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The Association of Familial Mediterranean Fever and Polyarteritis Nodosa: A Case Report

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Introduction: Familial Mediterranean fever (FMF) is the most common type of periodic fever syndromes. It is an autosomal recessive disorder characterized by acute, self-limited episodes of fever and polyserositis recurring at irregular intervals. Vasculitis has been frequently reported in patients with familial Mediterranean fever. The association of FMF and polyarteritis nodosa has been well established. Clinical presentation of polyarteritis nodosa in patients with familial Mediterranean fever has certain characteristics and it may be a feature of FMF itself. Herein, we report on a case of familial Mediterranean fever accompanied by polyarteritis nodosa with hepatic, renal and gastroinestinal involvement.

Case Presentation: A ten-year-old Iranian boy was referred to our department with history of recurrent abdominal pain followed by fever, chills, arthralgia and scrotal edema. He suffered from hematuria and gastrointestinal bleeding. His physical exam revealed fever (axillary temperature: 38.7°C), hypertension (150/90 mmHg), hepatomegaly (liver span: 13 cm), orchitis and subcutaneous painful nodules of both legs and arthritis of both shoulders and right ankle.

Conclusions: Mutations in MEFV gene provide a basis for the development of PAN both by forming a pro-inflammatory state and by resulting exaggerated response to infection.

Keywords: Familial Mediterranean Fever; Polyarteritis Nodosa; Aneurysm

1. Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent self-limited attacks of fever accompanied by polyserositis (peritonitis, pleuritis and arthritis) (1-3). Approximately 90% of cases had experienced their first attack under the age of 20 years (1). This illness occurs primarily among groups of Mediterranean origin but cases are also found among non-Mediterranean individuals (1, 3, 4). It is caused by mutations in the gene encoding pyrin (MEFV) (3, 5, 6). The five most common mutations (M694V, V726A, M694I, M680I, E148Q) are found in 74% of Mediterranean patients with FMF (7, 8). However, the most common mutation in patients with FMF is M694V (1, 4, 8, 9). FMF may coexist with various systemic inflammatory diseases including vasculitides, spondyloarthritis, multiple sclerosis, inflammatory bowel disease and Behcet's disease (2, 10). Vasculitis might be the main presentation of FMF (2, 11). Almost 5% of patients with FMF have been reported to have Henoch-Schonlein purpura (HSP) and about 1% have been reported to have polyarteritis nodosa (PAN) (12). Polyarteritis nodosa is a vasculitis of small and medium-sized muscular arteries caused by deposition of immune complex in vessels. Although gastrointestinal involvement is common in patients with PAN, the symptomatic involvement of the hepatobiliary system is rare (13). Herein, we introduced a case with FMF accompanied by PAN with gastroinestinal, renal and hepatic involvements.

2. Case Presentation

A ten-year-old Iranian boy was referred to our department with a history of recurrent abdominal pain followed by fever, chills, arthralgia and scrotal edema. He had hematuria and gastrointestinal bleeding. His physical examinations revealed fever (axillary temperature: 38.7°C), hypertension (150/90 mmHg), hepatomegaly (liver span: 13 cm), orchitis and subcutaneous painful nodules of both legs and arthritis of both shoulders and right ankle.

His laboratory findings were as follows: white blood cells: 23000/mm^3 (neutrophils: 85%-lymphocyte: 10%, eosinophil: 2%), red blood cells: 3920000/mm^3, hemoglobin: 10.8 gr/dL, platelet: 414000/mm^3, blood urea nitrogen: 73 mg/dL, creatinine: 5.5 mg/dL, C-reactive protein: +3, erythrocyte sedimentation rate: 85 mm/h, serum albumin: 2.8 g/dL, urine analysis: red blood cells: 8-10,

proteinuria: 3+, white blood cells: 10-12, urine random analysis: creatinine: 79 mg/dL, calcium: 16.2 mg/dL and negative urine, stool and blood culture. The levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, billirubin, HCV antibody, HBS antigen, amylase level, electrolytes, lactate dehydrogenize, 2-mercaptoethanol (2ME), Wright, anti-streptolysin O (ASO) antibody and peripheral blood smear were all negative or within normal limits.

His sera for rheumatic factor (RF), anti-nuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibodies (p-ANCA-Ab), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA-Ab), anti-glomerular basement membrane antibody (Anti-GBM-Ab), anti-double strand DNA antibody (Anti-ds-DNA-Ab), and anti-cyclic citrullinated polypeptides antibody (Anti-CCp-Ab) were all negative. Endoscopic examination showed severe inflammation of the lower part of the esophagus and first and second parts of the duodenum accompanied by mild erythema in the cardial part of the stomach. Colonoscopy revealed severe inflammation in the rectosigmoid part and multifocal erythema in other sites of the colon accompanied by reduction in mucosal vascularity pattern. His chest X-ray showed interstitial infiltrations in both lungs and echocardiography showed mild tricuspid valve regurgitation and mild pericardial effusion.

Sonography showed gallbladder wall thickening with edema and sludge, hepatomegaly (134 mm) with three cystic lesions including venous blood flow. Doppler sonography also confirmed three mass lesions with regular margin including turbulent blood flow (congenital aneurysm) in the right lobe of the liver and increased size of the kidneys, with parenchymal lesions. In contrast, the CT scan showed multiple hyperdense lesions in the liver (arteriovenous malformation) and the result of his magnetic resonance angiogram (MRA) revealed an abnormal enhanced area in the right lobe of the liver with significant neovascularization. The genetic study of MEFV gene mutation confirmed the homozygote M694V mutation. According to his clinical manifestation and laboratory studies he was diagnosed with FMF.

3. Discussions

The literature review suggests that PAN occurs more commonly in patients with FMF than would be expected in the general population (14). It seems that PAN occurs at a younger age in cases with FMF compared with other patients with PAN (the age at diagnosis of PAN, among FMF, patients varies from 3.5 to 37 years); our patient's age was within the expected range (3).

Study of 23 children with FMF-associated vasculitis suggested that most children with FMF-associated vasculitis had identifiable mutations in the MEFV gene (15). These patients showed a significant homozygote M694V mutation.

In an investigation of patients with PAN without any symptoms of FMF, the prevalence of MEFV gene mutations was 38% with 10.3% having homozygous mutation of M694V (16). In our study the patient had homozygous M694V mutation. It seems that alterations in the MEFV gene are important susceptibility factors for the development of PAN (16). It is believed that mutations in MEFV gene provide a basis for the development of PAN both by forming a pro-inflammatory state and by resulting exaggerated response to streptococcal infections (16). Our patient did not have a significant history of pharyngitis before this episode of illness; however, his ASOT (anti-streptolysin O titer) was 540 T odd.

Study on 452 children with FMF living in Turkey reported more severe clinical presentation for patients with two-allele mutations, besides 32.6% of patients with M694V/M694V had splenomegaly (9). Although our patient did not show splenomegaly, his multi-organ involvement indicated the severity of illness. According to reports by Ozturk et al., acute orchitis as a rare clinical finding was more common in M694V homozygotes (9) and presence of orchitis in our patient confirms the association of homozygote M694V mutation with orchitis.

In patients with overlapping FMF and PAN, peri-renal hematomas are reported more frequently compared with other patients with PAN (3). However, our patient did not show this clinical feature. Another presentation associated with FMF, mostly by homozygote M694V mutation, is cryptogenic cirrhosis (17) yet we could not find any evidence of cirrhosis in our patient. This patient was firstly treated as a case of PAN alone using prednisolone 1 mg/kg and azathioprine 3 mg/kg/day. However, his genetic study confirmed him as a patient with FMF. Therefore, azathioprine was replaced by colchicine.

Finally, patients with FMF associated with PAN showed an overall better prognosis than other patients with PAN (3, 12). Our patient also showed a favorable response to medical therapy.

In FMF-endemic areas, MEFV mutations, particularly M694V, might be searched, especially in young patients having PAN without any predisposing disease.

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Authors' Contributions

Hajar Sadat Ahadi: contributions to conception and design, and acquisition of data; Shirin Farivar: analysis of MEFV gene mutation and analysis and interpretation of data; Shirin Sayyahfar: critical revision; Reza Shiari: final approval of the version for submission and any revised version.

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