Turk J Gastroenterol 2008; 19 (1): 64-68

A rare cause of ascites: Familial Mediterranean Fever

Nadir bir asit nedeni: Ailevi Akdeniz Ateşi

Mehmet BEKTAŞ, İrfan SOYKAN, Deniz GÖREN, Mehmet ALTAN, Esin KORKUT, Hülya ÇETİNKAYA, Ali ÖZDEN

Department of Gastroenterology, Ankara University, School of Medicine, Ankara

Familial Mediterranean fever is an autosomal recessive disorder characterized by sporadic, paroxysmal attacks of fever and serosal inflammation. In Familial Mediterranean fever, peritoneal effusion during abdominal attacks is usually mild, is not detected by clinical evaluation, and disappears during clinical remission. Chronic ascites has rarely been described in patients with Familial Mediterranean fever. Genetic analysis is highly specific and sensitive for diagnosis of Familial Mediterranean fever. All of the four cases discussed in our study had no benign or malignant pathology that could explain the ascites. They had suffered from repetitive periods of fever and ascites since childhood. Genetic analysis of these four cases revealed that one was M694V/M694V homozygote, one was M694V/? heterozygote, and the other two were M694V/V726A compound heterozygote. Ascites regressed with colchicine therapy. Since Familial Mediterranean fever is common our country, it should be kept in mind in the differential diagnosis in patients with ascites of unknown etiology.

Key words: Familial Mediterranean fever, ascites, colchicine therapy

Ailevi Akdeniz Ateşi, paroksismal ateş atakları ve serozal inflamasyon ile karakterize sporadik, otozomal resesif bir bozukluktur. Ailevi Akdeniz Ateşinde karın ağrısı atakları esnasında peritoneal effüzyon sıklıkla hafiftir, klinik değerlendirme esnasında tespit edilemez ve klinik remisyon ile kaybolur. Kronik assit Ailevi Akdeniz Ateşili hastalarda nadiren tanımlanmıştır. Ailevi Akdeniz Ateşi tanısında genetik testler yüksek derecede spesifik ve sensitiftir. Mevcut dört vakamızda assit etyolojisini açıklayacak benign veya malign patoloji saptanmadı. Hastalarımızın çocukluk döneminden beri tekrarlayan ateş periyodları ve assit yakınmaları mevcuttu. Yapılan MEFV gen mutasyon analizinde bir hastada M694V/ M694V homozigot, bir hastada M694V/? heterozigot ve iki hastada ise M694V/ V726A compound heterozigotluk saptandı. Kolşisin tedavisi ile assit geriledi. Ailevi Akdeniz Ateşi ülkemizde sık görüldüğünden nedeni bulunamayan assit etyolojisi ayırıcı tanısında akılda bulundurulmalıdır.

Anahtar Kelimeler: Ailevi Akdeniz Ateşi, assit, kolşisin tedavisi

INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disease that most commonly occurs in Sephardic Jews, Armenians, Arabs and Turks. FMF is characterized by recurrent and self-limited attacks of fever accompanied by peritonitis, pleuritis, synovitis, or erysipelas- like erythema (1). Genetic testing is highly specific and sensitive for diagnosis of FMF. The localization of the disease-associated mutations on exon 10 was described in the MEFV gene in 1997 (2, 3). Three missense mutations clustered in the carboxyl-terminal portion of the MEFV gene (M680I, M694V, and V726A) were observed in the previously indicated ethnic panel for FMF patients, accounting for 80% of affected alleles (2-4). The disease is characterized by acute episodes of pain, usually in the abdomen, chest, joints, skin, and muscles, accompanied by fever. The attacks are associated with serosal membrane inflammation at the affected sites, with massive influx of polymorphonuclear neutrophils. Inflammation of all serosal membranes can be seen during attacks, such as pleuritis, synovitis, and pericarditis. Small amounts of peritoneal fluid are often seen at laparoscopy of FMF patients. This finding reflects a peritoneal reaction to repetitive inflammation, which is a process that in extreme cases may develop into ascites (5). Ascites with large amounts of peritoneal fluid is an uncommon manifestation of FMF. In this report, we present four FMF patients with recurrent ascites.

Address for correspondence: Mehmet BEKTAŞ
Kavacık Subayevleri Cihangir Cad. 19/4
Keçiören, Ankara, Turkey
Tel: +90 312 318 20 16 • Fax: +90 312 363 62 13
E-mail: mbektas70@hotmail.com

Manuscript received: 08.02.2007 **Accepted:** 09.10.2007

CASE REPORTS

Case 1

A 34-year-old female patient was admitted to our clinic in September 2003 with the complaint of abdominal distention. In 2001, she had applied to a clinic with complaints of abdominal distention, and had undergone an abdominal ultrasonographic examination revealing ascites. Since then, her ascites had increased in amount. The patient was hospitalized in our clinic for further investigation. In her personal history, she had a diagnosis of acute rheumatic fever at the age of 15, and was operated two years before admission to our clinic for inguinal hernia and cyst located in the tuboovarian region. Histopathological diagnosis of the cyst was serous cyst adenoma. In her family history, FMF was present in her mother, sister and her mother's brother. On her systemic evaluation, she complained of abdominal distention, fatigue, weakness, generalized joint pain, abdominal pain and intermittent high fever. On her abdominal examination, she had massive ascites. Her laboratory test results are displayed in Tables 1 and 2. The patient's chest X-ray revealed fibrotic projections in the apices bilaterally. She had both a negative family history of tuberculosis and an anergic tuberculin skin test (TST), and adenosine deaminase was found to be 15.5 IU/L. Thorax computerized tomography (CT) revealed no mediastinal-hilar masses or pathologically large lymph nodes on short axis. Except for minimal fibrous remnants in the apices, the pleural surfaces and the rest of the lung parenchyma were normal. The case was consulted to the Chest Diseases Department, and tuberculosis was commented to be unlikely. Acid-resistant bacilli culture result of the ascites sample was negative. Although the patient's aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were normal, ultrasonographic examination revealed granularly increased hepatic parenchymal echo patterns, and her abdominal CT revealed a hypertrophied left hepatic lobe. Venous Doppler ultrasonographic examination of the hepatic and portal systems was evaluated as normal. The patient was asked for laparoscopic peritoneal and liver biopsy but she refused. She was tested for MEFV gene mutations, and was found to be compound heterozygote (M964V/V726A). The patient was discharged with recommendations of colchicine 0.5 mg tablets per 8 hours. However, during the follow-up period, her ascites showed no reduction in amount as compared with the initial examination. About three months later, the patient was re-hospitalized for increased ascites, underwent laparoscopic examination, and peritoneal biopsy was performed. Histopathologic evaluation of the biopsy specimens revealed that amyloid was negative. Reactive changes were documented in histopathologic evaluation of liver wedge biopsy.

Case 2

A 25-year-old female patient applied to our clinic on 15 September 2003 with complaints of abdominal pain and ascites. She previously had fever accompanied by abdominal and chest pain. Colchicine treatment had been recommended six years before for possible diagnosis of FMF, but she discontinued this treatment two months later of her own will. An ultrasonographic examination performed four years before this admission revealed ascites in her abdomen. However, its etiology was obscure. She had her last attack of fever seven months before admission, with increase to 39°C and lasting for three days, which was relieved partially with the use of analgesics. In her family history, her mother and sister had attacks of abdominal pain and fever, and her mother's brother had FMF. On abdominal examination, percussion revealed the presence of little ascites extending to the flanks. The laboratory test results are given in Table 1 and the results of ascites assessments in Table 2. The patient had an exudative ascites; heart and liver diseases, tuberculosis and gynecological malignancy were considered unlikely based on results. As the patient had a history of periodic fever and previous diagnosis of FMF, a genetic test was performed, revealing compound heterozygosity (M964V/V726A). Colchicine treatment was started at a dose of 0.5 mg per 8 hours. During the follow-up period, her ascites persisted, though it reduced in amount as compared with the initial examination. She is still continuing with colchicine and has had no further attacks of FMF.

Case 3

A 26-year-old female patient was hospitalized in our clinic in January 2004 in order to determine the etiology of her ascites. The patient had a complaint of abdominal distention for two months, and was referred after an abdominal ultrasonographic examination performed in another medical center revealed ascites in the pelvis. In her personal history, she had been diagnosed with FMF at the age of 11 due to abdominal pain and high fever attacks lasting 1-2 days since her childhood. She disconti-

Table 1. Characteristics of patients

Characteristic	Case 1	Case 2	Case 3	Case 4
Sex	Female	Female	Female	Female
Age	34	25	26	17
Time of ascites	2 years	4 years	2 months	One month
Time of FMF	New	6 years	15 years	7 years
Family history of FMF	Yes	Yes	Yes	Yes
Hb	11.5	12.1	11.5	11.9
Htc	34.5	36.2	34.9	36.2
White blood cell count	7000	5600	7700	6200
Serum glucose	80	84	99	77
Serum albumin	3.3	4.2	3.9	4.4
Serum LDH	104	76	158	128
Proteinuria	Negative	Negative	Negative	Negative
Sedimentation	13	7	25	29
C-reactive protein	8.68	3.2	16.3	4.49
Abdominal ultrasonography	Manifest ascites	Pelvic ascites	Minimal ascites	Pelvic ascites
Abdominopelvic CT	Manifest ascites	Pelvic ascites	Pelvic ascites	Pelvic ascites
Echocardiography	Minimal left atrial dilatation	Normal	Normal	Normal
Amyloidosis (rectum biopsy)	Negative	Negative	Negative	Negative
Posteroanterior chest radiograph	Bilateral hilar and perihilar fibro-calcifications	Normal	Normal	Normal
Tuberculin skin test	Anergy	20 mm	15 mm	No
Mutations analysis	M694V/V726A	M694V/V726A	M694V/M694V	M694/?
Colchicine response	None	Yes	Yes	Yes

nued the colchicine treatment of her own will five years later. In her family history, her brother also had FMF. The laboratory results of this patient are shown in Tables 1 and 2. The tests revealed no heart, liver or kidney diseases and there were no signs of tuberculosis or any malignancy. Two days after hospitalization, she developed fever as high as 38.6°C, with accompanying abdominal pain and mild sensitivity on abdominal palpation. Her blood tests in that period revealed a leukocyte count of 15,600/mm^3 and a serum C-reactive protein (CRP) of 6.2 mg/dl. In the ascites specimen, 800 leukocytes/mm^3 were found, and *Escherichia coli* was grown in the culture medium. The case was diagnosed as spontaneous bacterial peritonitis, and ciprofloxacin 500 mg per 12 hours was started. As the patient's fever had subsided, leukocyte count in the ascites was repeated on the 7th day of hospitalization, and found as 300 cells/mm^3. Genetic tests for MEFV gene mutation revealed that the patient was homozygote for M694V/M694V gene mutation. We started the colchicine treatment at a dose of 0.5 mg per 8 hours and the patient was discharged. Approximately one month later, ultrasonographic examination was performed, and the ascites was found to have regressed.

Case 4

A 17-year-old female patient was hospitalized in September 2003 in order to determine the etiology of her ascites. She had applied to an outpatient clinic for severe abdominal pain that persisted for a month, and abdominal ultrasonography revealed massive ascites in the pelvic cavity. In her personal history, she had appendectomy at the age of seven, was diagnosed as having FMF at the age of 10, and had received colchicine treatment for five years. In her family history, her sister had FMF. Physical examination of the abdomen was normal. Laboratory test results are given in Tables 1 and 2. No signs of heart, liver or kidney disease, tuberculosis or malignancy were found in this patient. Due to presence of FMF in her personal history, genetic test was performed, and the patient was heterozygote for M694V/? gene mutation. Colchicine treatment was started at a dose of 0.5 mg per 8 hours. Six months after the treatment, ultrasonographic examination revealed complete resolution of the ascites.

DISCUSSION

Small amounts of peritoneal fluid are often seen at laparoscopy or on radiological imaging techniques such as ultrasonography or CT of FMF patients (6). This finding reflects a peritoneal reaction to repetitive inflammation, a process that, in extreme cases, may develop into ascites (5). However, ascites with large amounts of peritoneal fluid is an uncommon manifestation of FMF. In this study, we were unable to detect any clinical or laboratory signs of benign (heart, liver, kidney, gynecological

Table 2. Results of ascites fluid examination

Characteristic	Case 1	Case 2	Case 3	Case 4
Color	Yellow	Yellow	Clear	Clear
White blood cell count (cell/mm^3)	100	120	250	200
Albumin (g/dl)	2.6	3.5	2.6	2.9
Serum-ascites albumin gradient (≤1.1)	0.6	0.5	1.3	1.5
Glucose	103	79	75	80
LDH	125	115	105	138
Culture	Negative	Negative	Negative	Negative
Cytology	Benign	Benign	Benign	Benign
Adenosine deaminase (ADA <30 IU/ml)	15.3	11.6	19.9	12.5
Acid resistant bacille staining	Negative	Negative	Negative	Negative

diseases, tuberculosis) or malignant disorders in any of the four female patients admitted to our clinic with ascites of unknown etiology. However, all of the patients had had complaints of episodic abdominal pain with fever lasting 1-2 days since their childhood. Some of these patients had previously received colchicine treatment in other clinics for suspected FMF diagnosis. They had reported discontinuing colchicine of their own will, after taking the drug for different periods of time. However, all of them had fewer episodes of abdominal pain and fever when they had taken the drug. Furthermore, first-degree relatives of each patient had FMF. Our cases 1 and 2 were sisters. Genetic tests of these four cases revealed that one was homozygote for M694V/M694V, two were compound heterozygote for M694V/V726A, and one case was heterozygote for M694V/? gene mutations.

In FMF, peritoneal effusion during abdominal attacks is usually mild, is not detected by clinical evaluation, and disappears during clinical remission. Chronic ascites has rarely been described in patients with FMF (1, 7, 8). In patients with FMF, ascites in the asymptomatic phase can be found on physical examination, or CT or ultrasonographic examinations (9). Peritoneal mesothelioma preceded by episodes of recurrent ascites has been associated with FMF in the absence of asbestos exposure (10,11). In our patients, we ruled out peritoneal mesothelioma with histologic examination of the peritoneal fluid and/or biopsy.

In all of the cases discussed in our study, ascites was detected on physical examination. Laboratory tests in these patients revealed no signs of portal hypertension or increased hepatic enzymes. Serum-ascites albumin gradients were found <1.1 in two cases. Liver biopsy was performed in case 1 and reported as reactive changes. For the other two cases, serum-ascites albumin gradients were >1.1. Cell counts in the ascites samples were ≤250/mm^3.

Colchicine is the most effective treatment to control FMF attacks. During the follow-up period with colchicine treatment, ascites may resolve with a reduction in the frequency of abdominal pain episodes. In the medical literature, three patients with ascites were reported who had received colchicine, and the ascites had resolved on follow-up in two of them. The third had an encapsulated peritonitis and unresolving ascites that remitted with short-term corticosteroids, but relapsed when the dose was reduced, and was finally treated surgically (8, 12, 13). In our study, each patient received colchicine treatment at a dose of 0.5 mg per 8 hours, and at the end of an average of six months of treatment, ascites had resolved in cases 2, 3 and 4. Ascites did not resolve in case 1, and this patient had therapeutic paracentesis twice, followed by laparoscopic examination. During laparoscopy, 5 liters of ascites was drained, and peritoneal biopsy was taken, which helped to rule out tuberculosis and malignancy, and the histological examination of the specimen agreed well with chronic peritonitis. During the follow-up period of case 1, colchicine was continued after laparoscopy, and no further ascites collection was observed.

In conclusion, ascites may develop in FMF patients due to chronic peritoneal irritation. After confirming the diagnosis of FMF with genetic tests in these patients, colchicine treatment may help to resolve the ascites. In countries like Turkey, where FMF is more frequently encountered, this disease must be considered in the differential diagnosis of ascites.

REFERENCES

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and reviews of literature. Am J Med 1967; 43: 227-53.
2. The International FMF Consortium. Ancient missense mutations in a new member of the RORet gene family are likely to cause Familial Mediterranean fever. Cell 1997; 90: 797-807.
3. The French Consortium. A candidate gene for Familial Mediterranean fever. Nature Genetics 1997; 17: 25-31.
4. Bernot A, da Silva C, Petit JL, et al. Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever (FMF). Human Mol Genetics 1998; 7: 1317-25.
5. Bellin MF, Deutsch JP, Bletry O, et al. [Encapsulating peritonitis in periodic disease. Apropos of a case studied by x-ray computed tomography]. Ann Radiol (Paris) 1989; 32: 302-4.
6. Zissin R, Rathaus V, Gayer G, et al. CT findings in patients with familial Mediterranean fever during an acute abdominal attack. Br J Radiology 2003; 76: 22-5.
7. Mor A, Gal R, Livneh A. Abdominal and digestive system associations of familial Mediterranean fever. Am J Gastroenterol 2003; 98: 2594-604.
8. Cekin AH, Dalbudak N, Kunefeci G, et al. Familial Mediterranean fever with massive recurrent ascites: a case report. Turk J Gastroenterol 2003; 14: 276-9.
9. Aharoni D, Hiller N, Hadas-Halpern I. Familial Mediterranean fever: abdominal imaging findings in 139 patients and review of the literature. Abdom Imaging 2000; 25: 297-300.
10. Belange G, Gompel H, Chaouat Y, Chaouat D. [Malignant peritoneal mesothelioma occurring in periodic disease: apropos of a case]. Rev Med Interne 1998; 19: 427-30.
11. Chahinian AP, Pajak TF, Holland JF, et al. Diffuse malignant mesothelioma. Prospective evaluation of 69 patients. Ann Intern Med 1982; 96: 746-55.
12. Bitar E, Rizk A, Nasr W, et al. [Familial paroxysmal polyserositis. Previously unpublished peritoneal complications. A case]. Presse Med 1985; 9; 14: 586-8.
13. Lelievre JD, Ranque-Francois B, Aslangul-Castier E, et al. Chronic ascites related to encapsulating peritonitis in familial Mediterranean fever. Am J Med 2002; 113: 80-1.