Familial Mediterranean fever without cardinal symptoms and role of genetic screening

T. Ulas¹, H. Buyukhatipoglu¹, C. Bes², M.S. Dal³, I. Hacibekiroglu¹, H.G. Apucu⁵, F. Borlu⁶

¹Faculty of Medicine, Department of Internal Medicine, Harran University, Sanliurfa, Turkey; ²Faculty of Medicine, Department of Rheumatology, Abant Izzet Baysal University, Bolu, Turkey; ³Faculty of Medicine, Department of Hematology, Dicle University, Diyarbakir, Turkey; ⁴Department of Oncology, Deşkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey; ⁵Department of Internal Medicine, Avukat Cengiz Gökçek State Hospital, Gaziantep, Turkey; ⁶Department of Internal Medicine, Sisli Etfal Training and Research Hospital, Istanbul, Turkey

INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited autosomal recessively transmitted inflammatory disease that commonly occurs in Mediterranean descent (1, 2). The diagnosis is made by clinical findings, presence of inflammatory episodes of fever and serositis, family history and genetic studies. Identification of the most prevalent mutations of the MEFV gene may confirm atypical or incomplete forms of FMF disease, which are difficult to be recognized by the classical diagnostic criteria (3). In this report, we present a case of incomplete abdominal pain episodes of FMF disease limited to epigastrium and presented with no fever, peritoneal signs, arthritis, chest pain, and family history. This study was performed in Sisli Etfal Training and Research Hospital, Istanbul, Turkey.

CASE REPORT

A 34-year-old male patient was admitted to our hospital with complaints of epigastric abdominal pain and vomiting that had been continuing for 5-6 years. The painful episodes occurred monthly or bimonthly and resolved spontaneously within 4-5 days. Fever, arthralgia, chest pain and diarrhea did not accompany with his abdominal pain. He has no relevant family history regarding his atypical complaints. His pain was prominent especially at nights and his urine was always dark in the mornings. Because of this atypical complaints he admitted several times to hospital but a diagnosis had never been made. On physical examination the pain was limited to epigastrium and no peritoneal sign was apparent. Cardiovascular, pulmonary and genitourinary system examinations were found to be normal. Epigastric tenderness was

SUMMARY

Familial Mediterranean fever is an autosomal recessive disorder characterized by paroxysmal episodes of fever and serosal inflammation. The classical presentation is fever and severe recurrent abdominal pain due to serositis that lasts for one to three days and the resolves spontaneously. Between the episodes patients are asymptomatic. Ninety-five percent of patients with familial mediterranean fever have painful episodes localized to the abdomen, which is usually the dominant manifestation of the disease. Herein, we present a case of a 34-year-old man with incomplete abdominal pain episode of familial mediterranean fever limited to the epigastrum and had no cardinals symptoms of this disease. The diagnosis was made by genetic screening. Successful treatment response was achieved by colchicine.

Key words: Abdominal pain, familial Mediterranean fever, screening, genetic.
the sole clinical finding on entire physical examination. Laboratory examinations revealed the following: Erythrocyte sedimentation rate: 72 mm/h, CRP: 127 (0-6 mg/L); fibrinogen: 462 (212-488 mg/dL); WBC: 6900/uL, Hgb: 12.8 gr/dL, Hct: 39%; Plt: 355000/uL, Ferritin: 142 (30-400 ng/mL); vitamin B12: 538 (197-886 pg/mL); folic acid: 15 (3.1-17.5 ng/mL); total protein: 8.3 (6.6-8.7 gr/dL); albumin: 3.9 (3.4-4.8 gr/dL); globulin: 4.4 (1.5-3.7 gr/dL); IgA: 466 (70-400 mg/dL); IgG: 2036 (700-1600 mg/dL); IgM: 53 (40-320 mg/dL). There were 2-3 leukocytes/hpf on urine analysis, and no proteinuria was detected in 24-hour urine collection. Imaging studies of the abdomen including abdominal ultrasonography and tomography were normal.

Gastroscopic examination was unremarkable. Upon his history of recurrent abdominal pain and dark urine the diseases of porphyria and paroxysmal nocturnal hemoglobinuria were considered in differential diagnosis.

Although we did not detect a color change in the urine during the follow-up, we analyzed porphyria derivatives in 24-hour urine, CD55 and CD59 levels, and acid ham test. The test results were as follows: Porphobilinogen: 0.64 (0-2 mg/day); ALA: 6.20 (0-7 mg/day); Uroporphyrin I, III: 18.60 (0-25 ug/day); Heptacarboxyporphyrin: 0.71 (0-5 mmol/L); Hexacarboxyporphyrin: 0.1 (0-2 mmol/L); Pentacarboxyporphyrin: 0.95 (0-5 mmol/L); Coproporphyrin I: 29.6 (0-25 mmol/L); Coproporphyrin III: 10.3 (0-75 mmol/L). CD55 and CD59 were positive and acid ham test was negative.

Therefore, based upon the test results, porphyria and PNH were excluded. Thus, we suspected a diagnosis of incomplete FMF disease which presented with only abdominal pain episodes. M694V mutation homozygous was found on genetic analysis. According to the lack of proteinuria on 24-hour urine collection and to the negative staining for amyloidosis in duodenal biopsy sample, the diagnosis of FMF phenotype II was excluded. Once the diagnosis of FMF was made by genetic screening, the patient was started on colchicum 0.5 mg three times daily. His complaints resolved noticeably and inflammatory markers returned to normal levels. The patient has been doing well on follow-up visits since discharge.

DISCUSSION

To the best of our knowledge this is the first documented case of incomplete FMF with abdominal pain episodes limited to epigastrium without the cardinal signs of FMF. FMF is an autosomal recessive disorder virtually restricted to certain ethnic groups originating from the Middle East: Sephardic Jews, Armenians, Arabs, Druze and Turks. It is characterized by recurrent episodes of serosal inflammation, chest pain and arthritis, usually accompanied by fever (4). The disease is caused by mutations in a gene named MEFV, which encodes a protein called pyrin/marenostrin (5, 6).

Clinical signs and symptoms, family history and genetic screening tests are important in order to make the diagnosis; criteria of Tell-Hashomer are most often used for the diagnosis (7). Only one major criterion was present in our case (good response to continuous colchicum therapy), while minor criteria were not. Among the other criteria proposed proposed by Livneh et al. (8), one major criteria (incomplete abdominal attacks), one minor criteria (good response to colchicines) and four supportive criteria (ethnicity, attacks regressing spontaneously, no symptoms at attack intervals, abnormal test results of temporary inflammation) were present in our case. Given this, our case should have met the required criteria of complete FMF disease.

Genetic screening is highly specific and sensitive for the diagnosis of FMF. Identification of the most prevalent mutations of the MEFV gene can confirm atypical or incomplete forms of FMF that are difficult to recognize considering only the classical major and minor criteria (3). To date, 30 mutations in the MEFV gene have been found to be associated with FMF. M694V
mutation (51.5%) is the most common type in FMF patients in Turkey. The diagnosis of FMF is relatively easy in patients who presented with typical clinical manifestations, had family history, and were from certain ethnic origins (9, 10); but it may be difficult in subjects in whom these components are atypical or unhelpful. Cloning of MEFV now allows a new and reliable diagnostic test for FMF (11). We found homozygous M694V mutation in our case; thus, our patient was diagnosed as FMF by genetic screening. After definitive diagnosis, he was started on colchicine treatment, his symptoms alleviated and inflammatory markers reduced on follow-up visits. He has been doing well and did not experience abdominal pain since he started colchicine.

In conclusion, FMF disease should be kept in mind in the differential diagnosis of abdominal pain, especially in patients from Mediterranean origin, as it was in our patient. At that point molecular analyses for FMF genes can be helpful. Further knowledge of this more extensive clinical spectrum could help in having new diagnostic and therapeutic perspective based on the treatment of colchicines and secondary prevention of amyloidosis. Correct recognition of these cases and patient follow-up after diagnosis are important.

■ REFERENCES