An Extraordinary Complication in a Child With Combined Familial Mediterranean Fever and Inflammatory Bowel Disease

Multiple Ileal Perforations

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Abstract: Familial Mediterranean fever (FMF) is a recurrent disease with autosomal recessive trait and fever that is generally self-limiting. Clinical manifestations are pain in the abdomen, chest, and joints as a result of inflammation in the serous surfaces. No case of multiple intestinal perforations has been reported in children with FMF, whereas cases with a single intestinal perforation have been encountered, although very rarely. In addition, co-occurrence of FMF and inflammatory bowel disease is a situation that is very rarely reported in the literature. Here, we report a case of a 5-year-old girl who was being followed up with the diagnosis of FMF and who also had inflammatory bowel disease, which was complicated with multiple ileal perforations. Our aim is to point out a rarely encountered co-occurrence and also the importance of evaluation of additional diseases with FMF that are unresponsive to treatment so as to prevent complications.

Key Words: Familial Mediterranean fever, inflammatory bowel disease, multiple ileal perforations

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Familial Mediterranean fever (FMF) is a disease with autosomal recessive trait that has a clinical course of recurrent fever, associated with *MEFV* (MEditerranean FeVer) gene and is generally seen in the Mediterranean region.[1,2] The disease was first described by Janeway and Mosenthal in 1908 as "unusual recurrent peritonitis." It was named as "benign recurrent peritonitis" in 1945 by Siegal and finally as the currently used name "familial Mediterranean fever" by Heller et al. in 1958.[3] The episodes of FMF are characterized by inflammation and serositis that cause recurrent short-term fever that is generally self-limited for 12 to 72 hours, peritonitis, synovitis, pleuritis, and rarely pericarditis.[4] The incidence of inflammatory bowel disease has been reported to be increased in patients with FMF in some studies.[5] Peritoneal involvement is present in more than 95% of the patients, and this condition occasionally mimics acute abdomen that results in unnecessary surgical interventions.[6] Intestine perforation is extremely rare in children with FMF and is considered to be secondary to steroids.[7] We aimed to point out a rarely encountered co-occurrence in the literature and also the importance of evaluation of additional diseases in FMF that are unresponsive to treatment to prevent complications.

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CASE

A 5-year-old girl was being followed up with the diagnosis of FMF since she was 3 years old. There was no history of FMF in the family. Episodes of fever started when she was 3 months old. Familial Mediterranean fever gene analysis was performed since she started to have arthritis accompanying the attacks of fever starting from the age of 2 years, and gene analysis was heterozygous for M680I. She was treated with colchicine and oral steroids. During the follow-up, canakinumab was added to the treatment since she had 10 episodes yearly. Then, the episodes of fever resolved for about 2 months; however, attacks of fever and abdominal pain started again later on. She was brought to the emergency department with complaints of fever, severe abdominal pain, and vomiting in the fifth month of treatment with canakinumab. The physical examination revealed that the abdomen was tender in all quadrants, with guarding and rebound tenderness. Laboratory analysis was suitable with acute inflammation: white blood cell count 29,900/μL, hemoglobin 8.9 g/dL, platelet count 1,085,000/μL, and C-reactive protein 14.54 mg/dL. Ileal curves were edematous at abdominal ultrasonography, and a large amount of free fluid was present in the abdomen. She underwent laparotomy with a preliminary diagnosis of appendicitis. The appendix was normal in appearance. Surprisingly, during laparotomy, multiple (7) ileal perforations resembling punch holes at the antimesenteric side of an ileal segment measuring 45 cm in length, starting 15 cm proximal to the ileocecal valve, were present (Figs. 1A, B). A partial ileal resection and ileostomy were performed. Microscopic evaluation revealed a necrotic exudate on the intestine surface, inflammatory granulation tissue, active chronic inflammation up to the serosa (Figs. 2A, B). Upper and lower gastrointestinal system endoscopy performed postoperatively was unremarkable, and biopsies were taken from certain areas. Histopathologic examination disclosed active-chronic inflammation. No signs of *Ascaris lumbricoides*, typhoid fever, or tuberculosis were encountered. Subsequently, the treatment for the child was continued with colchicine, steroids, and anakinra. Ileostomy was closed 2 months after the operation. She continued to have occasional episodes of abdominal pain and diarrhea. She was hospitalized 2 months after the operation due to an attack with fever and abdominal pain. Abdominal computed tomography was unremarkable other than thickening in the terminal ileal curves. Endoscopy and colonoscopy were repeated, and colonoscopy was found to be compatible with terminal ileitis. Histopathologic examination revealed signs of active ileitis (acute inflammation). Treatment with anakinra was changed to canakinumab. She continued to have fever and diarrhea despite this treatment for

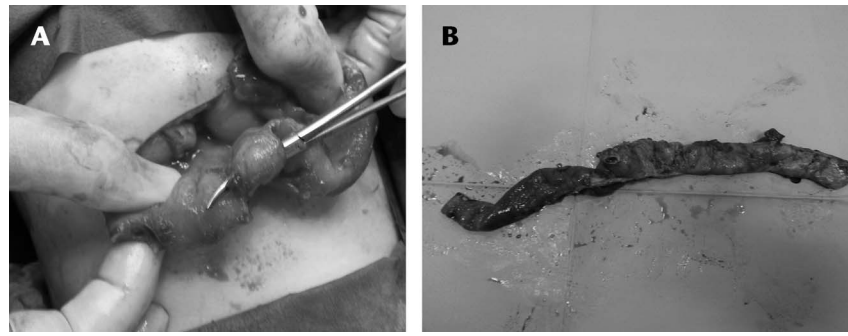

FIGURE 1. A, Intraoperative view. B, Resected small bowel loop.

approximately 3 weeks. Upon physical examination, she had tenderness in the abdomen, and the area of previous incision was edematous and swollen. Also, the level of acute phase reactants was high, and she had leukocytosis (C-reactive protein 21.14 mg/dL, procalcitonin 1.74 ng/mL, white blood cells 25,800/μL, hemoglobin 8.19 g/dL, platelets 957,000/μL). A co-occurrence of FMF and inflammatory bowel disease was considered for this case, and infliximab treatment was started (5 mg/kg on weeks 0, 2, and 6 and subsequently every eighth week). Her fever regressed after the treatment, and abdominal pain and diarrhea completely resolved. Acute phase reactants became negative. She has had no new episodes in the past 1 year.

DISCUSSION

Familial Mediterranean fever is most widely seen in the Mediterranean region and in the Middle East and is rare in the rest of the world.[1] The classic symptoms of FMF are periodical fever and abdominal pain. Abdominal pain is commonly acute and generalized with diarrhea and vomiting generally accompanying this clinical picture.[8] Abdominal attacks are present in 95% of the cases with FMF, and abdominal pain is the first sign in almost 50% of the cases; these attacks spontaneously resolve in almost 3 days.[3,9] Typical abdominal findings of an FMF episode resemble very much the clinical picture of acute appendicitis, and thus the differential diagnosis is very challenging. Therefore, the rate of patients who undergo appendectomy is higher among patients with FMF compared to the general population.[10] In a study by Tunca et al,[11] approximately one-fifth of the patients with FMF were reported to undergo appendectomy. Also, Masatlioglu et al[12] demonstrated that FMF attacks constitute 2% of patients admitted to emergency service with acute abdominal pain. Familial Mediterranean fever can mimic the syndrome of acute abdomen due to the presence of abdominal pain, guarding, tenderness, and rebound tenderness; however, no prophylactic appendectomy is recommended in order to prevent such a misdiagnosis.[8]

Acute phase response during FMF attacks is elevated; nevertheless, acute phase reactants continue to be high during the remission periods.[4] Recurrent peritoneal inflammation may result in visceral adhesions and in turn intestine obstruction.[9,13] Adhesive intestinal obstruction that may result in bowel strangulation and volvulus is a rare complication of FMF. Nevertheless, it should be kept in mind that this complication is a life-threatening emergency condition.[6]

Colchicine has been used since 1972 for the prevention of FMF attacks.[2,9] Colchicine is a well-tolerated drug among children, including infants. However, its therapeutic index is very narrow since its toxic dose is 0.5 to 0.8 mg/kg, whereas doses greater than 0.8 mg/kg are lethal.[2] Also, according to a study, cardiogenic shock and death might be seen in doses even less than 0.5 mg/kg.[14] The early signs of colchicine intoxication (0–24 hours after ingestion) are nausea, vomiting, diarrhea, abdominal pain, and leukocytosis, and this clinical picture may be confused with acute abdomen syndrome.[14]

Approximately 5% to 10% of the cases are resistant to colchicine in FMF. Anti–interleukin 1 and anti–tumor necrosis factor–related agents have been used in resistant cases.[15] In this case, anti–interleukin 1 agents were used initially; however, the attacks were not completely controlled, although a partial response was achieved. The patient had undergone a laparotomy due to the suspicion of acute appendicitis. She had severe abdominal pain, fever, and elevated acute phase reactants. By the laparotomy, she had a diagnosis of multiple ileal perforation. After the resection of necrotic tissue, fever had normalized, clinical status improved, and acute phase reactants normalized. On follow-up, she had an attack resembling the previous one, and with endoscopic

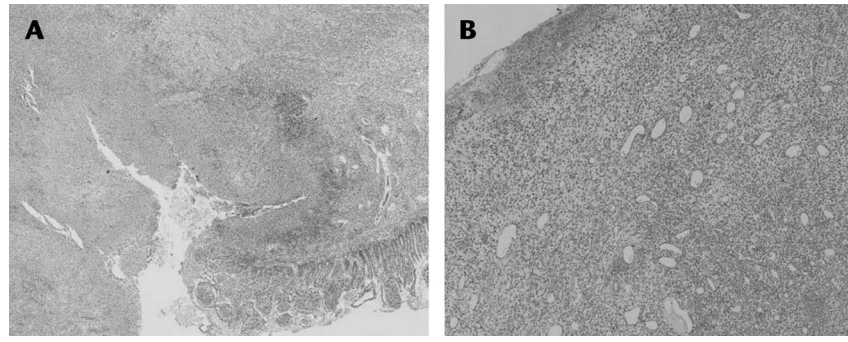

FIGURE 2. A, Ulceration on the surface inflammatory granulation tissue, ischemic changes (hematoxylin-eosin stain, original magnification ×40). B, Mixed inflammatory cell infiltration rich in neutrophil that continued until the serosa (hematoxylin-eosin stain, original magnification ×100).

investigation, similar lesions were shown. Although the pathological findings were nonspecific in this patient, the treatment was switched to infliximab with the consideration of possible clinical co-occurrence of inflammatory bowel disease with FMF. A complete response was achieved because no episodes were encountered during the last year and acute phase reactants were negative.

Oral steroid use carries the risk of development of gastrointestinal bleeding and perforation in all age groups. The proposed mechanisms of the effect of steroids for bleeding and perforation are that steroids decrease the lymphoid cell groups (lymphoid patches) and this thins out the intestinal wall, which in turn causes bleeding and perforation. This situation is most frequently encountered in the duodenum, although it may also be seen in the intestine and colon.[7] No definite cause was detected for multiple ileal perforations in this case presented here, and it was considered to be a complication that developed secondary to the oral steroid treatment and/or secondary to inflammatory bowel disease co-occurrence.

CONCLUSIONS

Probability of negative exploration is high in patients who have FMF and undergo an operation for acute appendicitis. It is important to carefully observe the entire intestinal system in cases when a normal appendix is encountered during the operation. An extensive terminal ileal resection was performed in this case as FMF presented with the complication of multiple ileal perforations. Therefore, because the episodes of abdominal pain may cause serious mortality and morbidity in patients with FMF, taking a thorough anamnesis of the patient (especially history of oral steroid use) and close follow-up are of utmost importance when the abdominal findings cannot be differentiated from a surgical abdomen. Also, the possibility of an accompanying inflammatory bowel disease and a probable infliximab treatment should be considered for the control of FMF attacks as well as keeping the acute phase reactants in reference ranges, which is impossible under the current treatment protocols.

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