

Atypical Henoch-Schonlein Purpura: A Forerunner of Familial Mediterranean Fever

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ABSTRACT: Intussusception is the most common cause of intestinal obstruction in early childhood. The cause of most intussusceptions is unknown but it can complicate the course of Henoch-Schonlein purpura (HSP) as a result of the vasculitic process. Familial Mediterranean fever (FMF), a common disease in Israel, is also associated with HSP. In a few patients, particularly in children, HSP has been reported to precede the diagnosis of FMF. We describe two patients with an unusual clinical course of severe abdominal pain as a result of intussusception. The correlation between intussusception, HSP and FMF are discussed.

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KEY WORDS: abdominal pain, intussusception, Henoch-Schonlein purpura, familial Mediterranean fever, vasculitides

Henoch-Schonlein purpura is among the most common vasculitides of childhood. It classically presents with the triad of palpable purpura, abdominal pain and arthritis. The typical colicky abdominal pain occasionally precedes by several weeks the characteristic vasculitic rash, which involves mainly the lower limbs and buttocks [1]. Intestinal intussusception can occur in the course of HSP and is attributed to edema and damage to the vasculature of the gastrointestinal tract as a result of the vasculitic process. However, intussusception that precedes the overt clinical picture of HSP is rare.

Familial Mediterranean fever is a hereditary inflammatory disease characterized by recurrent attacks of fever and polyserositis. Several types of vasculitis are associated with FMF; the most frequent one is HSP, which occurs in about 5% of FMF patients. Approximately 1% of FMF patients suffer from polyarteritis nodosa, and a few have protracted febrile myalgia or Behcet syndrome [2].

HSP = Henoch-Schonlein purpura
FMF = familial Mediterranean fever

In a few patients, particularly in children, HSP has been reported to precede the diagnosis of FMF [3]. Considering the fact that FMF is common in the Middle East [4] and that HSP is the commonest of the vasculitides in children [1], we present two cases with atypical presentations of FM-related HSP, one of which led us to a diagnosis of FMF.

PATIENT DESCRIPTIONS

PATIENT 1

A 3 year old boy was brought to the emergency room because of severe abdominal pain. His past history was unremarkable except for recurrent streptococcal infections, the last one occurring a few weeks before admission. He began to feel sick several days before admission, when he complained of severe bouts of abdominal pain and occasional diarrhea, accompanied by low-grade fever (38.3°C). On admission, the patient appeared febrile and was irritable. Lung and heart examination was unremarkable. The abdomen was diffusely tender but without signs of peritoneal irritation or organ involvement. Rectal examination elicited watery yellowish stools with traces of blood. No arthritis or skin lesions were observed. Laboratory tests showed increased serum C-reactive protein (120 mg/L, normal < 5 mg/L), hemoglobin 10.5 g/L, white blood cells $15 \times 10^3/\text{ml}$ with a shift to the left, and platelets $478 \times 10^3/\text{ml}$. Blood levels of glucose and electrolytes and liver and renal functions were all within normal limits. An emergency ultrasound of the abdomen demonstrated an ileoileal intussusception, which was successfully reduced by an air enema. The patient was treated conservatively by withholding of oral feeds and administration of intravenous fluids. However, the child continued to suffer from recurrent attacks of excruciating abdominal pain.

Three days after the episode of intussusception, an explorative laparotomy was performed that showed an edematous small intestine with recurrent ileoileal intussusception. The intussusception was reduced and biopsies were taken from the intestine and from enlarged mesenteric lymph nodes. Frozen sections showed severe acute inflammation, without

any signs of malignancy. On the seventh day after his admission, the patient had another severe attack of abdominal pain, this time with vomiting, bloody diarrhea and high fever. Another intussusception was diagnosed, this time warranting an excision of 15 cm of distal small intestine due to ischemic changes. Histological examination demonstrated multiple mucosal ulcers, severe acute inflammation, and neutrophilic and eosinophilic infiltration of the mucosa and of the intestinal wall near the ulcerations. Several vessels in the submucosa showed fibrinoid necrosis of the walls, with focal nuclear debris. A diagnosis of acute inflammation or vasculitis of the intestine was suggested. On day 15 of admission, a vasculitic rash appeared – first on the auricles and then on the face. A rheumatologist consultant suggested a diagnosis of systemic vasculitis, probably HSP. The child was transferred from the surgical to the pediatrics ward, and intravenous treatment of hydrocortisone in high doses was instituted. The abdominal pain and fever subsided almost immediately and the child began to recover. Additional blood tests showed an increased immunoglobulin A level (440 mg/ml), a factor 13 activity of 90%, and normal serum complement levels. No autoantibodies were detected. A skin biopsy was compatible with leukocytoclastic vasculitis.

One week after the initiation of corticosteroid treatment, the patient was discharged from hospital on oral steroids, which were gradually tapered down. On follow-up 4 weeks after stopping the steroids, the patient began to suffer from recurrent attacks of fever and abdominal pains lasting 3 to 4 days. The family history was positive for FMF and Crohn's disease. Genetic tests for mutations in the *MEFV* gene revealed that the child was a compound heterozygote for M694V and V726A mutations. Colchicine treatment was started, and a few weeks later the child was fully asymptomatic. In the course of the following months he regained his previous weight and returned to his regular activities while his health condition remained stable.

PATIENT 2

A 4 year old girl was admitted because of fever, abdominal pain, rectal bleeding and a vasculitic rash. The patient was of Sephardic Jewish origin, and her mother suffered from FMF. At age 2 she was diagnosed both clinically and genetically to have FMF and was treated with colchicine 1 mg/day.

Upon admission she began taking prednisone 20 mg/day, but despite treatment her condition deteriorated due to profuse bloody diarrhea, a drop in her hemoglobin to 7.8 g/dl, and the appearance of a skin rash over her buttocks and legs. Ultrasonography of the abdomen revealed an ileoileal intussusception, which was successfully reduced by an air enema. The child was given intravenous pulses of methyl prednisolone (30 mg/kg) three times a day and her condition gradually improved. During the following 3 months

she continued to experience bouts of abdominal pain and waves of vasculitic-type rash, in spite of continuing steroid and colchicine therapy, but eventually, after 3 more months, she had fully recovered.

COMMENT

The two children described here had an unusual and severe clinical course of Henoch-Schonlein purpura. In the first patient the intussusception and intractable abdominal pain preceded the appearance of the typical vasculitic rash, and he was eventually diagnosed with familial Mediterranean fever.

Intussusception occurs in 0.7–13.6% of children with HSP [1,5,6]. During the course of the disease, however, we could not find a case report in the literature about intussusception that preceded the evolution of the clinical picture of HSP. The frequent association of FMF and HSP, the causal relationship of which remains unclear, has been extensively reported [3,7,8]. In a previous study [9] we were able to identify covert cases of FMF in a large cohort of HSP patients. The prevalence of *MEFV* mutations in these patients significantly exceeded the prevalence of *MEFV* mutations in the general Israeli population [10]. Subsequently, a group from Turkey [11] also found an increased prevalence of *MEFV* mutations among their patients with HSP, with results that were similar to ours (34% in the Turkish group and 27% in the Israeli group). From these reports, and from additional other case reports [12], we can conclude that *MEFV* mutations are important genetic factors that predispose carriers to develop HSP, perhaps as a consequence of impairment in the control of the inflammatory response.

In addition, some infectious agents, such as *Streptococcus*, have been proposed as a trigger of vasculitis in FMF. Indeed, both HSP and polyarteritis nodosa [13], as well as attacks of FMF, do occur after streptococcal infection [14]. Tekin et al. [2], in their series of 23 patients with FMF and vasculitis, found that 12 of the 16 patients tested had high levels of ASLO titers. Our first patient suffered from recurrent proven streptococcal throat infections, the last developing 2 weeks before admission.

CONCLUSION

FMF and HSP bear obvious clinical similarities, and the frequency of the co-occurrence of the two diseases is indeed high. It appears that streptococcal infection may trigger the disease more readily in patients with *MEFV* mutations. These intriguing associations merit clarification by future investigation. We suggest that it might be advisable to perform genetic testing for FMF in children of Mediterranean extraction who present with an unusual and complicated clinical picture of HSP.

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References

1. Chang WL, Yang YH, Lin YT, et al. Gastrointestinal manifestations in Henoch-Schönlein purpura: a review of 261 patients. *Acta Paediatr* 2004; 93 (11): 1427-31.
2. Tekin M, Yalçinkaya F, Tümer N, et al. Clinical, laboratory and molecular characteristics of children with familial Mediterranean fever-associated vasculitis. *Acta Paediatr* 2000; 89 (2): 177-82.
3. Ozdogan H, Arisoy N, Kasapçapur O, et al. Vasculitis in familial Mediterranean fever. *J Rheumatol* 1997; 24 (2): 323-7.
4. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. *Am J Med* 1967; 43 (2): 227-53.
5. Ebert EC. Gastrointestinal manifestations of Henoch-Schonlein purpura. *Dig Dis Sci* 2008; 53 (8): 2011-19.
6. Schwab J, Benya E, Lin R, et al. Contrast enema in children with Henoch-Schönlein purpura. *J Pediatr Surg* 2005; 40 (8): 1221-3.
7. Saatçi U, Ozen S, Ozdemir S, et al. Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis. *Eur J Pediatr* 1997; 156 (8): 619-23.
8. Majeed HA, Quabazard Z, Hijazi Z, et al. The cutaneous manifestations in children with familial Mediterranean fever (recurrent hereditary polyserositis). A six-year study. *Q J Med* 1990; 75 (278): 607-16.
9. Gershoni-Baruch R, Broza Y, Brik R. Prevalence and significance of mutations in the familial Mediterranean fever gene in Henoch-Schönlein purpura. *J Pediatr* 2003; 143 (5): 658-61.
10. Shinawi M, Brik R, Berant M, et al. Familial Mediterranean fever: high gene frequency and heterogeneous disease among an Israeli-Arab population. *J Rheumatol* 2000; 27 (6): 1492-5.
11. Ozçakar ZB, Yalçinkaya F, Cakar N, et al. MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura. *J Rheumatol* 2008; 35 (12): 2427-9.
12. Balbir-Gurman A, Nahir AM, Braun-Moscovici Y. Vasculitis in siblings with familial Mediterranean fever: a report of three cases and review of the literature. *Clin Rheumatol* 2007; 26 (7): 1183-5.
13. Glikson M, Galun E, Schlesinger M, et al. Polyarteritis nodosa and familial Mediterranean fever: a report of 2 cases and review of the literature. *J Rheumatol* 1989; 16 (4): 536-9.
14. David J, Ansell BM, Woo P. Polyarteritis nodosa associated with streptococcus. *Arch Dis Child* 1993; 69 (6): 685-8.