The Coincidence of Familial Mediterranean Fever and Hypereosinophilia in a Patient with Hereditary Elliptocytosis

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Abstract Familial Mediterranean fever (FMF) is a genetic disease with autosomal inheritance characterized by recurrent fever, abdominal pain, and serositis attacks. It is relatively common in the races and ethnical groups around Mediterranean Sea (Sephardic Jews, Armenians, Turks and Arabians). Hereditary elliptocytosis (HE) is common genetic defect of the red blood cell membrane skeleton. Spectrin mutations are the predominant causes of HE. Hypereosinophilia is defined as a number of eosinophil granulocytes equal or greater than $0.5 \times 10^9/L$ of circulating blood. The main causes are allergies and parasitic infections. This case report describes a Turkish female HE patient who presented with FMF and hypereosinophilia. Genetic analysis revealed heterozygous mutation in exon 10 of the *MEFV* gene (V726A). The patient was successfully treated with colchicine and steroid treatment at 3-month follow-up. To the best of our knowledge, this is

the first report of association between FMF, HE, and hypereosinophilia.

Keywords Familial Mediterranean fever · Hereditary elliptocytosis · Hypereosinophilia

Introduction

Hypereosinophilia is defined as a number of eosinophil granulocytes equal or greater than $0.5 \times 10^9/L$ of circulating blood [1]. The main causes are allergies and parasitic infections. Hypereosinophilia may result from numerous causes most of which can be identified by throughout patient's history. It is secondary to an infection, an environmental allergen, or a medication [2]. Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by self-limiting recurrent attacks of fever and serosal inflammation, leading to abdominal, thoracic or articular pain [3]. A previous epidemiological study has shown that the prevalence of FMF carriers is 20 % in the Turkish population [4]. It has been generally accepted that the clinical onset of FMF begins before 20 years of age in most patients. Onset of the disease at an older age may occur but is rare [5]. Hereditary elliptocytosis (HE) reflects a diminished elasticity of the erythrocyte membrane skeleton [6]. This disease is diagnosed by the appearance of the characteristic elliptocytes microscopically [7]. Inheritance can be autosomal dominant or recessive. Patients with HE are generally asymptomatic but approximately 10 % have moderate to severe anemia including a few reported cases of hydrops fetalis and the severe variant hereditary pyropoikilocytosis, characterized by important membrane fragmentation and reduced membrane surface area [8]. In the present study, we reported a HE case accompanied by

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FMF and hypereosinophilia, as it hasn't been reported in the literature so far.

Case

A 27 years old female patient visited emergency room of Erciyes University for fever, abdominal pain and vomiting. It was found that anemia and splenomegaly was found and she was diagnosed as HE by peripheral blood smear when she was two years old, in pediatrics clinic; followed by splenectomy. She had no past another medical history, family history and history of tobacco, alcohol, illegal drug use, and travel. She had been suffering from recurrent periodic fever, abdominal pain, and vomiting every two months since 6 months ago. She complained of abdominal discomfort for three days and fever for two days followed along with whole abdominal pain and vomiting, and then the symptoms resolved spontaneously. Her vital signs were blood pressure 110/70 mmHg, pulse 88/min, respiratory rate 23/min, and body temperature 38.7 °C on admission. In abdominal examination, there was generalized tenderness but not defense or rebound tenderness. Hypoactive bowel sounds were checked on the abdomen. There was no hepatomegaly or lymphadenopathy. Initial laboratory results showed that leukocyte was 35,860/ μ L (neutrophil 28,330/ μ L, eosinophil 5,080/ μ L), hemoglobin 15.5 g/dL, platelet 521,000/ μ L, C-reactive protein 53.68 mg/L, and the erythrocyte sedimentation rate 40 mm/h. There were diffuse elliptocytes and increased eosinophils on the peripheral blood smear (Fig. 1).

Her past medical history is negative for atopic diseases. No abnormal finding was detected in viral, bacteriological and autoimmune evaluations; in addition, no growth was found in culture tests: cytomegalovirus (CMV), rubella

Fig. 1 Elliptocytosis red blood cells and increased eosinophils in the peripheral blood smear (magnification $\times 200$, Wright stained)

virus, herpes simplex virus (HSV), varicella zoster virus (VZV) and Epstein–Barr virus evaluations, hepatitis markers and brucellosis test were found as negative. Antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), anti smooth muscle antibody (Anti Sm), anti-topoisomerase I (anti-Scl-70) antibody, anti-Sjögren's syndrome A (anti-SSA), anti-Sjögren's syndrome B (anti-SSB) were also negative. Folic acid, vitamin B12, liver and kidney function tests; serum electrolytes, albumin levels, and prothrombin time were in the normal ranges. Investigations to detect a possible parasitic infection or an atopic cause were negative. Immunoglobulin levels were normal. On the abdominal ultrasonography, free fluid was observed at perihepatic area and between intestinal loops at pelvis. Patient was admitted to internal medicine clinic. A sonography-assisted sampling from intraabdominal fluid was planned; however, it was failed to obtain sample due to profound location of free fluid. The chest X-ray, ECG and echocardiogram, lung function tests, and CT of the chest and abdomen were normal. Upper gastrointestinal tract endoscopy and colonoscopy were performed, which were reported to be normal. No abnormal finding was detected in bone marrow evaluation. In blood sample molecular analysis of patient, the PDGFRA-FIP1L1 was found negative [9]. PDGFRA-FIP1L1 fusions were sought by polymerase-chain-reaction (PCR) assays with the use of messenger RNA (mRNA) from purified eosinophil populations and DNA from blood leukocytes obtained. Hemoglobin electrophoresis was within normal range. The JAK2 V617F mutation status was determined in the cohort using amplification refractory mutation system (ARMS) polymerase chain reaction. In order to detect mutations in the kinase domain of *BCR-ABL*, RNA from peripheral blood samples was reverse transcribed and amplified by nested PCR using previously published primers to generate an amplicon covering the entire *BCR-ABL* kinase domain. JAK-2 V617F gene mutation and *BCR-ABL* fusion was found to be negative in polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) method. Her symptoms lasted for around 2 days and then were spontaneously subsided. We performed *MEFV* gene test for definite diagnosis. We investigated the patient with reverse-hybridization test by using the FMF Strip Assay (Vienna Lab Labordiagnostika GmbH, Austria). DNA samples were obtained from peripheral venous blood samples of the patient. Mutational analysis was performed for patient covering 22 mutations in the *MEFV* gene: E148Q, P369S, H478Y, F479L, S675 N, G678E, M680L, M680I (G/A), M680I (G/C), T681 T, I692del, M694 V, M694L, M694I, K695R, K695 M, R717S, I720 M, V722 M, V726A, A744S, and R761H. Mutational analysis detected gene mutation on one allele in patient, and one missense mutation was detected in the exon 10 of the *MEFV* gene, V726A

in heterozygous. Diagnosis of FMF was determined according to Tel Hashomer criteria for FMF [10]. It was failed to perform spectrin mutations evaluation, as it was unavailable in our facility. The patient is current under treatment with colchicine 1.2 mg/day, oral prednisolone 1 mg/kg and hydroxiurea three tablets of 500 mg a day [11]. The progress is being followed up with gradually improved severity and duration of the symptoms. Eosinophil count reduced to $0.370/\mu\text{L}$ at the week 3 after initiation of therapy. Steroid treatment was stopped after 1 month and the patient is now, 3 months after diagnosis, in normal health.

Discussion

In the present study, we discuss FMF with adult onset and hypereosinophilia in a patient with HE, and the causes of this situation. FMF is characterized by febrile episodes of serosal and synovial inflammation causing marked increase in the acute phase response. The frequency of FMF in any location depends on the ethnic background of the population, and it caused by mutations in *MEFV* gene that encodes pyrin protein. A major symptom of this disease is recurrent periodic fever accompanied with pain in abdomen, chest or joint. Abdominal pain is most common, observed in around 90 % of the patients [11]. Our case also presented with abdominal pain. Spontaneous resolution of the tenderness in the abdominal examination and fever leaded us to consider FMF in the patient. Anyway, free fluid detected on abdominal sonography at presentation wasn't detected at abdominal CT scan performed on the next day. All these findings were consistent to FMF. Patient immediately responded to colchicine therapy. The incidence of FMF with disease onset after 20 years of age is 14 % in the FMF Turkish population [5]. Adult onset FMF may be a form of disease with distinct clinical, demographic and molecular characteristics. Our case was 27 years old. She had a history of splenectomy at 18 months of age in addition FMF warranted to obtain a detailed family history. However, no significant characteristic was found in the family history. FMF can be diagnosed based on characteristic clinical patterns, response to treatment for colchicines, and gene test results. Talaat et al. [3] revealed that E148Q, V726A and M680I were the most common mutations detected in the heterozygous group. In our case, FMF diagnosis was made based on Tel Hashomer criteria and a heterozygote V726A mutation was detected in gene analysis. This result is consistent to heterozygote FMF cases in literature [12, 13]. In a study on Turkish FMF patients, Caglayan et al. [14] reported the frequency of heterozygote V726A as 17 %. We failed to detect any disease including parasitic, allergic

or auto-immune diseases as well as malignancy in the evaluations aiming to reveal the cause of eosinophilia (Rarely, eosinophilia is associated with pulmonary affections, malignant tumors, gastroenteritis, and autoimmune diseases [15]. In the study by Tefferi et al. [16], conditions causing eosinophilia was described in details; thus we conducted the evaluations according to recommendations. We screened JAK-2 V617F gene mutations and BCR-ABL in order to detect myeloproliferative disease, which were found to be negative. PDGFRA-FIP1L1 was also negative, which was ordered to diagnose hypereosinophilic syndrome. However, the patient had a relative short course of eosinophilia dating back to 6 months and we failed to show any organ involvement. Thus, the case was considered as idiopathic hypereosinophilia. Due to probability of eosinophilic gastroenteritis which is important in differential diagnosis, the upper gastrointestinal tract endoscopy and colonoscopy were performed, which were found to be normal. This finding excluded eosinophilic gastroenteritis. No significant finding was detected in terms of drugs, endocrine disorders and pulmonary disease causing eosinophilia. Eosinophil count returned normal range by steroid and hydroxiurea therapy in short term. We evaluated the potential relationship of congenital HE with FMF and/or hypereosinophilia; however, we found no data suggesting such relationship. In addition, we investigated whether splenectomy performed 25 years ago has a role in the development of eosinophilia in this case; however, we failed to find such information in the literature. Currently; Soriano and Manna revealed that also heterozygous mutation carriers can suffer from a mild or incomplete form of FMF, named 'FMF-like' disease. The influence of other modifiers genes and/or environmental factors can contribute to the variable penetrance and to the phenotypic variability of FMF [17]. In conclusion, this case is considered to be important as it is first case with association of HE, FMF and hypereosinophilia.

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