Eosinophilic Gastroenteritis and Familial Mediterranean Fever in a Child With *MEFV* Gene Mutation

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Received: 15 Apr. 2018; Accepted: 16 Dec. 2018

Abstract- Eosinophilic gastroenteritis (EG) is a rare inflammatory disorder affecting both children and adults. The exact etiology of the disease is not clear. A child presented with episodic generalized abdominal pain since a year ago without fever at first. After endoscopic and colonoscopic examinations, histopathological examination showed an increased number of eosinophils and diagnosis of EG was made. After elimination of dairy products from his regimen, abdominal pain attacks was reduced, but he got a fever. Familial Mediterranean Fever (FMF) diagnosis was made by genetic evaluation which showed MEV gene mutation. Symptoms were resolved with the treatment of colchicine which confirmed FMF diagnosis.

Acta Med Iran 2019;57(5):328-331.

Keywords: Eosinophilic gastroenteritis; Familial mediterranean fever; *MEFV* gene mutations; Iran

Introduction

Eosinophilic gastroenteritis (EG) is a rare inflammatory disorder affecting both children and adults, which is characterized by eosinophilic infiltration of gastrointestinal (GI) tract (1). The exact etiology of the disease is not clear, while in recent years, its incidence is increasing, and a higher prevalence among males is shifted towards females (2,3). Based on the site of involvement, the clinical manifestations may vary including fecal blood loss, anemia, weight loss, gastric outlet or small-bowel obstruction, and eosinophilic ascites (4,5). Asthma, rhinitis, eczema, and drug or food intolerances, celiac disease, ulcerative colitis, and systemic lupus erythematosus are also reported to be associated with EG (6-8).

Familial Mediterranean Fever (FMF) has been considered an autosomal recessive and an auto-inflammatory disease affecting mostly eastern Mediterranean people (9-12). Fever, peritonitis, pleuritis, arthritis, and erysipelas-like erythema are the characteristics of FMF (13). The diagnosis is based on the genetic evaluation. *MEFV* gene mutations are responsible for FMF development (14), which induces a component of the NLRP3 complex (10). Kocak' s study reported *MEFV* gene mutation in an adult patient with EG (15). Hereby, we are also reporting a patient with the diagnosis of concomitant EG and FMF that rarely has been reported previously.

Case Report

A 13-year-old boy was admitted in Amirkola Children Hospital in the north of Iran with generalized abdominal pain for one year, occurring once a week and lasting for two days. He did not have nausea and vomiting or diarrhea. Abdominal examination revealed generalized tenderness and guarding. Cellulitis-like lesions were observed on abdominal skin. Other aspects of the examination were unremarkable. He reported history of appendectomy (one year ago) and atopic dermatitis. His weight was 37 kg (5-15 percentiles), and his height was 145 cm (5-15 percentiles). His vital signs were: Heart Rate: 80 beat/min, Respiratory Rate: 20 breath/min, Blood Pressure: 100/70 mmHg, and Temperature: 37/5 Celsius.

His lab data were as follows

CBC: WBC=4700/µl (Poly=42%; Lymph=44%; E=10%; Mono=4%); Hb=14 gr/dl; MCV=75 fl; MCH=26 pg; MCHC=35 gr/dl; Platelet=281000/µl;

U/A, S/E: Normal, ESR=5 mm/h, CRP=7 mg/dl, Amylase & Lipase & BUN & Cr & K & Na & Ca & *P*=Normal

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AST=24U/L; ALT=11U/L; Alp=750U/L; Total pr=7 g/dl; Alb=4 g/dl; PT & PTT & INR=Normal, U/A=Normal; U/C=Negative,

25(OH) D=30 ng/ml (≥30 sufficient); Uric Acid=2.6 mg/dl, ASCA (Anti-Saccharomyces cerevisiae antibodies)=Negative; PANCA (perinuclear antineutrophil cytoplasmic)=Negative; Fecal H.pylori=Negative, Fecal calprotectin=25 μgr/gr (<50 μgr/gr normal range);
SC=Negative;IgM & IgG=Normal

IgE=>500 IU/ml (<127 IU/ml normal range); Anti TTG (IgA)=Normal; NBT (nitroblue tetrazolium) test=Normal.

Abdominopelvic sonography, barium transit, and IV/oral contrast abdominopelvic CT scan revealed normal findings.

However, upper GI endoscopy showed erythema in the antrum of the stomach along with nodularity and erosion in duodenal bulb, and erythema in the 2nd segment of the duodenum (D2). The pathologic evaluation showed chronic gastritis with the presence of plasma cells and lymphocyte cells, along with increased number of eosinophils (Figure 1). Duodenal histology also revealed increased number of plasma cells, lymphocytes and eosinophils (more than 30/HPF) (Figure 2). The macroscopic colonoscopy result was normal, while its pathology showed increased number of plasma cells, lymphocytes, and eosinophils, along with some lymphatic follicles suggestive of chronic non-destructive colitis or allergic colitis.

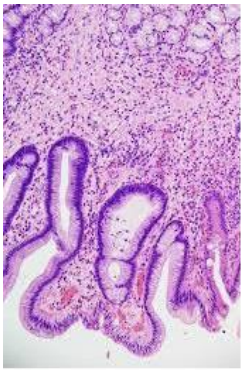

Figure 1. Microscopic findings of stomach

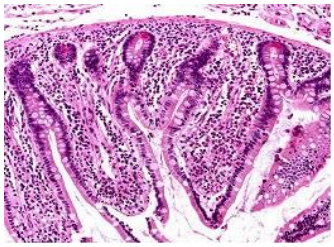

Figure 2. Duodenal microscopic findings

Eliminating dairy products from the patient's regimen, the recurrence rate of abdominal pain was reduced, but he still had episodic abdominal pain (less severe than before) with fever (lasting 3 days) and chest pain, that occurred monthly. He had morning stiffness between the attacks. He was then evaluated for infectious and inflammatory diseases including Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Behcet disease, all of which had negative results, so FMF gene mutation assessment was done.

The genetic results showed heterozygote gene (V726 A, R653H). Colchicine treatment was successful in controlling abdominal pain and other symptoms. At the end of a 6-month follow-up, his endoscopy showed less than 25 eosinophils per high-power field (eos/hpf) of the specimen and his abdominal pain was disappeared.

Discussion

EG is a rare disorder with an incidence rate of 1-20 cases per 100,000 cases (16). Different organs such as the esophagus, large intestine and rectum could be affected by the disease, while stomach and small intestine are the most affected organs (17). The disease could present symptoms such as dyspepsia, abdominal cramps, diarrhea, gastrointestinal bleeding, abdominal tenderness, and allergic enterocolitis (18). The three clinical diagnostic criteria include gastrointestinal symptoms, biopsies showing eosinophil infiltration of one or more areas of the GI tract, and absence of other causes of eosinophilia (15). Our patient had chronic abdominal pain, tenderness and guarding, along with eosinophilic infiltration in the gastric and duodenal area.

Imaging techniques such as ultrasound and Computed Tomography (CT) scan can be helpful for diagnosis. Ultrasound could show ascites and intestinal wall thickening, and CT scan can reveal diffuse thickening of mucosal folds, intestinal wall thickening, ascites, and obstruction. However, in the present study, ultrasound and CT scan evaluation findings were all normal.

In general, upper endoscopy with biopsy can be safely done for suspected patients. In our case, upper GI endoscopy showed erythema in the antrum, along with nodularity and erosion in duodenal bulb and erythema in the 2nd segment of the duodenum (D2). The pathologic evaluation showed chronic gastritis with the presence of plasma cells and lymphocyte cells, along with increased number of eosinophils.

The pathogenesis of EG is not well understood. In

near 70% of EG cases, food allergies, atopic diseases, and family history of allergies could be found (15). In our patient, atopic dermatitis was present since infancy. He also had elevated levels of eosinophil and IgE, which indicates hypersensitivity reactions as the pathogenesis of EG (19).

FMF is an autosomal recessive inherited auto-inflammatory disease characterized by recurrent, self-limited flares of fever and inflammation in the peritoneum, pleura, joint, or skin (20). The most important symptom of FMF is fever with a spontaneous emergence and rapid increase which reaches the plateau and then rapidly decreases. It could be accompanied by weakness, fatigue, myalgia, arthralgia, headache, lower back, and back pain. The predominant GI manifestation is abdominal pain, observed in near 90% of cases. The examination may reveal swelling, tenderness, sensitivity, stiffness, defense, and rebound (21). Our case had episodic abdominal pain, fever lasting 3 days, and monthly and morning stiffness between attacks.

FMF is the result of the point mutation in the Mediterranean Fever (*MEFV*) gene, which is located on the short arm of chromosome 16 (21). The gene is composed of 10 exons and could have 35 mutations. The V726A mutation is mostly observed in Ashkenazi and Iraqi Jews, Druzes, and Armenians (14). In a cohort study, the prevalence of V726A mutation in Iranian population was reported as 1% (22).

MEFV mutation is associated with Leukocyte apoptosis alteration, secretion of interleukin (IL)-1beta, and activation of the NF-kappa B pathway (23). It has been found in cases with ulcerative colitis and prostate cancer (23,24).

Colchicine is the main treatment for FMF, which aims to prevent acute attacks and amyloidosis, and decreases chronic inflammation. It also could prevent secondary amyloidosis in FMF patients (25). Previous studies demonstrated that colchicine treatment would result in complete remission in 66% and partial remission in 33% of affected children (26,27). Clinical response to colchicine treatment could confirm FMF diagnosis (28).

In this study, because of the continuation of abdominal pain after the elimination diet and the periodic pattern of the disease accompanied by fever, FMF was suspected, which was later confirmed by mutation analysis. Our case was followed up for 6 months, and colchicine treatment was successful in controlling abdominal pain and other symptoms.

We reported a case of eosinophilic EG coexisting with FMF that was rarely reported previously.

Acknowledgments

We are grateful to the Clinical Research Development Committee of Amirkola Children's Hospital of Babol University of Medical Sciences for their contribution to this study.

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