

## Bloody Diarrhea as a Presentation Manifestation of Familial Mediterranean Fever in a Patient with Compound Heterozygote Mutations of the *MEFV* Gene

Gholam Hossein Fallahi\*, Nima Rezaei<sup>†,‡</sup>, and Nooshin Sadjadei\*

\*Department of Gastroenterology, <sup>†</sup>Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences School of Medicine, and <sup>‡</sup>Molecular Immunology Research Center and Department of Immunology, Tehran University of Medical Sciences School of Medicine, Tehran, Iran

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by episodic fever and inflammatory polyserositis, which could lead to a variety of manifestations, including recurrent abdominal pain. Herein, a 12-year-old boy who has suffered from fever and bloody diarrhea since early childhood is described. All structural and underlying disorders leading to bleeding were excluded. Genetic studies indicated compound heterozygote mutations of M680I/R761H in the *MEFV* gene, which confirmed the diagnosis of FMF. Therefore, treatment with colchicine was started, which led to symptom relief. As gastrointestinal manifestations appear to be the main features of FMF, bloody diarrhea could also be considered an initial symptom of FMF. (Gut Liver 2013;7:497-499)

**Key Words:** Bloody diarrhea; Familial Mediterranean fever; *MEFV* gene, mutation

### INTRODUCTION

Autoinflammatory diseases are heterogeneous group of disorders, characterized by inflammatory attacks of fever and certain clinical features along with high acute phase reactants.<sup>1</sup> Familial Mediterranean fever (FMF, OMIM#249100) is the most common form of autoinflammatory diseases, characterized by recurrent self-limited attacks of fever along with inflammatory polyserositis. Although the disease is usually presented with abdominal pain, chest, and joints could also be involved.<sup>2,3</sup> FMF is an autosomal recessive disease, caused by mutations in the *MEFV* gene (OMIM\*608107), encoding pyrin, which seems to be involved in

regulation of interleukin-1 $\beta$  activation.<sup>2,4</sup>

Several abdominal and gastrointestinal (GI) manifestations, including abdominal pain, diarrhea, ascites, and bleeding have been reported in patients with FMF.<sup>3</sup>

Herein, a child with fever and bloody diarrhea is presented in whom the diagnosis of FMF was confirmed.

### CASE REPORT

A 12-year-old boy was referred to the Children's Medical Center Hospital, the Pediatrics Center of Excellence in Iran, for evaluation of episodic fever, abdominal pain, and bloody diarrhea. He has experienced these symptoms since 9 years ago. In some of the episodes, he also suffered from nausea and vomiting. The attacks recurred bimonthly recently, which lasted 2 to 3 days.

On the admission, the patient was febrile (39.1°C), and complained of abdominal pain and bloody diarrhea. The abdomen was diffusely mildly tender, but without organ enlargement. Rectal examination revealed watery stool with traces blood. No fissure, no tag, and no hemorrhoid were detected.

Laboratory tests showed erythrocyte sedimentation rate 57, C-reactive protein 157 mg/L (normal, <20 mg/L), hemoglobin 12.7 g/dL, white blood cells 13,400/mm<sup>3</sup>, neutrophil count 8,300/mm<sup>3</sup>, eosinophil count 340/mm<sup>3</sup>, and platelet 376,000/mm<sup>3</sup>. Serum electrolytes were normal; Other laboratory results were as follow: prothrombin time 13, international normalized ratio 1, partial thromboplastin time 30, serum cholesterol 127 mg/dL, serum triglyceride 58 mg/dL, aspartate aminotransferase 20 U/L, alanin aminotransferase 11 U/L, alkaline phosphatase 338 IU/L,

Correspondence to: Nooshin Sadjadei

Department of Gastroenterology, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences School of Medicine, P.O.BOX 14155-6447, Tehran 1417613151, Iran

Tel: +98-9122188037, E-mail: nooshin.sadjadei@yahoo.com

Received on February 20, 2012. Revised on April 28, 2012. Accepted on June 19, 2012.

pISSN 1976-2283 eISSN 2005-1212 <http://dx.doi.org/10.5009/gnl.2013.7.4.497>

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

and serum albumin 4.8 g/dL. Blood culture was negative. Stool examination showed no ova, no parasite, white blood cells 3 to 5, red blood cells many; stool culture showed normal flora. Urine analysis was also normal, and urine culture was negative. Perinuclear antineutrophil antibody was negative and antisaccharomyces cervisiae antibody was 7.1 (normal, <20). Serum immunoglobulin levels were also normal, except high serum immunoglobulin E. Chest and abdominal X-rays and abdominal ultrasonography were all unremarkable. The upper GI series showed mild enhancement of jejunal folds. The esophagogastroduodenoscopy was unremarkable, while biopsies of esophagus, antrum, fundus, duodenum, and jejunum were normal. Three days later, colonoscopy, sent up to terminal ileum, was done, but no apparent pathologic finding was detected. Multiple biopsies were obtained, while the crypts appearance was normal; no inflammation, no crypt abscess, and no infiltration in lamina propria were detected. Gablet cell depletion and vasculitis were not detected.

After exclusion of possible structural defects, and as of suspicious to FMF, genetic studies were performed. Sequencing of the *MEFV* gene showed compound heterozygote mutations of M680I/R761H. Therefore 1 mg/day of colchicine was administered; subsequently, he responded well with total remission.

## DISCUSSION

FMF is a hereditary episodic febrile syndrome with hallmarks of fever and serositis in different organs, including GI system and the joints.<sup>2,3</sup>

As episodic abdominal pain is the main problem of FMF patients, affecting 95% of FMF patients.<sup>3</sup> In addition to abdominal pain, a variety of GI manifestations could be seen in these patients, including constipation, diarrhea, ascites, ileus, malabsorption, and bowel infarction. These manifestations are results of either primarily the FMF nature or secondary to the disease associations with other conditions, including vasculitis, amyloidosis, or colchicine side effects.<sup>3</sup> Association of bleeding with FMF is rarely reported, which was as a complication of vasculitis such as polyarteritis nodosa and henoch schonlein purpura or ischemic colitis.<sup>3</sup> Although bloody diarrhea unrelated to vasculitis or medication had not reported as presenting manifestation of FMF, a very recent paper reported a case of Crohn disease with chronic bloody diarrhea and failure to thrive in whom the diagnosis of FMF was made subsequently.<sup>5</sup> It should be noted that there was not any evidence of vasculitis in this patient; and indeed the symptoms had been started before initiation of colchicines therapy. Indeed there was no evidence of Crohn disease, while the symptoms were completely resolved after colchicines therapy without any need of additional medications.

Although clinical manifestations could help the physicians to make probable diagnosis of FMF, identification of mutation

in the *MEFV* gene can confirm the diagnosis. Among different mutations that have been described yet, it seems that more than half of the cases are caused by four mutations clustered on exon 10 of the *MEFV* gene,<sup>6</sup> while in a meta-analysis study, it has been shown that the most frequent mutations were M694V (40%), V726A (14%), M680I (11%), E148Q (3%), and M694I (3%).<sup>7</sup> A study on Iranian patients of Azeri Turkish origin with FMF showed that the most common mutation were M694V (42%), V726A (17%), E148Q (16%), and M680I (15%), while the R761H was the most frequent (5%) of the rare alleles, which was advised to be included in routine molecular diagnosis of FMF patients with this ethnic group.<sup>8</sup>

The presented case has compound heterozygote mutations of M680I/R761H; the first mutation is a common one, but the second mutation, which is rare in the world, is quite frequent in the country. Compound heterozygote mutations of the *MEFV* gene have also previously been reported in the patients with FMF.<sup>9</sup>

Considering the fact that abdominal manifestations of FMF are prominent, bloody diarrhea without any known predisposing factor could also be considered as an initial symptom of FMF. It should be noted that although FMF is an autoinflammatory disease, which is classified as a group of primary immunodeficiency diseases,<sup>10</sup> affected patients usually visit gastroenterologists rather than clinical immunologists or rheumatologists. Therefore being aware on all symptoms associated with the disease, including typical and even rare conditions, could lead to better quality of life of affected patients, while prompt diagnosis and appropriate treatment are the keys in management of patients with FMF.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## REFERENCES

- Ozen S, Frenkel J, Ruperto N, Gattorno M; Eurofever Project. The Eurofever Project: towards better care for autoinflammatory diseases. *Eur J Pediatr* 2011;170:445-452.
- Akkoc N, Gul A. Familial Mediterranean fever and seronegative arthritis. *Curr Rheumatol Rep* 2011;13:388-394.
- Mor A, Gal R, Livneh A. Abdominal and digestive system associations of familial Mediterranean fever. *Am J Gastroenterol* 2003;98:2594-2604.
- Shohat M, Halpern GJ. Familial Mediterranean fever: a review. *Genet Med* 2011;13:487-498.
- Kuloğlu Z, Kansu A, Ustündağ G, Birsin Özçakar Z, Ensari A, Ekim M. An infant with severe refractory Crohn's disease and homozygous *MEFV* mutation who dramatically responded to colchicine. *Rheumatol Int* 2012;32:783-785.
- Resource of Asian Primary Immunodeficiency Diseases. *MEFV*

- mutation database [Internet]. [place unknown]: Resource of Asian Primary Immunodeficiency Diseases; c2009 [cited 2012 Feb 16]. Available from: [http://rapid.rcai.riken.jp/RAPID/mutation?pid\\_id=AGID\\_94](http://rapid.rcai.riken.jp/RAPID/mutation?pid_id=AGID_94).
7. Papadopoulos VP, Giaglis S, Mitroulis I, Ritis K. The population genetics of familial mediterranean fever: a meta-analysis study. *Ann Hum Genet* 2008;72(Pt 6):752-761.
  8. Bonyadi M, Esmaili M, Jalali H, et al. MEFV mutations in Iranian Azeri Turkish patients with familial Mediterranean fever. *Clin Genet* 2009;76:477-480.
  9. Gershoni-Baruch R, Shinawi M, Shamaly H, Katsinetz L, Brik R. Familial Mediterranean fever: the segregation of four different mutations in 13 individuals from one inbred family: genotype-phenotype correlation and intrafamilial variability. *Am J Med Genet* 2002;109:198-201.
  10. Berg S, Fasth A. Autoinflammatory disorders. In: Rezaei N, Notarangelo LD, Aghamohammadi A, eds. *Primary immunodeficiency diseases: definition, diagnosis, and management*. 1st ed. Heidelberg: Springer, 2008:215-219.