Case Report

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A Case of Henoch-Schönlein Purpura with P369S Mutation in MEFV Gene

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Abstract

Background: Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood. HSP can affect multiple organs presenting with a characteristic rash in most of the patients. Familial Mediterranean Fever (FMF) is an inherited inflammatory disease common in mediterranean populations. HSP is the most common vasculitis seen in children with FMF.

Case Presentation: A 16 year old boy was referred with history of abdominal pain lasting for 20 days. He was hospitalized and had appendectomy. Due to the persistence of his abdominal pain after surgery he was admitted to our hospital. His physical examination showed palpable purpuric rashes symmetrically distributed on lower extremities. Abdominal examination revealed periumbilical tenderness. Laboratory tests showed elevated erythrocyte sedimentation rate, C-reactive protein and fibrinogen. Urinalysis revealed microscopic hematuria and severe proteinuria. The fecal occult blood testing was positive. Based on these clinic findings, the patient was diagnosed as HSP with renal, gastrointestinal tract and skin involvement. We performed DNA analysis in our patient because he had diagnosis of vasculitis with severe symptoms and found that he was carrying heterozygote P369S mutation.

Conclusion: Our case is noteworthy as it indicates that it may be important not to overlook presence of FMF mutations in patients with a diagnosis of severe vasculitis.

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Key Words: Henoch-Schönlein Purpura; Familial Mediterranean Fever; P369S Mutation; MEFV Gene

Introduction

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood[1]. The annual incidence of HSP is 22.1/100000 children and 75% of cases are seen between 3 and 10 years of age [2,3]. HSP can affect multiple organs with a characteristic rash present in all patients [1]. The

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diagnostic criteria include palpable purpura with at least one of the following manifestations: abdominal pain, IgA deposition, arthritis or arthralgia, or renal involvement [4]. The disease is characterized by deposition of immunglobulin A (IgA) containing immune complexes and complements within small vessel walls, and often within renal mesangium [5].

Renal involvement occurs in 20-60% of patients with HSP, usually manifesting as hematuria, and often associated with proteinuria [3]. Most of the patients with renal involvement have a good prognosis. However, some patients progress to end-stage renal disease, and renal involvement in HSP is one of the major causes of chronic renal failure in childhood [6]. Gastrointestinal (GI) involvement occurs in 51-74% of patients. There is no specific GI symptom pattern for HSP. Abdominal pain is the most common symptom. Also some patients may develop serious complications, such as intestinal intussusception, perforation or obstruction [4,7].

Familial Mediterranean Fever (FMF) is an inherited inflammatory disease common in mediterranean populations. It is characterized by recurrent episodes of fever, peritonitis, pleurisy, rashes and arthritis and may be complicated by renal amyloidosis. FMF is caused by mutations in the gene MEFV, which encodes pyrin/marenostrin, a protein implicated in the regulation of neutrophil activity [8]. Some types of vasculitis are more frequent in FMF, including HSP, polyarteritis nodosa (PAN) and Behçet's disease. HSP is the most common vasculitis seen in children with FMF[9].

We present a 16-year old boy with Henoch-Schönlein vasculitis who had severe renal and gastrointestinal involvement and rarely seen heterozygote P369S mutation in MEFV gene

Case Presentation

A 16-year old boy was referred to hospital with a history of abdominal pain for 20 days. He was hospitalized and had appendectomy. Due to the persistence of abdominal pain after surgery he was admitted to our hospital. He had also sudden onset of palpable purpuric rashes, first on periumblical and gluteal zone, then on the extensor surface of his lower extremities. He also reported coffee ground vomiting and dark color urine on the day of admission.

There was no history of recent drug exposure, immunization, or upper respiratory tract infection. He did not have recurrent attacks of abdominal pain and fever. Family history for FMF was negative. In physical examination blood pressure was 140/90 mmHg (95-99 percentile), other vital signs were normal. Palpable purpuric rashes were symmetrically distributed on his lower extremities. He also had periumbulical tenderness and an operative scar at right lower quadrant. Cardiac and respiratory auscultation was normal.

Laboratory tests showed an erythrocyte sedimentation rate (ESR) of 55mm/h (normal: <20mm/h), C-reactive protein: 1,7 mg/dl (normal: <1 mg/dl), fibrinogen 501 mg/dl (normal: 200-400 mg/dl), hemoglobin 12.1g/dl, hematocrit 35.3%, white blood cell count (WBC) 23.500/mm^3, platelet count 944.000/mm^3, serum urea 23 mg/dl, creatinine 0.6 mg/dl, albumin 2.8 g/dl, alanine aminotransferase 47 U/L, aspartate aminotransferase 91 U/L, amylase 70 mg/dl, lipase 29 mg/dl. The anti-streptolysin-O titer was 100 IU/ml (normal: 0-150 IU/ml). Serum complement-3, complement-4 and serum immunoglobulin (Ig) levels were normal. Antinuclear antibody (ANA), anti dsDNA, antineutrophil cytoplasmic antibody (ANCA), and anticardiolipine antibody were negative.

Urinalysis revealed macroscopic hematuria and proteinuria with 24-h urinary protein excretion of 104.7 mg/m^2/h. Urine output was oliguric (0.7ml/kg/h). The fecal occult blood testing was positive. Abdominal ultrasound, renal Doppler ultrasound and renal magnetic resonance angiography (MRA) were normal. On histopathological examination, 25 glomeruli were seen in routine stains including Hematoxylen and Eosine, Periodic acid schiff and Masson-trichrome stains. In two of the glomeruli, slightly increased mesangial matrix was noted, and other glomeruli were normal in appearance. Tubulointerstitial area was normal.

On direct immunofluorescence examination, coarsely granular IgA deposits were seen diffusely, i.e. in all glomeruli in mesangial area, while as far

as IgM is concerned, mesangial deposits were detected in two glomeruli. Based on these clinic findings, the patient was diagnosed as having HSP with renal, gastrointestinal tract and skin involvement.

Since there are reports of increasing frequency of accompanying MEFV mutations in patients with HSP and alterations in the MEFV gene is an important susceptibility factor for the development of vasculitis and, also since it affects clinical presentation and is associated with a more severe course, we performed DNA analysis in our patient who had severe vasculitic involvement and found that he was carrying heterozygote P369S mutation.

Alternate day pulse steroid treatment (30mg/kg) was administered to the patient for 3 times and followed by oral maintenance steroid treatment (2mg/kg/day). Colchicine treatment was also initiated after detection of the FMF mutation. Because no amelioration in proteinuria was achieved with this therapy, cyclo-phosphamide (2mg/kg/day) was started in addition to oral maintenance steroid therapy. Improvement in gastrointestinal symptoms and proteinuria was observed with this therapy regimen.

Discussion

HSP is an immunologically mediated systemic vasculitis of small blood vessels. Despite being one of the most common vasculitides of childhood, definitive data on the etiology remains unknown, although many antigens, such as infective agents, vaccinations, drugs, and insect bites have been found to trigger HSP[5]. It occurs particularly in the autumn and winter suggesting an infectious etiology. Upper respiratory tract infections occur in 35-52% of patients [4].

HSP is mediated by immune deposits (typically with IgA), resulting in necrosis of the wall of small and medium-sized arteries with extravasation of erythrocytes, infiltration of tissue with neutrophils, and deposition of nuclear fragments from degenerating neutrophils, a picture called leukocytoclastic vasculitis (LCV) [4].

Renal involvement determines the long-term prognosis, and the prevalence ranges from 20% and 60% according to the different reports[3].

The most common clinical sign of Henoch-Schönlein nephropathy is isolated microscopic hematuria, often associated to proteinuria. The presence of renal failure, arterial hypertension, nephrotic proteinuria, and histological findings at renal biopsy (proportion of glomeruli with crescents) have traditionally represented a poor prognostic factor[3]. There have been some reports in which the renal involvement in HSP has been associated with several factors, such as the age at onset, abdominal symptoms, the recurrence of purpura, and treatment with corticosteroids and plasma coagulation factor XIII concentrate[6]. The risk of chronic renal failure is related to the initial clinical presentation, being less than 2% in those with hematuria and/or minimal proteinuria to 19% when both nephritic and nephrotic syndromes are found[4].

Gastrointestinal disease occurs in up to 85% of patients with varying syptoms like abdominal pain, sometimes associated with nausea, vomiting, or bleeding. 42% of patients have severe pain. In 12-19% of cases, abdominal pain is the presenting symptom. The pain is characteristically colicky and localized to the periumblical and epigastric regions. Mucosal lesions can develop anywhere in the GI tract, but the duodenum and small bowel are the most commonly involved sites. Complications of involvement of gastrointestinal tract in HSP include intramural hematomas, intussusceptions, bowel infarction, bowel perforation, pancreatitis, appendicitis, and cholecystitis. Intussusception is the most common surgical complication of HSP in childhood, occuring in 0.7-13.6% of patients[4,7,10,11].

In our patient, due to the renal biopsy findings consistent with HSP, negative ANCA and normal renal Doppler ultrasound and renal MRA, diagnosis of PAN was ruled out. The presence of typical rash, severe abdominal pain, nephrotic proteinuria and IgA deposition on kidney biopsy confirmed the diagnosis of HSP.

FMF is an autosomal recessive disease affecting people of Mediterranean ancestry with recurrent self-limited attacks of fever and inflammatory serositis[12]. FMF is caused by mutations in MEFV gene[9], which encodes pyrin/marenostrin, a

protein implicated in the regulation of neutrophil activity[8]. The FMF gene, MEFV, is located on chromosome 16p13.3[13]. In Turkey, the incidence of FMF is as high as 1/1000-2000, and the estimated carrier rate is 1/5 [14,15]. The most serious complication is the development of amyloidosis, causing chronic renal failure [16]. The four most commonly reported mutations in MEFV gene are M694V, M680I, V726A and E148Q [17]. The M694V mutation has been reported to be the most common among Turks [9].

Several types of vasculitis are associated with FMF, PAN, HSP, Behçet's disease and protracted febrile myalgia. The overall incidence of FMF vasculitis in patients with PAN is 1%, and in 5% HSP patients FMF vasculitis is detected, and it is significantly higher in FMF than in the general population [9,12,16,18]. HSP is the most common vasculitis seen in children with FMF [9]. There are increasing number of researches reporting association of HSP with FMF [19].

The pathogenesis of vasculitis in patients with FMF is unknown. Hypersensitivity, genetic and immune mechanisms are held responsible [19].

The occurrence of circulating immune complexes in 50% of patient with FMF, complement consumption, defective inhibition of complement activation and uncontrolled release of TNF during the attacks have been described.

Therefore an immune-related mechanism has been suggested to be involved in the pathogenesis of FMF and FMF-associated vasculitis [16,18].

The diagnosis of FMF is based on the clinical criteria, family history, exclusion of other hereditary periodic fever syndromes and the patient's response to colchicine treatment. The demonstration of MEFV gene mutations is necessary in only suspected patients to establish a definitive diagnosis. There are subjects who are homozygotes, or compound heterozygotes, but not having any symptom of FMF. On the other hand, there are FMF patients who respond to colchicine treatment, in whom no mutation in the MEFV gene has been demonstrated[9]. The appearance of vasculitis can preclude or follow typical FMF attacks. Generally patients with FMF develop vasculitis at younger ages. FMF and vasculitis have remarkable similarity: fever, abdominal pain, arthritis, skin lesions and blood in stool and urine. This makes a differential diagnosis extremely difficult[12].

It has been reported that in some rheumatic diseases MEFV mutations (in a single allele) were increased suggesting that the mutated MEFV allele was acting as a susceptibility factor[20], also MEFV mutations are known to promote inflammation and especially to favor the development of severe vasculitis [21].

Our patient did not demonstrate characteristic features of FMF such as abdominal pain, fever and family history of FMF. Recently, increased number of studies reporting MEFV mutations in patients with HSP suggests association of this gene with clinical presentation, especially with a severe course [22,23]. Depending on these results we performed DNA analysis in our patient and detected heterozygote P369S mutation.

P369S mutation is one of the 190 known mutations [13]. P369S mutation has been reported in Turks, Syrians, Armenians, Lebanese, Palestinians, and Japanese [15,24-28]. In a study performed in Turkey, frequency of rarely seen P369S mutation was reported as 2.55% [15,29].

Association of Behçet's disease, which is one of the FMF associated vasculitis, with P369S mutation was reported in the literature [24] but there are no reports regarding association of this mutation with HSP.

Our patient who was diagnosed to have HSP with severe renal and gastrointestinal involvement was found to have the rarely encountered P369S mutation in MEFV gene upon screening. This case which demonstrates the association of P369S mutation in FMF patients with HSP, is remarkable as it indicates the importance of this minor mutation with development of severe vasculitis.

Conclusion

In conclusion our case is noteworthy as it shows that it may be important not to overlook presence of MEFV mutations in patients with a diagnosis of severe vasculitis.

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