

Familial Mediterranean fever and acute anterior myocardial infarction in a young patient

Genç bir hastada ailevi Akdeniz ateşi ve akut ön cidar miyokard infarktüsü

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease found more commonly among Sephardic and North African Jewish people, Armenians, Arabs, Druze and Turks, and is manifested by recurrent self-limited febrile attacks of peritonitis, pleuritis and arthritis and characterized by clinical, histological and laboratory evidence for localized and systemic inflammation (1). Colchicine treatment usually prevents the attacks and the associated inflammation.

During the febrile attacks, an acute phase response develops, manifested by a marked increase in erythrocyte sedimentation rate (ESR), white blood cell count (Wbc), fibrinogen, serum Amyloid A, phospholipase A2 and C-reactive protein (CRP) (2). Inflammatory mediators like interleukin -6 (IL-6) and soluble receptors of tumor necrosis factor (TNF) were found also to be increased during FMF attacks (3).

Inflammation also plays an important role in the initiation and progression of atherosclerosis and ischemic heart disease (IHD) (4). A study showed that in normal men, serum levels of CRP may predict future myocardial infarction and ischemic stroke. The increased risk of elevated CRP was independent of lipid-related and non-lipid related cardiovascular risk factors.

We report a rare case of a patient with long-standing FMF who presented with acute myocardial infarction. With respect to the inflammatory background of atherosclerosis, we may expect an increased morbidity of ischemic heart disease in patients with FMF.

Case Report

A 22-year-old man was admitted with acute anterior myocardial infarction. He had no known coronary risk factors and was being followed because of FMF for ten years. He was on colchicine treatment except last two years. During FMF attacks, he had abdominal pain, high fever, skin eruption in his legs and dim eyesight. He had weakness, widespread abdominal pain, skin eruption in his both legs and 39°C fever for two days. He was taken to a private center for the complaining of retrosternal chest pain. After determining cardiopulmonary arrest, he was intubated and

resuscitated for five minutes and then transported to our hospital. Because of the patient developing cardiopulmonary arrest again after being taken to intensive care unit, rhythm was obtained by applying cardiopulmonary resuscitation (CPR) for an hour. On electrocardiogram (ECG) taken in the condition of the blood pressure 100/60 mmHg, the pulse 80/min, unconsciousness and intubation, ST elevation in D1, aVL, V1-V6 and ST depression in D2, D3, aVF were determined (Fig. 1). According to anamnesis received from his immediate family, it was reported that the patient described a squeezing chest pain in retrosternal area for the first time and it lasted for 4 hours, and then he was taken to the hospital because it didn't stop. Thrombolytic treatment was not applied to the patient because of traumatic CPR. The patient was followed by the antiedema, antiischemic and inotropic treatment. He was monitored hemodynamically. Central venous pressure of 9 mmHg and pulmonary capillary wedge pressure of 16 mmHg were measured. In the first blood results, troponin T - 23 ng/ml, aspartate aminotransferase - 139 U/L, alanine transaminase - 76 U/L, lactate dehydrogenase - 546 U/L, Urea - 23 mg/dl, Creatinine - 1.1 mg/dl, Na 139 meq/L, K⁺ - 37 meq/L, hemoglobin - 14.6 g/dl, Hematocrit - 43.5%, white blood cell count (Wbc) - 54200 cell/μL, PNL 96%, platelets - 400000/mm³, total cholesterol - 141 mg/dl, Triglyceride - 126 mg/dl, high density lipoprotein (HDL) - 50 mg/dl, Low density lipoprotein (LDL) - 66 mg/dl, fasting blood glucose - 101 mg/dl, creatine kinase - MB (CK-MB) - 1000 U/L were determined. In the laboratory values checked on the third day, the determined laboratory values were CK-MB - 427 U/L, Wbc - 36700 cell/μL, PNL % 93, erythrocyte sedimentation rate - 62mm/h, fibrinogen - 648 mg/dl, haptoglobin - 356 mg/dl, seruloplasmin - 67 ng/dl, CRP - 15 mg/L. On the third day of being hospitalized, inotrop need of the patient lasted and he was extubated. There were a 50 % stenosis in the left anterior descending artery after first diagonal ramus, and ectatic area after this stenosis on coronary angiography (Fig. 2) taken on the fourteenth day. Echocardiography was applied to the patient when he was taken to the service on the fifteenth day. On echocardiography left ventricular end-diastolic dimension was - 6.4 cm, left ventricular end-systolic dimension - 5.8 cm, interventricular septum - 0.7 cm, posterior wall thickness - 0.8 cm, aortic root dimension - 2.8 cm, left atrium size - 4.4 cm, ejection fraction - 25%, normal

basal segments, apical hypokinesis, apicolateral heavy hypokinesis, 2/3 distal septum akinesis, E/A ratio 2:1, deceleration time - 150 msn, isovolumetric relaxation time - 80 msn, 1(+) mitral regurgitation, and normal valve structures were determined. In this situation the patient had advanced left ventricle systolic dysfunction, restrictive pattern and dilatation of his left ventricular cavity. On the 21st day of hospitalization, he was discharged from the hospital with aspirin 100 mg 1x1, carvedilol 6.25mg 2x1/2, digoxin 1x1, spironolactone 25 mg 1x1, colchicine 0.6 mg 3x1 and Ramipril 2.5 mg 1x1. The patient was seen twice in the polyclinic with this treatment for three months. Then he applied to our hospital because of weakness and shortness of breath. After determining hypotension, he was taken to intensive care unit and inotrop treatment was started. At 24th hour, the patient was resuscitated but he did not respond to resuscitation.

Discussion

Attacks of FMF are associated with various markers of inflammation, which are reflected: a) clinically by fever and pain in the affected sites b) histologically by an invasion of polymorphonuclear leukocytes to the serosal membranes c) serologically by

activation of the cytokine cascade with elevated levels of IL-6 and soluble receptors of TNF and particularly by the increased production of the acute phase plasma proteins, fibrinogen, CRP, serum Amyloid A and phospholipase A2 (2).

Inflammation has a role in both the precipitation of acute ischemic events and the chronic development of atherosclerosis underlying IHD. This notion is supported by several lines of evidence. Elevated serum levels of CRP are predictive of future myocardial infarction and ischemic stroke, and administration of aspirin decreases this risk in direct correlation to the reduction in CRP values. Elevated levels of CRP were found in patients with unstable angina (5). In addition, inflammatory cell infiltrates and evidence for immunological activation of these cells may be found in atheromatous plaques in both acute and chronic ischemic syndromes (6). The IL-6 was found to be associated with the recruitment of macrophages and monocytes into atherosclerotic plaques (7).

In view of the fact that inflammation is a risk factor for ischemic events and is a sine qua non of FMF attacks, and that colchicine prevents attacks completely in 60% of FMF patients, with 30% experiencing a significant improvement but still suffering from some inflammatory FMF attacks, and the other 10% rema-

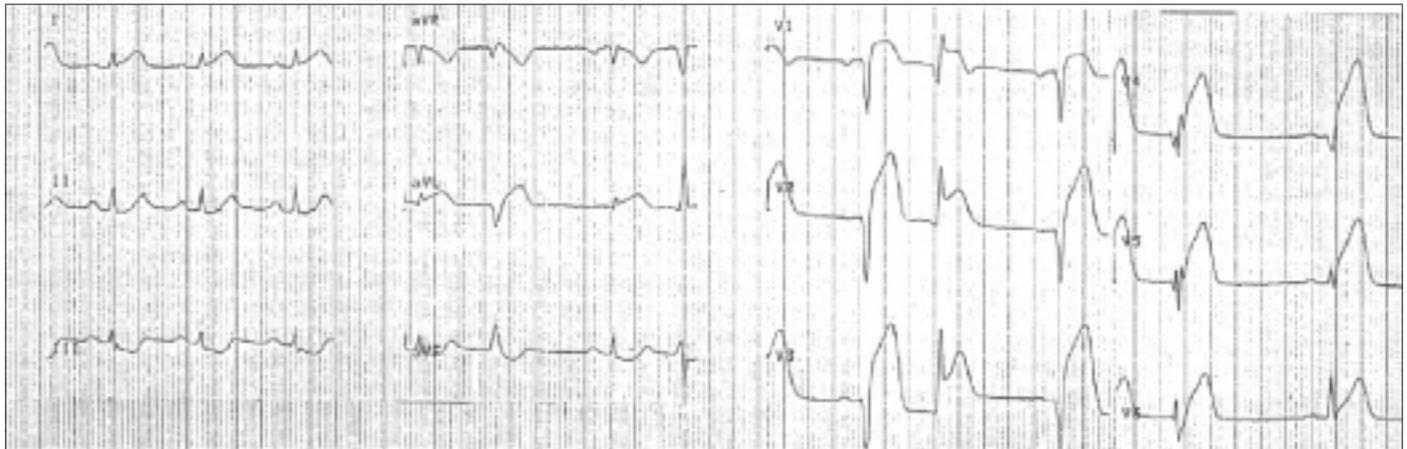


Figure 1. Electrocardiogram of the patient with familial Mediterranean fever

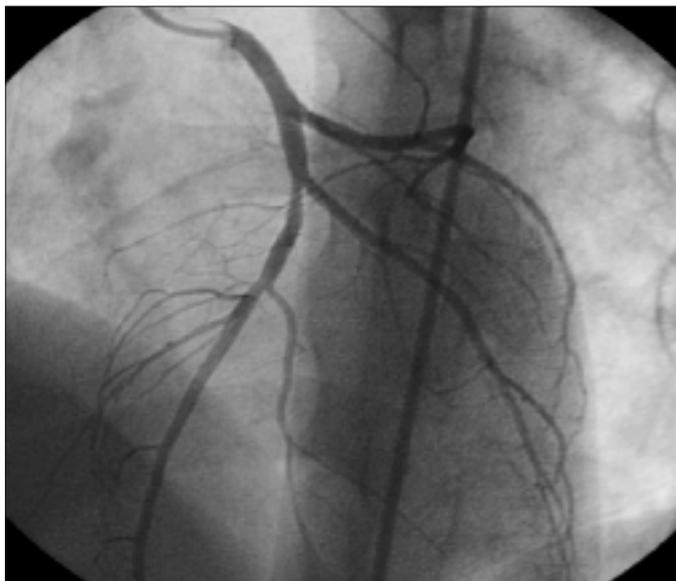


Figure 2. Angiogram of the patient with familial Mediterranean fever

ining unaffected. In a trial, failure to display higher than normal rates of ischemic heart disease in FMF may be attributed to the continuous lifelong therapy with colchicine (8), started in most FMF patients before age 20 (9).

This pathology is very common among the ethnically predisposed population. The frequency of the gene in carriers was computed to be 1:7-1:20 in North African Jewish people (10). Such frequency favors a protecting role for the gene. However in order to be widely scattered among the population, a protective gene should offer its benefits prior to or during the childbearing age. Protection against IHD, which is a disease of the elderly does not carry any evolutionary advantage and therefore it is unlikely to be related to the FMF gene. Langevitz et al (8) trial support a probable role for colchicine in the protection against inflammation induced by atherosclerosis. That our patient was being followed because of FMF for ten years and had been taking colchicine regularly until two years before he died, and appearance of retrosternal pain for the first time in the period when he stopped taking medicine, with further development of acute myocardial infarction with complications and the process which lead to the death of the patient may support the results of the studies mentioned above.

References

1. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43: 227-53.
2. Knecht A, de Beer FC, Pras M. Serum Amyloid A protein in familial Mediterranean fever. *Ann Intern Med* 1985;102: 71-2.
3. Gang N, Drenth JP, Langevitz P, Zemer D, Brezniak N, Pras M, et al. Activation of the cytokine network in familial Mediterranean fever. *J Rheumatol* 1999; 26: 890-7.
4. Munro JM, Cotran RS. The pathogenesis of atherosclerosis: atherogenesis and inflammation. *Lab Invest* 1988; 58: 249-61.
5. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, et al. The prognostic value of C-Reactive protein and serum Amyloid A protein in severe unstable angina. *N Engl J Med* 1994; 331: 417-24.
6. Fuster V, Badimon L, Badimon JJ, Chesebro YM. The pathogenesis of coronary artery disease and of the acute coronary symptoms. *N Engl J Med* 1992; 326: 242-50.
7. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, et al. Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996; 94: 874-7.
8. Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. *Isr Med Assoc J* 2001; 3: 9-. Zemer D, Revach M, Pras M, Modan B, Schor S, Sohar E, et al. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. *N Engl J Med* 1974; 291: 932-4.
10. Daniels M, Shohat T, Brenner-Ullman A. Familial Mediterranean Fever. High gene frequency among the Ashkenazic and Non-Ashkenazic Jewish population in Israel. *Am J Med Genet* 1995; 55:311-4.



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