

A rare cause of massive ascites: Familial Mediterranean fever

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Familial Mediterranean fever is an autosomal recessive disease characterized by recurrent fever and peritoneal and pleural inflammation. It is an inherited disorder commonly found in Armenians, Turks, Arabs, Balkans, and Jews originating from North African countries. A small amount of peritoneal fluid collection can be observed during peritoneal attacks in patients with Familial Mediterranean fever, but chronic ascites has been described rarely in these patients. A 42-year-old female patient was admitted to our clinic in June 2010 with fever, severe abdominal pain and abdominal distention that had continued for one month. There was no family history of periodic fevers or abdominal pain. We could not find any cause for ascites, including tuberculosis. A diagnosis of Familial Mediterranean fever was suspected based on the clinical findings and her family history. She was screened for mutations causing Familial Mediterranean fever, and when found to be homozygous for M694V, treatment with colchicine was initiated. After treatment, the amount of ascites decreased, and relief of symptoms was confirmed during a follow-up. In conclusion, because Familial Mediterranean fever is common in our country, it should be considered in the differential diagnosis of patients with ascites of unknown etiology in populations where hereditary inflammatory disease is endemic.

Key words: Familial Mediterranean fever, ascites, abdominal pain

Masif asitin nadir bir sebebi: Ailevi Akdeniz ateşi

Ailevi Akdeniz ateşi tekrarlayan ateş, periton ve plevral inflamasyon ile karakterize otozomal resesif geçişli bir hastalıktır. Ailevi Akdeniz ateşi Kuzey Afrika kökenli Yahudilerde, Ermeni, Türk, Arap ve Balkanlarda yaygın şekilde görülen kalıtsal bir hastalıktır. Ailevi Akdeniz ateşi'nde periton atakları esnasında küçük miktarlarda peritoneal sıvı birikimi görülebilir. Ancak kronik asit Ailevi Akdeniz ateş'li hastalarda nadiren tanımlanmıştır. Haziran 2010 tarihinde 42 yaşında bayan bir hasta bir aydır başlayan şiddetli karın ağrısı, karın şişliği ve ateş nedeniyle kliniğimize başvurdu. Hikâyesinde periyodik ateş ve karın ağrısı yoktu. Tüberküloz dâhil asit yapabilecek herhangi bir neden bulunmadı. Klinik bulgular ve aile hikâyesi nedeniyle Ailevi Akdeniz ateşi hastalığından şüphelenildi. Hasta Ailevi Akdeniz ateşi mutasyonu açısından tarandı ve M694V yönünden homozigot olduğu tespit edildi. Kolşisin tedavisi başlandı. Asit miktarı tedaviden sonra azaldı ve takipler esnasında hastanın şikâyetleri düzeldi. Sonuç olarak, ülkemizde Ailevi Akdeniz ateşi yaygın olması nedeniyle, herediter inflamatuvar hastalığın endemik olduğu toplumlarda nedeni bilinmeyen asidi olan hastalarda ayırıcı tanıda düşünülmelidir.

Anahtar kelimeler: Ailevi Akdeniz ateşi, asit, karın ağrısı

INTRODUCTION

Familial Mediterranean fever (FMF) is characterized by a periodic fever and polyserositis of the chest, abdomen and joints that generally lasts for one to three days and resolves spontaneously. It is

most common in Armenians, Turks, Arabs, Balkans, and Jews originating from North African countries (1). FMF is the most prevalent periodic fever syndrome, affecting more than 100.000 pati-

ents worldwide. Amyloidosis is the most severe complication of the disease. (2). A small amount of peritoneal fluid collection can be observed during peritoneal attacks in FMF patients, but chronic ascites has rarely been described in these patients. The typical manifestations of the disease are recurrent attacks of severe pain due to serositis and a fever that lasts one to three days and then resolves spontaneously. FMF is one of the most common causes of acute abdominal pain in Mediterranean countries (3). Ninety-five percent of patients with FMF have painful attacks localized to the abdomen. The abdominal pain can range from mild to severe and may be diffused or localized (4). Apart from abdominal pain, FMF patients may present with a variety of abdominal manifestations during acute attacks, such as acute peritonitis, mechanical intestinal obstruction, diarrhea, bowel infarction, bleeding, inflammatory bowel disease, amyloidosis, and small amounts of peritoneal fluid (5). Recurrent attacks of peritonitis may lead to adhesions. Inflammation of all serosal membranes can be observed during attacks, such as pleuritis, synovitis and pericarditis. No diagnostic test is available for FMA, so its diagnosis is based on clinical grounds and determined by diagnostic criteria instead (1).

A minimal amount of peritoneal fluid collection can be observed during serositis attacks in FMF patients. This finding reflects a peritoneal reaction to repetitive inflammation. The accumulation of the ascites is painful, and although it may require repetitive drainage, it may also be associated with a decrease in the number and severity of abdominal attacks (6). Chronic ascites resulting from FMF is an uncommon complication. To the best of the authors' knowledge, there have been few reports in the literature to date about massive chronic ascites in this genetic disease (7-10).

In this report, we present a 42-year-old female patient who was admitted due to fever, abdominal pain and abdominal distention lasting for one month. Furthermore, we review the approach to treating patients with recurrent massive ascites of unknown etiology in populations in which hereditary inflammatory disease is endemic.

CASE REPORT

A 42-year-old female patient was admitted to our clinic in June 2010 with fever, severe abdominal pain and abdominal distention lasting for one month. There was no family history of periodic fe-

vers, abdominal pain or ascites, but FMF was present in her sister. During her examination, she complained of abdominal distention, fatigue, abdominal pain, and an intermittent high fever. Her body temperature was 39.2°C, blood pressure 130/90 mmHg and pulse rate 88 beats/min and regular. Her heart and lung functions were normal.

Massive ascites was discovered during her abdominal examination. There was no organomegaly. An abdominal ultrasound revealed massive ascites and a normal liver. Splenic echogenicity and a gynecological ultrasound did not show any abnormalities. Other systems were normal on physical examination. Laboratory tests were performed, and the findings, including complete blood count, liver and kidney function tests, thyroid function tests, serum electrolytes, albumin levels, and prothrombin time were in the normal ranges. Other laboratory evaluations were as follows: C-reactive protein 49.7 mg/dl, fibrinogen 4.58 g/L, erythrocyte sedimentation rate 18 mm/h, and white blood cell count 11,200/mm³. Tumor markers (CA 125, CA 15-3, CA 19-9, CEA, and alpha-fetoprotein [AFP]) were normal. Immunoglobulin and complement levels were normal. Peritoneal fluid analyses were as follows: glucose 82 mg/dl, total protein 4.0 g/dl, albumin 3.1 g/dl, and lactate dehydrogenase 248 U/L. The serum ascites-albumin gradient was 0.9 g/dl. Ascitic evaluation showed characteristics of exudative ascites, with a cell count of 250/mm³ and a predominance of neutrophils. There were no malignant cells. Cultures for bacteria and *Mycobacterium tuberculosis* were negative. The patient was negative for the serum markers for hepatitis B and C viruses and for autoantibodies.

The diagnosis of FMF was made based on recurrent abdominal pain, fever and unexplained ascites. The patient was evaluated for mutations causing FMF and was found to be homozygous for the M694V mutation via denaturing gradient gel electrophoresis. Colchicine treatment was initiated at a dose of 0.5 mg tablets per 8 hours. One month after the treatment, an ultrasonographic examination was performed, and the amount of ascites fluid had decreased, and relief of symptoms was reported during the follow-up.

During follow-up at nine months after treatment, an ultrasonographic examination was again performed, and the amount of ascites fluid was very low. The patient continues to take colchicine regularly.

DISCUSSION

Familial Mediterranean fever (FMF) is an autosomal recessive disease. Mutations in the MEFV gene, which is located in the short arm of chromosome 16, have been demonstrated to cause FMF (3). The disease was first described as a distinct entity in 1945 (11). The diagnosis of FMF is generally based on clinical criteria, although the direct analysis of the MEFV gene is the only method to definitively diagnose FMF (12).

Also known as recurrent polyserositis, FMF is characterized by recurrent, self-limiting, frequent abdominal attacks that typically first appear at a young age. An acute episode has a sudden onset of pain associated with fever, which lessens within 12–24 hours (h) as the attack runs its course (13,14). Peritoneal and pleural involvement, skin lesions, arthralgia, and joint involvement are all well-documented features of FMF (14). In FMF, peritoneal effusion during abdominal attacks is usually mild, is not detected by clinical evaluation, and disappears during clinical remission. A minimal amount of peritoneal fluid collection can be observed during serositis attacks in FMF patients. Chronic ascites resulting from FMF is a rare complication. To the best of the authors' knowledge, there have been only a few case reports in the literature describing massive chronic ascites in this genetic disease (7–10). All were females. Our patient was also female. In patients with FMF, ascites in the asymptomatic phase can be found with physical, computerized tomography (CT) or ultrasonographic examinations (15).

Genetic testing is highly specific and sensitive for the diagnosis of FMF (16,17). Mutation analyses may help in arriving at the correct diagnosis in only a small number of clinically atypical cases (18). Mutation analyses were performed in seven of the nine FMF patients with massive ascites that have been reported previously. M694V homozygote mutation in four patients, M694V/V726A compound heterozygote mutation in two patients and heterozygote mutation for M694V in one patient were determined. Our patient had an M694V mutation. Hence, at least one M694V mutation is present in all FMF patients with chronic ascites complications.

Colchicine is the most effective treatment for the control of FMF attacks, and most patients become asymptomatic following colchicine treatment (19). A response to colchicine may be either complete or partial. After colchicine treatment, ascites comple-

tely disappears in some patients and decreases in others (8,20,21). Cakir *et al.* (10) reported a six-year-old child who presented with refractory ascites and was diagnosed with FMF. They found that ascites and other serosal inflammation improved within one week without any recurrence during the following 12-month period while on colchicine treatment. In another study, Cekin *et al.* (7) reported one patient with FMF who presented with massive recurrent ascites. They noted that for 13 months after colchicine therapy, the patient had been symptom-free, including no ascites. Another previously reported case described chronic ascites and peritoneal amyloidosis that was caused by FMF (9), in which the patient had a low serum-ascites albumin gradient related to FMF that responded to colchicine treatment. Furthermore, peritoneal mesothelioma preceded by episodes of recurrent ascites has been associated with FMF in the absence of asbestos exposure (22,23).

In our patient, the amount of ascites had reduced one month after the colchicine treatment, but it did not disappear completely, and relief of symptoms was reported during the follow-up. During her follow-up at nine months after treatment, an ultrasonographic examination was repeated, and the amount of ascites fluid was minimal. She continues to take colchicine treatment regularly.

Small amounts of peritoneal fluid are often observed in FMF patients with laparoscopy or radiological imaging techniques such as ultrasonography or CT (24). This finding reflects a peritoneal reaction to repetitive inflammation, a process that, in extreme cases, may develop into ascites (6). However, ascites with large amounts of peritoneal fluid is an uncommon manifestation of FMF.

Ascites that is discovered by abdominal ultrasonography during the follow-up period with colchicine treatment may resolve, with a reduction in the frequency of abdominal pain episodes. After a definitive diagnosis, our patient was treated with colchicine, and relief of symptoms and a reduction in ascites were observed on the follow-up. She has been free of abdominal pain for nine months with colchicine therapy.

In conclusion, chronic ascites may develop in patients with FMF due to chronic peritoneal irritation. Atypical presentations of FMF have been increasingly reported in the medical literature. After confirming the diagnosis of FMF with genetic tests in these patients, colchicine treatment may help to resolve the ascites. There was at least one M694V mutation in all reported FMF patients

with ascites complications, including our case. Because FMF is common in our country, it should be considered in the differential diagnosis of patients with ascites of unknown etiology in populations

where hereditary inflammatory disease is endemic. Molecular genetic tests should be considered, especially in patients of Mediterranean origin who have a family history of FMF.

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