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Unusual manifestations of familial mediterranean fever

Ailevi akdeniz ateşinin genel olmayan belirtileri

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ÖZET: *Ailevi Akdeniz Ateşi (FMF), kendi kendine iyileşen, etyolojisi bilinmeyen paroksimal ve inflamatuar bir hastalıktır. FMF, peritonal, ploral ve sinovial zarların serozal inflamasyonuyla birlikte ateşin bulunmasıyla belirgindir.*

Haziran 1987 Ocak 1996 yılları arasında 157 FMF'li hasta Hacettepe Hastanesi'nde teşhis ve takip edilmiştir. Bunlardan beşi daha önce rapor edilmemiş veya nadiren rapor edilmiş klinik belirtileriyle kendilerini göstermişlerdir. Hastaların yaş ortalaması teşhis anında 27.2±1.3 yıl idi (aralık 5-51). Hacettepe Hastanesi'ne gelmeden önce hastalar en az 2 ve 27 yıl öncesinden FMF belirtilerini gösteriyorlardı. %20 olguda kan bağı vardı. İki hastada ise belirtiler 40 yaşından sonra çıkmıştı.

Bu beş olguda, FMF'in klasik belirtileriyle uygunluk göstermeyen septomları ve belirtileri tartışılmıştır.

Anahtar Kelimeler: **Ailevi akdeniz ateşi, kolşisin**

SUMMARY: *Familial Mediterrenean Fever (FMF) is a paroxsymal self-limited inflammatory disease of unknown etiology which is characterized by recurring attacks of serosal inflammation of peritoneal, pleural and synovial membranes associated with fever.*

From June 1987 through January 1996, 157 patients with FMF have been seen at Hacettepe University Hospital, Ankara, Turkey. Five had an atypical or exceptional clinical presentation which either had been reported rarely or have not been reported previously. All but 3 of the 157 patients with FMP fulfilled the classical criteria for a diagnosis of FMF. Their mean age at presentation was 27.2±1.3 years (range 5-51). Each had had symptoms of FMF for at least 2 years ranging up to 27 years prior to their presentation to Hacettepe University. A history of consangüinity was present in 20%. Two had signs and symptoms of FMF with an onset of their disease after age 40 years.

The clinical details of the five cases with either a rare and/or exceptional findings consisting of febrile episodes without signs or symptoms of serositis, recurrent febrile peritoneal inflammation leading to intrabdominal mass formation, and periodic shoulder pain with disabling fibromyalgia.

Key Words: **Familial mediterrenean fever, colchicine**

FAMILIAL Mediterrenean Fever (FMF) is a recurrent, inflammatory disease of unclear etiology thought to have a genetic basis and is inherited as an autosomal recessive disease (1). FMF occurs at increased rates in people of Mediterranian stock, particularly Turkish, Armenian, Arabic or Jewish descent (2-3).

The usual clinical manifestations of FMF are an acute, self limited episode of fever with inflammation of one or another serosal surfaces (3). The case histories of 5 individuals with exceptional and/or rare presentations of FMF and the occurrence of FMF in patients with Behçet's disease and β Thalassemia trait within a family are reported.

MATERIAL AND METHODS

A total 157 patients with FMF have been seen by the Gastroenterology Division of Internal Medicine at Hacettepe University Hospital. As a group they have been followed from June 1987 though January 1996. Their mean age, when first seen at Hacettepe University, was 27.2±1.3 years (range 5-51) and the male to female ratio was 1.21 (86M/71F). All were examined during an acute attack and measures of acute inflammation consisting of acute phase reactants (sedimentation rate, C-reactive protein and fibrinogen) were elevated in all 157. Other possible explanations for their painful serositis and/or intermittent fevers were investigated thoroughly with upper and lower gastrointestinal endoscopy, barium studies of the small bowel, abdominal ultrasonography, computerized tomography of the abdomen and chest, intravenous pyelography and a Watson-Schwartz test which was accomplished in most. A history of consanguinity was present in 20% of the cases. 154 of the 157 cases fulfilled the requirements for a diagnosis of FMF a shown in Table 1. Five aty-

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Table 1. *Diagnostic Criteria for a Diagnosis of FMF*

Major Criteria	*Minor Criteria*
Recurrent fever	Recurrent arthralgia
Recurrent abdominal pain	Childhood onset
Recurrent pleuritis	Remission in pregnancy
Recurrent arthritis	Response to colchicine
Positive family history	Mediterrenaen ancestry
Recurrent skin lesion	Leucocytosis

The diagnostic requirements are recurrent fever plus 2 of the major or 3 of the minor criteria

pical cases, 3 of whom did not fulfill all of the criteria listed in Table 1 are the subjects of this report. All 5 had had some symptoms of FMF for at least 2 years up to as long as 27 years. Two of the 5 patients developed signs and symptoms of FMF after achieving 40 years of age.

The treatment protocol utilized at Hacettepe University of FMF consists of prophylactic colchicine 0.5 mg orally two or three times a day with breakthrough attacks being treated with additional colchicine consisting of 0.5 mg every hour for four hours, followed by 1 every 2 hours for 4 hours, and finally on every 12 hours for 3 days.

Case Reports

The following 5 cases had unusual presentations of FMF that bear reporting:

PATIENT 1

In November 1988, a 37 year old male was seen with a five month history of recurrent high fever and malaise. His febrile episodes characteristically lasted for 10 days, starting with chills and were accompanied by a diaphoresis. His physical examination was normal except for fever and the presence of two subcutaneous nodules on the volar aspect of the forearm that were excised and shown to be angiolipoma by histopathologic examination. Twenty six years previously, he had had a severe case of hepatitis A which was confirmed by serology. There was no history of FMF, Behçet's disease of tuberculosis in his family.

Hematological and biochemical tests were normal, apart from an elevated sedimentation rate (ESR) of 46 mm/hour a leucocyte count of 12500/mm^3 with a fibrinogen value of 650 mg/dl and the pressure of C-reactive protein. When first seen, he tested negative for all HBV antigens and antibodies. Cultures of blood, bone marrow, and cerebrospinal fluid for common bacteria, viral and parasitic infections were negative. Moreover, a bone marrow aspiration and biopsy as well as various radiological investigations including plain Xrays of thorax and abdomen, abdomino-pelvic ultrasound studies and cranial-thoracic and abdominal CT scanning, radionucleotide scintigraphy and upper and lower gastrointestinal endoscopic procedures as well as barium studies of the upper and lower gastrointestinal tracts were negative. A rectal biopsy for amyloidosis was negative. As part of a normal laparoscopic examination, a liver biopsy was obtained and revealed fatty changes but no granulomas, no evidence of a viral infection and was negative for amyloid. In February 1989, he was started on prophylactic colchicine 1.5mg/day. His physical examination has remained normal. He has experienced a markedly reduced number of febrile attacks with only low grade fever (less than 38° C) since intiating colchicine therapy. At one point, he went 1.5 years without an attack. He has been on colchicine treatment with a normal ESR and C-reactive protein as well as fibrinogen levels since 1989.

PATIENT 2

In November 1983, a 5 year old female presented with a febrile episode of 6 hours duration. Her physical examination was completely normal except for pyrexia with a temperature of 39°C occuring once or twice a month since 1 year of age with no signs or symptoms of abdominal, chest, joint or skin disease. The attacks of fever were preceded by chills and peaked within 12-24 hours. Blood, bone marrow, urine, sputum and CSF were cultured for bacterial, viral and parasitic agents without identifying a cause for the fevers. A serologic panel for collagen vascular disease was negative. Chest and abdominal plain X rays, abdominal ultrasound and abdominal-thoracic and cranial CT scans were all normal. The only positive findings were a leucocytosis (11000-13000/mm^3) and hemoglobin value at 7.5 gm/dl with hypochromic and microcytic erythrocytic indices. Her serum iron level was normal. Hemoglobin electrophoresis was consistent with B Thalassemia trait.

She was completely normal between attacks but continued to have regular attacks consisting of high feve lasting 10-12 hours without any other signs or symptoms of serositis. She has a family history of FMF in her 3 year old sister and her 36 year old mother. An uncle was diagnosed as having Behçet's disease. Moreover, her mother and sister had classic signs and symptoms of recurrent peritonitis together with high fevers which respond to colchicine consistent with a diagnosis

Table 2. *Unusual findings suggestive of a diagnosis of FMF in the 5 cases reported*

Case Number	*Characteristics*
Case 1	a) older age at onset and diagnosis b) negative family history c) monosymptomatic fever d) dramatic response to colchicine
Case 2	a) confounding unusual disease (βThalasemia trait) b) positive family history of FMF and Behçet's disease c) response to colchicine
Case 3	a) left lower quadrant abdominal mass b) confounding rheumatic fever c) response to colchicine
Case 4	a) older age b) unilateral shoulder pain c) dramatic response to colchicine
Case 5	a) splenomegaly b) confounding rheumatic fever c) response to colchicine

of FMF and a monosymptomatic variant (purely febrile) of FMF without evidence of serositis. She was started on colchicine treatment (1.5 mg/day) and has remained in remission for several years.

PATIENT 3

In September 1991, this 28 year old male was admitted to the Hacettepe University hospital because of recurrent abdominal pain and a left lower abdominal mass. Physical examination revealed a hard but non-tender mass with a regular surface, fixed to the skin extending from the umbilicus medially to the anterior axillary line laterally. His vital signs were normal as was the rest of his physical examination. Since the age of 1 year, he has had recurrent attacks of abdominal pain and peritonitis separated by periods of complete normalcy. He had had no abdominal surgical procedures. He had no prior medical history except for a history of acute rheumatic fever (ARF) at 13 years of age. He had been on penicillin prophylaxis for 5 years when he was first seen at Hacettepe University. A left lower quadrant abdominal mass was identified, 4 months prior to presentation at Hacettepe.

His family history was positive for non-insulin dependent diabetes mellitus in his father but was negative for illnesses such as FMF, Behçet's disease, tuberculosis or inflammatory bowel disease. All hematological and biochemical tests were normal except for a high ESR of 64 mm/hour, positive C-reactive protein, fibrinogen level of 420 mg/dl and a mild leucocytosis with a normal peripheral blood smear. An abdominal ultrasound revealed a paraumbilical hypoechoic lesion measuring 6 by 10cm, containing loculated fluid between the abdominal wall and large intestine. Abdominal tomography confirmed the ultrasonographic findings and revealed peritoneal thickening of the anterior abdominal wall most probably representing an inflammatory reaction. He had a negative tuberculin skin test and a normal chest Xray. An ultrasound guided aspirate of the loculated fluid revealed normal appearing lymphomononuclear cells. Cytology for atypical or malignant cells and microscopy as well as a culture for tuberculosis were negative. Because of his history of recurring episodes of serositis, he was started on colchicine treatment. He has subsequently been free of abdominal pain. The mass in his left lower abdomen resolved gradually and disappeared completely 3 months after the initiation of colchicine treatment.

PATIENT 4

In April 1991, a 52 year old nonsmoking male presented with a chief complaint of recurrent unilateral shoulder pain that had persisted for many years. Physical examination revealed tender fibrotic nodules on his back and a painful right shoulder with movement but no other signs of an arthritis. His vital signs and all other examinations were normal. He described a 30 year long complaint of recurrent shoulder pain lasting two or three days occurring as often as every week or month which were always on the same side and associated with pain in his back lasting several days and a low grade fever. The pain did not resolve with physical therapy or analgesic medication. He was investigated for a possible diagnosis of angina pectoris referred to the shoulder with a normal stress electrocardiogram. Disorders including calcific tendinitis, bicipital tendinitis, a rotator cuff tear, and adhesive capsulitis were all excluded with orthopedic consultation. Amyloid arthropathy was ruled out with a negative rectal biopsy. A panel of serologic tests for collagen vascular disorders and tests for a diagnosis of polymyalgia rheumatica were all negative. Moreover, his family history was negative for tuberculosis.

Hematological and biochemical tests revealed positive C-reactive protein, an elevated ESR of 67 mm/hour and a fibrinogen level of 492 mg/dl and a leucocyte count of 13,800 mm^3. Serologic mar-

kers for viral infections and routine bacteriologic cultures were all negative. Repeated aspirations of the shoulder joint revealed normal comptement levels, no crystals (monosodium urate, cholesterol, calcium pyrophosphate dihydrate), and a white blood cell count of 6000/mm3, 50% PMNS. The joint fluid cultured negative for tuberculosis and other infectious agents. Roentgenologic studies of the shoulder were normal. He was started on colchicine treatment for a diagnosis of periodic synovitis involving the right shoulder joint and since has remained well, free of symptoms of synovitis and fibromyalgia on colchicine.

PATIENT 5

In January 1992, a 26 year old male was admitted to the emergency clinic because of upper gastrointestinal bleeding, cough, chills and fever. His temperature was 39.5°C. Examination revealed epigastric tenderness with normal bowel sounds; a spleen that was palpable 6 cm below the left costal margin, and decreased breath sounds with rales at the base of the right lung. Chest Xray confirmed a diagnosis of right lower lobe pneumonia and documented a right sided pleural effusion. An abdominal ultrasound examination revealed splenomegaly and a normal echo appearance of the liver, pancreas and kidneys as well as the major vascular structures of the abdomen. His past history revealed frequent febrile episodes with diffuse abdominal pain occurring once or twice a month since 1979. He had no identifiable disease except acute rheumatic fever at age 5 years.

He was started on procaine penicillin with a diagnosis of lobar pheumonia with an associated parapneumonic effusion. Upper gastrointestinal endoscopy revealed a non-bleeding duodenal ulcer which was treated with an H^2 receptor blocker. His pneumonic symptoms resolved within 3 days of the initiation of antibiotic treatment. His admission laboratory studies revealed a leucocytosis (12,100/mm^3) and elevated sedimentation rate (ESR: 76 mm/hour) with a normal peripheral blood smear and a normal urine analysis without proteinuria. A rectal biopsy for amyloidosis was negative. The pneumonic process resolved completely within 4 weeks. He was further investigated for a cause of his splenomegaly with serologic studies for collagen vascular disease and serologic studies for hepatitis B,C, Ebstein Barr virus, and CMV as well as posibble parasitic and bacterial infectious agents including tuberculosis, brucella, malaria and leishmania with bone marrow aspiration, biopsy, and routine cultures. All tests were non diagnostic. A normal splenoportography excluded a diagnosis of portal hypertension. He was discharged on colchicine with a clinical diagnosis of FMF with splenomegaly. On colchicine treatment, he had no further recurrences of his periodic febrile episodes. His splenomegaly clinically decreased but persisted on follow up ultrasound examinations.

DISCUSSION

FMF is a genetic disorder virtually restricted to individuals originating from the Middle East. Moreover, it is often familial (4). A diagnosis of FMF is always based on clinical evidence as no specific diagnostic test for it exists. It is characterized by self-limited recurrent attacks of fever accompanied by serositis mainly involving the peritoneum, pleura and joints (5,6). Thus, recurrent fever and abdominal pain are the major clinical signs of FMF. Peritoneal inflammation is the most common presenting problem (4). Typically, extensive studies are performed to resolve the cause of fever and serosal inflammation and no specific disease process is identified. Recently, the disease has been conceptualized as a process where in the regulation of inflamatory cytokine activation is disturbed occurring in association with an inhibition of monocyte bactericidal and phagocytic function (7). A reduction in the normal inhibitor of complement derived anaphylotoxin C5a in the synovial membranes and peritonium of the patients with FMF has been reported as potentially having some etiologic importance as C5a inhibitor activity in synovial and peritoneal fluid of patients with FMF is reported to be less than 10% of that found in normal subjects (9).

The cardinal manifestation of FMF is fever. It is almost always accompanied by a serositis, mainly peritonitis but pleuritis or a synovitis can occur also. The inflammatory reaction may be due to an increased lysosomal release of proteases and other inflammatory reactants by neutrophils within serosal membranes in response to an increased body temperature (10-12). The trigger for the fever is not known; infectious agent (s) emotional and environmental/functional changes do not appear to be important pathogenetically.

Isolated febrile attacks remain a major diagnostic problem relative to a diagnosis of FMF. Febrile episodes without an associated serositis require a

thorough evaluation to determine their origin. In the present series, two patients with fever without signs of serositis were reported. Fourteen of 470 (3%) patients in the series reported by Sohar et al (3) and two of 175 (1.1%) patients in the series of Barakat et al(4) presented with fever alone. This monosymptomatic variant of FMF has been reported in a 2 year old female child also (13).

In the present series, patient 1 is unusual in that he presented at an older age, had no family history of FMF and experienced only periodic fever. A diagnosis of FMF was made based upon similar reports in the literature (3,4,13) coupled with the exclusion of other diseases and a dramatic reduction in the number of attacks with colchicine treatment.

Patient 2 was diagnosed as having FMF after exclusion of all other potential medical or surgical causes of fever, the finding of a positive family history of the disease, and an excellent clinical response to colchicine.

Interestingly, this girl had a second genetic disease which is found at high rates in individuals of Mediterrenean origin specifically β Thalassemia trait occurring in the same individual. The gene causing FMF has been located on chromosome 16 (14) while that for β Thalassema is located on chromosome II. This finding is probably a coincidence and represents a rare occurrence of two relatively common genetic diseases found in Turkish populations occurring in a given individual. Her family history was interesting in that her 22 year old uncle has Betçet's disease and since 1986 has attended the Behçet's disease clinic at Hacettepe University Hospital.

Both FMF and Behçet's disease are recurrent inflammatory diseases of unknown etiology. As far as could be determined, the occurrence of these two unusual diseases within the same family has not been reported previously. In both diseases, abnormalities controlling inflammatory cytokine synthesis and secretion regarding monocyte TNF a, IL 6 and IL 8 overproduction and enhanced neutrophil superoxide generation are reported in the literature(15). Again, the occurrence of these 2 diseases within the same family may reflect only a rare coincidence; conversely it may point out a common genetic mechanism for the two diseases. Further investigations of patients with FMF and Behçet's disease and their families may identify a common genetic factor responsible for the two diseases.

Recurrent attacks of abdominal pain occur in almost all individuals with FMF. Acute peritoneal inflammation characterized by a fibrinous exudate is routinely identified at the time of laparoscopy in cases with active disease. Recurrent attacks of peritonitis can lead to the development of peritoneal adhesions that may cause small bowel obstruction (16). The records of 335 pediatric patients with FMF have been reported in the literature; in this series 3%, without a history of a prior laparotomy, had an episode of small bowel obstruction (16). In the present series, another unusual complication of recurrent serosal inflammation was demonstrated in patient 3, who developed an inflamatory abdominal mass. He was initially thought to have an intra-abdominal malignancy and then tuberculosis before the diagnosis of FMF was considered. His dramatic response to colchicine treatment is more consistent with a diagnosis of FMF than any other disease process. Thererare no similar case reports in the literature. In case 3, the clues that the disease responsible for the patients complaints was FMF were the fact that his recurrent shoulder pain responded to colchicine and was associated with elevated plasma fibrinogen and C-reactive protein levels as well as an increased ESR. In addition, a thorough examination of the affected joint and synovial fluid analysis excluded all other forms of arthritis. Moreover, the additional disabling complaint of this patient; febrile fibromyalgia, has been reported in the literature in association with FMF. Finally the patient improved with colchicine treatment.

Splenomegaly is occasionally seen in individuals with FMF (2) but when it does, it often leads to a consideration of alternative erroneous diagnoses which contribute to a prolongation of hospitalized as was the case in patient 5. This particular patient was hospitalised for months in an effort to exclude other possible causes of splenomegaly. The mechanisms responsible for the splenomegaly associated with FMF is unknown. The absence of amyloid in his rectal biopsy material and the absence of proteinuria suggest that amyloid is not the cause of his splenomegaly. In summary 5 unusual cases of FMF are described. They highlight the problems in diagnosis of this disease process and the need for careful follow up and colchicine treatment of suspected cases.

REFERENCES

1. Sohar E, Pras M, Heller J, et al. Genetics of familial Mediterrenian Fever (FMF). A disorder with recessive inneritance in non-Ashkenazi Jews and Armanians. Arch Intern Med. 1961; 107: 529-538.
2. Yaacou M. Familial Mediterranean Fever an autoimmune disorder or a genetic defect in a regulatory mechanism of inflammation. Isr J Med Sci. 1989; 25: 547-549.
3. Sohar E. Gafnia J, Pras M, et al. Familial Mediterrenian Fever. A survey of 470 cases and review of the literature. Am J of Med. 1967; 43: 227-253.
4. Barakat MH, Karnik AM, Majeed HWA, et al. Familial Mediterranean Fever (Recurrent Hereditary Polyserositis) in Arabs. A study of 175 patients and review of the literature. Quart J Med. 1986; 223: 837-847.
5. Cook GC. Periodic disease, recurrent polyserositis, familial Mediterranean fever or simply FMF. Quar J Med 1985; 233: 819-823.
6. Priest RJ, Nixon RK. Familial recurring polyserositis: A disease entity. Ann Intern Med 1959; 51: 1253-1274.
7. Bar-Eli M, Gallily R, Levy M et al. Monocyte functions in familial Mediterranean fever. Am J Med Sci. 1977; 274: 265-270.
8. Matzner Y, Partridge REH, Levy M, et al. Diminished activity of a chemotactic inhibitor in synovial fluids from patients with familial Mediterranean fever. Blood 1984; 63: 629-633.
9. Matzner Y, Brezezinski A. C5a inhibitor deficiency in peritoneal fluids from patients with familial Mediterranean fever. N Eng J Med 1984; 311: 287-290.
10. Bar-Eli M, Territo MC, Peters RS, et al. A neutrophil lysozyme leak in patients with familial Mediterranean fever. Am J Hematol. 1981; 11: 387-395.
11. Bar-Eli M, Ehrenfeld M, Levy M, et al. Leucocyte chemotaxis in recurrent polyserositis (Familial Mediterranean fever) Am J Med Sci. 1981; 281: 15-18.
12. Territo MC, Peters RS, Cline MJ. Leucocyte function in familial Metiterrenean fever. Am J Hematol. 1976; 1: 307-311.
13. Bock A, Simbruner G. Monosymptomatic familial Mediterranean fever as the cause of fever of unknown origin. Monatsschr-Kinderheilkd. 1993; 141: 782-785.
14. Gruberg L, Assentie, Jevich I, et al. Mapping of the familial Mediterrenean fever gene to chromosome 16. Am J Reprod Immunol. 1992; 28: 241-242.
15. Mege JL, Disen N, Sanguedolce V, et al. Overproduction of monocyte derived tumor necrosis factor alpha, interleukin 6, interleukin 8 and increased neutrophil superoxide generation in Behçet's disease. A comparative study with familial Mediterranean fever and healthy subjects. J Rheumatol. 1993; 20: 1544-1549.
16. Çiftçi AO, Tanyel FC, Buyuk pamukcu N, et al. Adhesive small bowel obstruction caused by familial Mediterranean fever and the incidence and outcome. J Pediatr Surg. 1995; 330: 577-579.
17. Langevitz P, Zemer D, Livneh A, et al. Protracted febrile myalgia in patients with familial Mediterranean fever. J Rheumatol. 1994; 21: 1708-1709.