed a distended right jugular vein. Laboratory investigation revealed PLE with fecal concentration of alpha-1 antitripsin of 4.87 mg/g. Histopathologic examination of random biopsies obtained from the duodenum revealed markedly dilated lymphatics compatible with IL. Constrictive pericarditis was diagnosed by tagged cine cardiac magnetic resonance imaging.**

Results: **Pericardiectomy was performed for the patient. Genetic analysis was done and heterozygous mutation E148Q was detected as a disease-causing Mediterranean fever (MEFV) mutation. Colchicine was started after the operation. Six months after the initiation of regular colchicine therapy, echocardiography revealed disappearance of CP.**

Conclusion: **This is the first reported case of PLE with a distended right jugular vein due to CP secondary to familial Mediterranean fever associated with E148Q heterozygosity in the *MEFV* gene.**

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Key words: **constrictive pericarditis; familial Mediterranean fever; intestinal lymphangiectasia; protein-losing enteropathy**

Case report

Introduction

Familial Mediterranean fever (FMF) is associated with mutations in the Mediterranean fever (MEFV) gene that codes for pyrin and is transmitted in an autosomal-recessive manner.[1] A single mutation in the *MEFV* gene may be much more common than previously thought and may be seen in up to 25% of patients diagnosed with FMF.[2] Carriers have been shown to have higher levels of acute-phase reactants, a tendency to develop excessive febrile episodes, and more rheumatic diseases than the healthy population.[3] Pericardial involvement is a rare manifestation of FMF. In the largest studies to date, the frequency of definite pericardial involvement was reported to be 0.7%-1.4% in FMF patients.[1,4] In this study, we describe an 8-year-old boy with intestinal lymphangiectasia (IL) and protein-losing enteropathy (PLE) due to constrictive pericarditis (CP) secondary to FMF associated with E148Q heterozygosity presenting with a distended right jugular vein.

Case report

An 8-year-old boy with a history of FMF was introduced to our clinic for bilateral pretibial edema and swelling of the eyelids caused by hypoproteinemia. He was the second child of a nonconsanguineous marriage and the family history was negative for FMF. Two years earlier, at 6 years of age, he had developed swelling on the right side of the neck. Computerized tomography of the heart and neck had shown pericardial effusion and a distended right jugular vein (33 mm in diameter). Pericarditis was noted at that time and pericardiocentesis was performed. Laboratory investigations revealed no evidence of infective pericarditis. Bacterial cultures of the pericardial fluid was negative. Serological studies for echo and coxsackie viruses, hepatitis B and C viruses,

Author Affiliations: Department of Pediatric Nephrology and Rheumatology (Gökçe İ, Gök F), Department of Pediatric Gastroenterology (Gökçe S), Department of Pediatric Cardiology (Kılıç A), Department of Radiology (Bozlar U, Kocaoğlu M), and Department of Pathology (Öngürü Ö), Gülhane Military Academy of Medicine, School of Medicine, 06018, Etlik, Ankara, Turkey

Corresponding Author: İbrahim Gökçe, Department of Pediatric Nephrology, Gülhane Military Medical Academy, School of Medicine, 06018, Etlik, Ankara, Turkey (Tel: 0 (506) 7035001; Fax: 09 0312 304 43 81; Email: gokcemd@yahoo.com)

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adenovirus, Epstein-Barr virus, and cytomegalovirus were all negative. Genetic analysis for *MEFV* mutation revealed a heterozygous E148Q mutation and treatment with colchicine (0.5 mg/dose, bid) was initiated. Echocardiography revealed no pericardial effusion, and no signs were observed related to pericarditis during the one-year follow-up under regular colchicine treatment. However, the jugular vein distention persisted until his admission to our unit. The patient did not comply with the medication well during the follow-up. None or 0.5 mg of colchicine once a day was given instead of the prescribed dose (0.5 mg/dose, bid).

On admission to our unit at 8 years of age this time, physical examination revealed a distended right jugular vein, edema of the eyelids and pretibial regions, and a painless hepatomegaly. Complete blood count and acute phase reactants were within normal limits. Serum total protein was 4.1 g/dl (normal range: 6.4-8.3 g/dl) and serum albumin was 2.31 g/dl (normal range: 3.5-5.5 g/dl). Tests of kidney and liver function were normal. Protein excretion in a 24-hour urine collection was normal (73 mg/day). His C3 complement level was as low as 83 mg/dl (normal range: 90-180 mg/dl) and C4 complement level was normal at 140 mg/dl (normal range: 120-430 mg/dl). The levels of ANA, anti dsDNA, p-ANCA, and c-ANCA were negative. The repeated serological studies for echo and coxsackie viruses were negative. There was no family history of tuberculosis or exposure. He had a negative Quantiferon test and his chest X-ray was normal. MRI of the neck revealed the distended right jugular vein (29 mm in diameter). The presence of hypoproteinemia in the absence of malnutrition, renal or liver disease suggested PLE. A fecal concentration of alpha-1 antitripsin was 4.87 mg/g (normal range <2 mg/g), which was consistent with the value for PLE. Upper gastrointestinal endoscopy showed macroscopically normal results. Histopathologic examination of random biopsies obtained from the duodenum revealed markedly dilated lymphatics compatible with IL (Fig. 1).

Because of the history of pericarditis, distended jugular vein and hepatomegaly at physical examination, and IL, a cardiac anomaly was suspected. Cardiac catheterization failed to show any obstruction to blood flow; however, the inferior and superior caval veins were dilated and pressures were elevated throughout the right heart chambers. Cardiac MRI was performed with the tissue tagging technique and additional short axial sections. A prominent remnant of Eustacchian valve was seen (Fig. 2) and the pericardium was found to be adhered to the heart at the apical and inferior aspects, causing restriction to cardiac motion and septal bouncing (Fig. 3). With these findings, a diagnosis of CP was made and the patient was referred for pericardiectomy. Under general anesthesia, a median sternotomy was done and the adhered part of the pericardium was removed. Histopathological examination of the operative specimen confirmed the diagnosis of CP, with no evidence of infections. The patient recovered dramatically after the operation. The serum albumin level returned to normal. The colchicine dosage was increased to 1 mg/day after the operation. Six months after the operation, echocardiography revealed no pericardial effusion. The distention of the right jugular vein persisted; however, it was expected to improve during the follow-up.

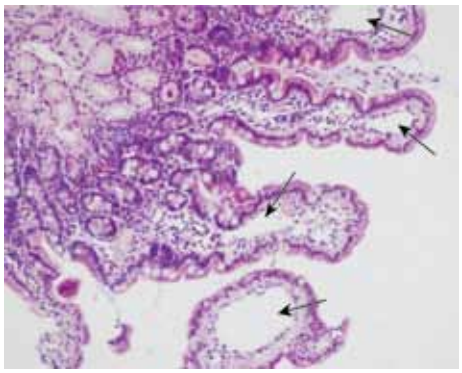

Fig. 1. Histopathological examination of the endoscopic biopsy shows dilated lymphatic channels in lamina propria beneath the surface epithelium (arrows) (HE stain, original magnification × 200).

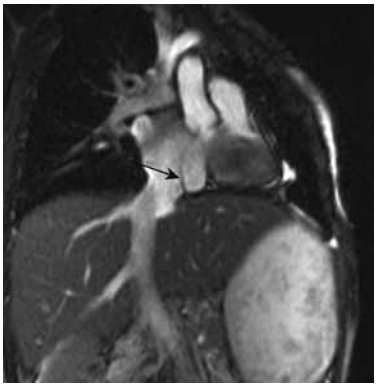

Fig. 2. Steady-state free precession imaging coronal image shows prominent Eustachian valve (arrow).

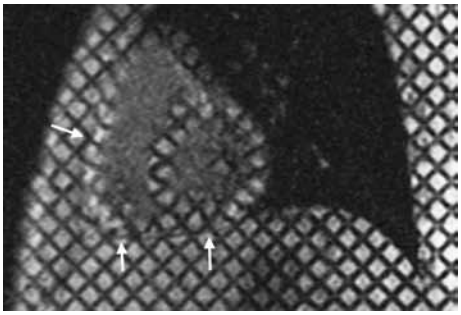

Fig. 3. Short axis myocardial tagging image shows intact tagging lines where inferior wall and right atrial free wall which consists of pericardial construction although pericardial thickness is in normal range (arrows).

Discussion

The present case was diagnosed as CP by cardiac MRI and confirmed at surgery. Laboratory investigations failed to reveal any evidence of infective pericarditis. There was no history of radiation therapy, operative or invasive (catheterization) procedure by which the pericardium had been opened, malignancy, uremia, blunt or penetrating trauma to the chest wall or use of drugs like procainamide and hydralazine. Clinical history, physical examination, and laboratory findings were not suggestive of connective tissue disorders. Despite the absence of typical clinical features, FMF was diagnosed because there was no underlying disease causing pericarditis.

Pericarditis, myocarditis, and cardiac amyloidosis are typical cardiovascular manifestations seen in FMF.[5] Pericardial attacks are usually mild with only minimal effusion and subside spontaneously in almost all patients without sequelae. In some patients, however, the course is complicated with massive effusion and pericarditis may cause chronic changes.[6] Kees et al[4] suggested that colchicine may play a role in reducing the frequency of pericarditis in FMF. It is well known that colchicine can be effective in controlling FMF at doses not less than 1-2 mg/day. Gasparyan and Ugurlucan[7] suggested that cardiovascular complications in FMF patients occur mostly due to irregular colchicine therapy and they recommended regular life-long colchicine therapy to avoid not only serositic attacks and amyloidosis but also cardiovascular manifestations.[7] The situation is similar to what happened in our patient. Echocardiographic examinations revealed no pericardial effusion in our patient during one-year of follow-up under regular colchicine treatment. When the patient discontinued regular treatment and used none or 0.5 mg/day of colchicine, pericardial effusion and signs related to constrictive pericarditis recurred. We speculate that CP in the present case was due to insufficient suppression of inflammation by colchicine. No recurrent signs of CP after initiation of regular colchicine therapy supported the diagnosis of FMF.

Two *MEFV* mutations are found in most patients who have been diagnosed with FMF. As mentioned above, a single mutation in the *MEFV* gene may be much more common than previously considered. Initially it was assumed that these patients harbored less common *MEFV* mutations on the second allele in *MEFV*, but a number of studies failed to detect such mutations even when complete sequencing of the gene was performed. Thus, it is evident that FMF is not fully recessive and that in some cases heterozygous mutations are associated with clinical symptoms.[2] An inter-population variation was observed in Turks regarding FMF and the presence of E148Q mutation in FMF patients from different regions of Turkey ranges 3.2%-13.9% (mean 5.5%).[8] However, no studies have shown the frequency of E148Q mutation exactly in FMF patients living in this region. The carrier frequency of the E148Q mutation has also been reported to be 6% in Turks.[9] Some researchers suggest that the E148Q mutation has an upregulating effect on inflammation in FMF.[10] Why subclinical inflammation in many heterozygous patients with FMF transforms into overt disease is largely unknown, but it is likely to involve other modifier genes and environmental factors.

In conclusion, our case suggested that FMF should be kept in mind in the differential diagnosis of CP in pediatric patients.

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