Familial mediterranean fever (recurrent polyserositis): the gastroenterologist's viewpoint

Ailevi akdeniz ateşi (tekrarlayan poliserözitis): gastroenterologun görüş açısından

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ÖZET: *FMF daha çok ortadoğu miletlerinin bir hastalığı olup tekrarlayan peritonitle belirgin etiolojisi belli olmayan kalıtımsal bir bozukluktur. Hastalar sıklıkla gereksiz yere cerrahi mudahale geçirirler. Korkulan en önemli koplikasyonları renal ve intestinal amiloidosisdir. Bu derlemede özellikle gastrointestinal komplikasyonlarına yer verilmiştir.*

Anahtar kelimeler: **Ailevi akdeniz ateşi, renal amiloidosis**

SUMMARY: *Familial mediterranean fever (FMF) is an heritable disease of unclear etiology that results in recurrent episodes of peritonitis that occurs predominantly in people of Arabic and non-Ashkenazi origins. Clinical manifestations often lead to unnecessary surgery in patients who are nor recognized as having the disease. The major long-term significance of FMF is enteric and renal amyloidosis that leads to clinical pseudoobstruction and renal failure, respectively, with all of the clinical consequences of each. Treatment with colchicine is effective and rate of amyloidodis may be affected.*

Key words: **Familial mediterrranean fever, renal amyloidosis**

FAMILIAL Mediterranean Fever (FMF) is an inherited disorder of unknown etiology characterized by recurrent episodes of fever and inflammation of the peritoneal, pleural and synovial membranes causing abdominal and pleuritic pain and arthralgia respectively (1). Because of its clinical features, a variety of names has been applied to the condition, FMF. None of the names, including FMF, is completely satisfactory. Two, however, have had important roles in characterizing the disease. Benign paroxysmal peritonitis had been proposed by Siegal (2). Familial paroxysmal polyserositis may be a better name as it identifies the genetic and recurrent nature of the polyserositis that characterized the disease (3).

Although FMF has been reported to occur in patients of Italian and Anglo-Saxon descent, it occurs predominantly in individuals of Turkish, Arabic and Jewish origin (4). Despite the fact that the disease is often familial, 43 to 50% of the cases have a positive family history of the disease (5,6). a high rate of consanguinity is seen among the parents of individuals with FMF (5,7). The disease is transmitted by a single autosomal recessive gene with a male-to-female ratio of 3: 2 (5,7).

In 1908, Janeway and Mosenthal described the first case of FMF as individual with "unusual paroxysmal syndrome" (8). Subsequently, most individuals with the disorder have met criteria for a recurrent polyserositis. In 1945; Siegal reported 16 cases of FMF using the term "benign paroxysmal peritonitis" to describe the disorder (2). Later on, he substituted the trem" familial paroxysmal polyserositis" (9). Since, many reports from around the world have described cases and characterized the clinical features and complications of the disorder.

Etiology

Although numerous pathogenic mechanisms consisting of infection, pyrogenic hormone hypersecretion and autoimmunity have been suggested, the specific pathogenic mechanism of FMF is currently unknown (10,11). Fever and inflammation are such major signs of the disorder that frequent attempts have been made to implicate various infectious agents and/or their products as the cause

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Table 1. *Diagnostic criteria for a diagnosis of FMF*

Major Criteria	Minor Criteria
Recurrent fever	Recurrent artralgia
Recurrent abdominal pain	Childhood onset
Recurrent pleuritis	Remission pregnancy
Recurrent arthritis	Response to colchicine
Positive family history	Mediterranean ancestry
Recurrent skin lesion	Leukocytosis

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

of the disorder. Extensive serologic, immunologic and pathologic studies, however, have failed to demonstrate an exact cause or combination of factors responsible for FMF. It was initially thought that an allergic basis for the disorder might exist because of its onset early in life, its familial incidence, the histologic changes associated with the disease, its intermittent occurrence, and its frequent association with other hypersensitivity diseases (1-3, 10). This hypothesis however has not been supported by the accumulated clinical and laboratory data relative to the disease (10,11). The fact that the inflammatory reaction seen in FMF occurs in all serous membranes and fever is a hallmark of the disorder strongly suggest that some mediators or process dependent upon inflammation is responsible for the disease. Each of the cellular and physiologic abnormalities seen in patients with FMF has generated considerable pathogenic interest. None has lead to a clearer concept of the precise pathogenesis of the disease process.

Current hypothesis concerning the pathogenesis of FMF include 1) an abnormality of monocyte function particularly as it relates to the mononuclear cells bactericidal and phagocytic activity (10,12); 2) an increased release of lysosomal enzymes from peripheral neutrophils in response to high temperature (13); 3) increased neutrophil aggregating activity which is associated with increased level of lipooxygenase products in the serum (14); and 4) an increase in the number and function of B lymphocytes (10).

Recently, a deficiency of an inhibitor of C5a, a fragment of complement and an anaphylatoxin has been suggested as the cause of the disease (15-17). Matzner at al described an inhibitor of C5a in peritoneal and synovial fluids of normal subjects produced by fibroblasts (16). Peritoneal and synovial fluids obtained from individuals with FMF contain less than 10% of the amount of C5a inhibitor found in normal subjects. Since synovial and peritoneal cavities are the most frequently involved areas in FMF, this observation could explain the inflammatory characteristics of this disease as a deficit or complete absence of C5a inhibitor could lead to prolonged activation of C5a, a recognized mediator of inflammatory reaction.

Clinical Manifestation of FMF

In the vast majority of the patients, the symptoms of FMF have their onset between the ages of 5 and 15 years (7,18). Attacks can begin however, as late as 40 years of age. The duration and frequency of episodes vary markedly even in the given patient. The typical attack lasts 24 to 48 hours, but can last as long as 7 to 10 days. The most frequent time interval between successive attacks is 2-4 weeks but attacks can occur as often as twice a week to as uncommonly as once a year. Importantly individuals with FMF are completely free of pain between attacks. Another interesting point about FMF is that the frequency and severity of attacks decrease with time. This reduction in symptomatic episodes with time may reflect the development of amyloidosis. In the latter case, the neuropathic effects of amyloidosis may account for the reduction in received attacks.

Abdominal Pain

Abdominal pain occurs in all patients with FMF. However, its severity varies greatly. Minor premonitory abdominal discomfort may precede an acute attack by as much as 24 to 48 hours. As a result, most patients can predict when an attack is about to occur after a couple of episodes.

The description of the pain is very important in differential diagnosis of FMF. Typically, the pain begins in one abdominal quadrant, most often around the umbilicus, and then diffuses out to involve the entire abdomen. The pain can spread to the chest, shoulders, and occur either unilaterally or bilateral. The original site of pain on the abdomen is tender. The tenderness associated with attacks can extend to other area, particularly the back.

Nausea and vomiting can occur during attacks. The abdomen is usually distended and rigid. Bowel sounds can either be decreased or absent. Abdominal x-rays demonstrate an ileus as well as

air-fluid levels. Very rarely, an abdominal mass can be palpable during attacks. Attacks can be precipitated or aggravated by procedure such as laparascopy, laparatomy or other invasive diagnostic studies.

Cilnical Course and Complications

Abdominal laparotomy performed during acute attacks reveals acute inflamation of the involved membrane (7,10). The exudate present in the serous fluid present in active cases containes a predominance of polymorphonuclear leukocytes and has a moderately cloudy appearance although it is always sterile. These findings disappear between attacks. In patients with numerious attacks or a previous laparatomy, adhesions often develop between the various abdominal viscera and adjacent parietal peritoneum. These adhesions can cause episodes of intestinal obstruction in late cases (7,10, 19-21). No specific histopathologic features of the disease are recognized despite the well-defined clinical manifestations of the disease.

A disproportionate number of male patients with FMF develop symptoms of gallbladder disease which leads to a cholesistectomy. Typically no histopathologic evidence of cholesistitis is demonstrable in the resected gallbladder.

Amyloidosis is the most feared complication of FMF (22). The amyloid is found in the intima and media of medium-size arterioles, the subendothelial region of medium-sized venules, renal glomeruli and the spleen. Thus, the amyloidosis in FMF involves the kidneys, gastrointestinal tract, and adrenal glands predominantly. The heart and liver are rarely involved. Ayloidosis occurs more often in Turkish and non-Ashkenazi Jewish individuals with disorder than in individuals with other racial grounds.

The clinical onset of amyloidosis in cases of FMF is independent of the individual's age and duration of disease but appears to be related to a familial history of amyloidosis, racial background, and the presence of joint involvement (10). Kidneys biopsy is the most reliable method for establishing a diagnosis of amyloidosis in case of FMF but rectal biopsy is easier and safer and yield a positive result in 75% of the cases subsequently confirmed by the kidney biopsy.

Many investigators believe that amyloidosis is an invariable consequence of recurrent inflamation and can be expected to occur eventually in all patients with FMF. Others believe that amyloidosis can be retarded and even reversed with colchicine therapy. Kidney transplantation is often necessary in cases of advanced renal failure due to amyloidosis. In such cases, it is essantial that the colchicine therapy be reinstituted immediately after kidney transplantation or new amyloid deposits will develop in the transplanted kidney. Other complications of amyloidosis include: intestinal pseudo-obstruction, gastrointestinal bleeding, emotional instability, and growth retardation (7,21). Sterility can occur in women as a result of mechanical problems as a consequence of pelvic adhesions (23). Decreased sperm counts have been reported in men with FMF (24).

Manifestations of Amyloidosis

Amyloidosis occurs as a consequence of FMF in 90% of untreated patients (22). Its development appears to be dependent both on the ethnic origin of the individual and the length of follow-up (3,5,7,25). The amyloidosis can be characterized as occurring over four sequential stages: a preclinical, a proteinuric, a nephrotic, and an uremic stage (7,22). Virtually all FMF patients, who have gastrointestinal symptoms such as diarrhea, intestinal pseudo-obstruction and altered bowel habits also have proteinuria. Specifically, all FMF patients with gastrointestinal involvement, occuring presumably as a consequence of visseral neuropathy, have renal involvement. In contrast, not all individuals with renal amyloid have intestinal symptoms and neuropathy.

The gastrointestinal signs and symptoms of amyloidosis associated with FMF include anorexia, macroglossia, intestinal pseudo-obstruction, diarrhea, and malabsorption.

The amyloid deposits can be documented throughout the entire gastrointestinal tract in involved cases (26,27). A rectal biopsy is positive for amyloidosis in 75% of involved cases. In advanced cases, macroglossia, intestinal pseudoobstruction (28,29), lower gastrointestinal bleeding (26), drug resistant diarrhea (26), and malabsorption occur. Perforation of the colon as a consequence of ischemic colitis and colonic amyloid infiltration of the colonic wall has been reported (30,31). Intestinal pseudo-obstruction occurs as intestinal amyloidosis impairs gastrointestinal motility as a consequence of both muscle and neuropathic involvement (29,31). Chronic intestinal pseudo-

obstruction has been reported in 7% of FMF patients with amyloidosis.

Endoscopic Findings of Gastrointestinal Amyloidosis Seen in FMF

The usual findings of amyloidosis seen at colonoscopy are mucosal friability, erythema and sign of intestinal ischemic changes consisting of mucosal edema, atrophy, stricture and ulcers. Rarely luminal narrowing resembling a colonic tumor can be seen (22). The most encountered abnormalities in the upper gastrointestinal tract are erosions and mucosal friability. When biopsy are taken from either suspected areas or normal appearing mucosa, amyloid deposits are usually found (33).

Small bowel contrast studies in cases of amyloidosis occurring in FMF demonstrate mucosal nodularity, edema and stasis. In advanced cases, a pattern typical of malabsorption can be seen. Rarely, amyloidomas or masses of amyloid can be identified.

Diarrhea

Bacterial overgrowth as a result of intestinal neuropathy is a major clinical problem in late cases of intestinal amyloidosis (34,35). Antibiotic therapy can temporarily improve an individual's symptoms but rarely provides long-term improvement. Frequent changes in the antibiotic being used is required to prevent the development of antibiotic resistant bacterial flora.

Macroglossia

Macroglossia occurs in 20% of cases of amyloidosis regardless of the etiology (36). Macroglossia never occurs in FMF without amyloidosis.

Other Manifestation of FMF

Pleuritic chest pain due to inflammation of the parietal and visceral pleura occurs in more than half the patients with FMF (7). Transient pleural effusions may occur as well. Pleuritic attacks usually subside within 12 to 72 hours and typically last less long than does abdominal pain. Joint involvement in FMF occurs in 3 different forms and can be seen in 20% to 70% of cases depending on their ethnic background. 10% of patients with FMF experience tender, red hot plaques, mimicking erysipelas on their extensor surfaces of the lower legs and over the ankle joints. Other less lesions are erythema nodosum, urticaria, and angioneurotic edema.

Diagnosis

When a typical acute attack of FMF occurs in an individual of appropriate ethnic background who has a family history of FMF, the diagnosis can be made easily (Table 1). When an individual is seen for the first time in the absence of such a history, a variety of other febrile illnesses and diseases characterized by abdominal pain must be excluded by appropriate studies and observation before a diagnosis of FMF can be made. These include acute appendicitis, acute pancreatitis, acute cholecystitis, porphyria, intestinal obstruction due to any causes and an acute urinary tract infection.

Physical Examination

During asymptomatic intervals, individuals with FMF typically have no abnormal physical findings. Splenomegaly occurs in approximately 10% of cases. On the other hand, during acute attacks, the typical physical findings are those of localized or generalized peritonitis, pleuritis, or acute arthritis. In patients complicated with neuropathic amyloidosis, the individual's complaints of pain are less severe or even absent.

Laboratory Tests

Only a few laboratory tests are helpful during acute attacks of FMF. The white cell count can be increased up to 20.000/mm3. The WBC count rapidly returns to normal value 24-36 hours of the initiation of an attack. Fibrinogen levels and the sedimentation rate are increased during acute attacks. Other serum proteins such as C-reactive protein, alphal globulin, alpha2 globulin, and beta2-macroglobulin, as well as haptoglobin and cryofibrinogen levels are often increased during attacks. However, none of these change in serum protein levels are specific or diagnostic for FMF. Moreover their absence does not exclude the diagnosis of FMF. The presence of proteinuria indicates renal disease, usually due to amyloidosis.

Treatment of FMF

Daily colchicine therapy effectively prevents recurrent attacks in more than 70% of patients (10). Colchicine is absorbed from small intestine and concentrates in leukocytes. It inhibits a number of leukocyte functions associated with a reaction to inflamation. The inhibition of leukocyte chemotaxis by colchicine may be responsible for the suppressive effect of the drug on frequency and severity of the attacks.

Colchicine is indicated in individuals with the following signs of the disease: 1) frequent attacks, 2) for the children who have developmental problems, 3) individuals at risk for amyloidosis, and 4) those with biopsy-proven amyloidosis. Usually the drug is administered in two divided doses of 1.2 to 1.8 mg daily. Occasional patients require doses as much as 2.4 mg daily to prevent attacks.

Mild diarrhea can occur with the use of colchicine. The diarrhea tends to subside after 2 to 3 days off drug. Colchicine should be discontinued 3 months before planned conception and during first trimester of the pregnancy in an effort to avoid fetal toxicity.

It is essantial that patients be instructed that intermittent colchicine therapy is not beneficial for controlling attacks and worseyetnot prevent amyloidosis.

REFERENCES

1. Ehrenfeld EN, Eliakim M, Rachmilewitz M. Recurrent polyserositis (familial Mediterranean fever; periodic disease). A report of fifty-five cases. Am J Med 1961; 31: 107-123.
2. Siegal S. Benign paroxysmal peritonitis. Ann Intern Med 1945; 23:1-21.
3. Siegal S. Familial paroxysmal polyserositis. Analysis of fifty cases. Am J Med 1964; 36:893-918.
4. Meyerhoft J. Familial Mediteranean fever: report of large family, review of the literature and discussion of the frequency of amyloidosis. Medicine 1980; 59:66-70.
5. Barakat MH, Karnik AM, Majeed HWA, El-sobki NI and Fennech FF. Familial mediteranean fever (recurrent hereditary polyserositis in Arabs- A study of 175 patients and rewiev of the literature. Quart J Med 1986; 223:837-847.
6. Schwabe AD, Peters RS. Familial Meditatennean Fever in armenians. Analysis of 100 cases. Medicine 1974; 53:453-462.
7. Sohar E, Gafni J, Pras M, et al. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967; 43:227-253.
8. Janeway TC, Mosenthal HO. An unusual paroxysmal syndrome, probably allied to recurrent vomiting, with a study of nitrogen metabolism. Trans Assoc Am Physicians 1980; 23:504-518.
9. Siegal S. Benign paroxysmal peritonitis. Second series. Gastroenterology 1949; 12:234-247.
10. Eliakim M, Levy M, Ehrenfeld M. Recurrent Polyserositis (Familial Mediterranean Fever, Periodic Disease). Amsterdam: Elsevier/North Holland, 1981.
11. Ben-Chetrit E, Levy M. Autoantibodies in familial Mediterranean fever (recurrent polyserositis). Br J Rheumatol 1990; 29:459-461.
12. Bar-Eli M, Gallily R, Levy M, et al. Monocyte functions in familial Mediterranean fever. Am J Med Sci 1977; 274: 265-270.
13. 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.
14. Aisen PS, Haines KA, Given W, et al. Circulating fatty acids in familial Mediterranean fever. Proc Natl Acad Sci USA 1985; 82:1232-36.
15. Matzner Y, Brzezinski A. C5a-inhibitor deificiency in peritoneal fluids from patients with familial Mediterranean fever. N Engl J Med 1984; 311:287-290.
16. Matzner Y, Gavison R, Shlomai Z, et al. Production of C5a antogonist by synovial and peritoneal tissue fibroblasts. J Cell Physiol 1986; 129:215-220.
17. Matzner Y, Ayesh SK, Hochner-Celniker D, et al. Proposed mechanism of the inflammatory attacks in familial in Mediterranean fever. Arch Intern Med 1990; 150:1289-91.
18. Heller H, Sohar E, Sherf L. Familial Mediteranean Fever. Arch Intern Med 1958; 102:50-71.
19. Schwabe AD, Peters RS. Familial Mediterranean fever in Armenians. Analysis of 100 cases. Medicine (Baltimore) 1974; 53:453-462.
20. Nixon RK, Priest RJ. Familial recurring polyserositis simulating acute surgical condition of the abdomen. N Engl J Med 1960; 263:18-21.
21. Tal Y, Berger A, Abrahamson J, et al. Intestinal obstruction caused by primary adhesions due to Mediterranean fever. J Pediatr Surg 1980; 15:186-187.
22. Livneh A, Zemer D, Langevitz P, Laor A, Sohar E, Pras M. Colchicine Treatment of AA amyloidosis of familial mediterranean fever: An analysis of factors affecting outcome. Arthr Rheum 1994; 37:1804-11.
23. Priest RJ, Nixon RK. Familial recurring polyserositis: a disease entity. Ann Inter Med 1959; 51:1253-74.
24. French DJ, Leeb CS, Jecht EW. Reduction in sperm output by febrile attacks of familial mediterranean fever: a case report. Fertil Steril 1973; 24:490-493.
25. Gafni J, Ravid M, Sohar E. The role of amyloidosis in familial Mediterranean fever. Isr J Med Sci 1968; 4: 995-999.
26. Brandt K, Cathcart ES, Cohen ES. Clinical analysis of the course and prognosis of 42 patients with amyloidosis. Am J Med 1968; 44:955-969.
27. Tada S, lida M, Iwashita A, et al. Endoscopic and biopsy findings of the upper digestive tract in patients with amyloidosis. Gastrointest Endosc 1990; 36:10-14.
28. Legge DA, Wollaeger EE, Carlson HC. Intestinal pseudoobstruction in systematic amyloidosis. Gut 1970; 11:764-767.
29. Wald A, Kichler J, Mendelow H. Amyloidosis and chronic intestinal pseudo-obstruction. Dig Dis Sci 1981; 26:462-465.
30. Takhashi S, Morita T, Koda Y, Murayama H, Hivasawa Y. Gastrointestinal involvement of dialysis-related amyloidosis. Clin Nephrol 1988; 30:168-71.
31. Kyzer S, Korzets A, Zevin D. Oschemic Colitis complicating AA amyloidosis and f. Isr J Med 1993; 29:212-214.

32. Battle WM, Rubin MR, Cohn S, Snape WJ Jr. Gastrointestinal motility dysfunction in amyloidosis. N Engl J Med 1979; 301:24-25.

33. Lee JG, Wilson JAP, Gottfried MR. Gastrointestinal Manifestations of Amyloidosis. South Med J 1994; 87:243-247.

34. French JM, Hall G, Parish DJ, et al. Peripheral and autonomic nerve involvement in primary amyloidosis associated with uncontrollable diarrhea and steatorrhea. Am J Med 1965; 39:277-284.

35. Feurle GE. Pathophysiology of diarrhea in patients with familial amyloid neuropathy. Digestion 1987; 36:13-17.

36. Burke TS, Tatum JL, Fratkin MJ. Accumulation of Tc-99m MDP in amyloidosis involving the tounge. Clin Nucl Med 1990; 15:107-109.