

# Familial Mediterranean fever mimicking Crohn disease

## A case report

Kensuke Asakura, MD<sup>a,\*</sup>, Shunichi Yanai, MD, PhD<sup>a</sup>, Shotaro Nakamura, MD, PhD<sup>a</sup>, Keisuke Kawaski, MD, PhD<sup>a</sup>, Makoto Eizuka, MD, PhD<sup>b,c</sup>, Kazuyuki Ishida, MD, PhD<sup>b</sup>, Masaki Endo, MD, PhD<sup>d</sup>, Tamotsu Sugai, MD, PhD<sup>b</sup>, Kiyoshi Migita, MD, PhD<sup>e</sup>, Takayuki Matsumoto, MD, PhD<sup>a</sup>

### Abstract

**Rationale:** Familial Mediterranean fever (FMF) is the most common form of autoinflammatory disease. We report a rare case of FMF with gastrointestinal lesions mimicking Crohn disease.

**Patient concerns:** A 21-year-old Japanese man was referred to our institution, complaining of refractory diarrhea and weight loss of 14 kg during the past two years. He had presented with recurrent fever, abdominal pain, anal fistula and stomatitis. His father and one of his brothers had ulcerative colitis. Colonoscopy revealed longitudinal ulcers in the terminal ileum and aphthous erosions in the colorectum. Esophagogastroduodenoscopy revealed multiple linear erosions in the gastric corpus and circular erosions in the duodenal second portion. Biopsy from these lesions failed to detect epithelioid cell granulomas.

**Diagnoses:** Analysis of the genomic DNA revealed compound heterozygous mutations of E148Q/L110P in exon 2 of MEFV gene, suggesting a diagnosis of FMF.

**Interventions:** The patient was subsequently given 0.5 mg of colchicine per day.

**Outcomes:** Follow-up colonoscopy 6 months later demonstrated that both the longitudinal ulcers in the terminal ileum and aphthous lesions in the colorectum had completely disappeared.

**Lessons:** Our case suggests that patients with FMF possibly manifest gastrointestinal lesions mimicking Crohn disease.

**Abbreviations:** BD = Behçet's disease, CD = Crohn disease, CRP = C-reactive protein, EGD = esophagogastroduodenoscopy, FMF = familial Mediterranean fever, IBD = inflammatory bowel disease, MEFV = Mediterranean fever gene, UC = ulcerative colitis, WBC = white blood cell.

**Keywords:** Crohn disease, Endoscopy, Familial Mediterranean fever

Editor: N/A.

KA was involved in patient management, performed endoscopy, obtained patient consent, and drafted the manuscript. SY performed small-bowel radiography and revised the manuscript. KK performed endoscopic examinations. ME, KI, and TS reviewed the histological specimens. KM performed genetic analyses. SN and TM critically reviewed and revised the manuscript. All authors have read and approved the final version of the manuscript.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The authors report no conflicts of interest.

<sup>a</sup> Division of Gastroenterology, Department of Internal Medicine, School of Medicine, Iwate Medical University, <sup>b</sup> Division of Molecular Diagnostic Pathology, Department of Pathology, <sup>c</sup> School of Medicine, Iwate Medical University, <sup>d</sup> Kaiunbashi Endoscopy Clinic, Morioka, <sup>e</sup> Department of Rheumatology, Fukushima Medical University, Fukushima, Japan.

\* Correspondence: Kensuke Asakura, Division of Gastroenterology, Department of Internal Medicine, Iwate Medical University School of Medicine, Uchimaru 19-1, Morioka 020-8505, Japan (e-mail: asaken@iwate-med.ac.jp).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2018) 97:1(e9547)

Received: 20 August 2017 / Received in final form: 8 December 2017 /

Accepted: 12 December 2017

<http://dx.doi.org/10.1097/MD.0000000000009547>

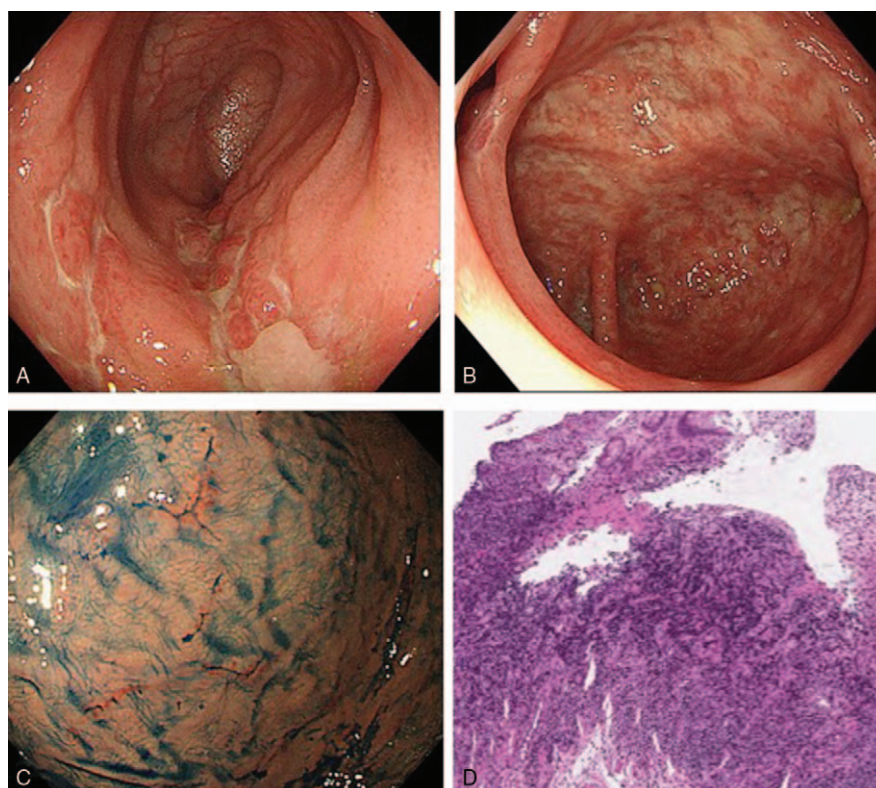
## 1. Introduction

Familial Mediterranean fever (FMF) is one of most common forms of autoinflammatory diseases, characterized by periodic fever accompanied by sterile peritonitis, pleuritis, arthritis or erysipelas-like erythema affecting the lower limbs.<sup>[1–3]</sup> FMF is an autosomal recessive disorder caused by mutations in the Mediterranean fever gene (MEFV) encoded on the short arm of chromosome 16. It has also been known that mutations in exons 1–3, 5, and 10 of MEFV are involved for the pathogenesis of FMF.<sup>[4,5]</sup>

MEFV gene encodes the pyrin protein, which has a regulatory effect in the inflammasome-related innate immune response.<sup>[2]</sup> The symptoms of FMF often resemble those of inflammatory bowel disease (IBD), such as Crohn disease (CD), ulcerative colitis (UC), and intestinal Behçet disease (BD).<sup>[6–10]</sup> To date, however, only a few endoscopic findings of gastrointestinal lesions in patients with FMF have been described so far.<sup>[6–12]</sup> In the present article, we report a case of FMF in which both the clinical symptoms and endoscopic findings resembled those of CD.

## 2. Case report

A 21-year-old Japanese man visited a proctology clinic because of anal pain in July 2015. The patient was diagnosed as having anal fistulas, and was subsequently treated with seton drainage. He had been suffering from recurrent diarrhea and weight loss of



**Figure 1.** A, B, Colonoscopic images showing longitudinal ulcers in the terminal ileum (A) and aphthous erosions in the caecum (B). C, Esophagogastroduodenoscopic image showing of stomach linear erosions in the gastric corpus. D, Histologic picture of the biopsy specimens from the ileal ulcerative lesion reveals dense lymphoplasmacytic infiltrate without any evidence of epithelioid cell granulomas.

14 kg during the past 2 years. His father and one of his brothers had been diagnosed as having UC. In September 2015, the patient visited a gastroenterological clinic because of severe abdominal pain with high fever of 39°C. Colonoscopy showed longitudinal ulcers in the terminal ileum and aphthous erosions in the colorectum. Since he was suspected as having CD, 1.5 g/day of oral mesalazine was initiated and then he was referred to our hospital.

At the time of the first visit, the patient presented with fever of 39°C, abdominal pain and recurrent stomatitis. His body mass index was 14.9 kg/m<sup>2</sup>. Physical examination revealed tenderness in his epigastrium. The laboratory data showed a white blood cell (WBC) count of 14,040/μL (neutrophils: 90.0%), serum C-reactive protein (CRP) 13.16 mg/dL, total protein 6.9 g/dL and albumin 3.8 g/dL. The interferon-gamma release assay (T-SPOT tuberculosis blood test) and cytomegalovirus antigenemia test showed negative results. The bacterial cultures from blood and fecal samples detected no infectious pathogens. Because of the possibility of mesalazine allergy, we ceased the medication of mesalazine. Three days later, however, both his fever and abdominal pain had resolved spontaneously with laboratory data of 4970/μL (neutrophils: 58.4%) in WBC count and 0.52 mg/dL in serum CRP value.

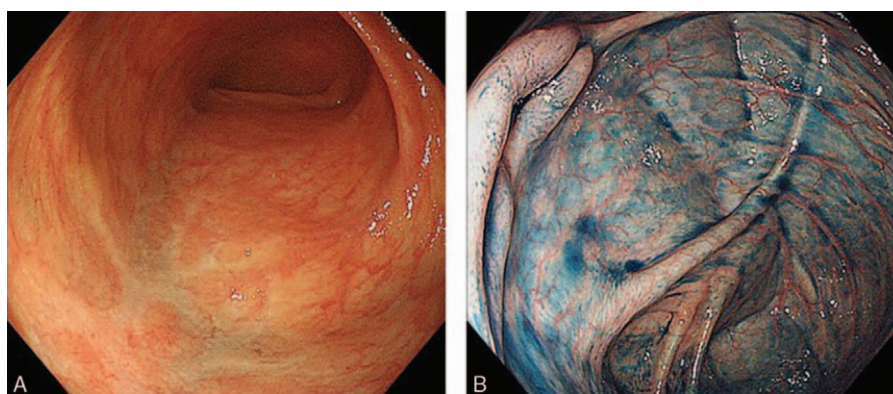
Colonoscopy revealed longitudinal ulcers in the terminal ileum and multiple aphthous erosions in all areas of the colorectal mucosa (Fig. 1A, B). These endoscopic findings suggested a diagnosis of CD. Esophagogastroduodenoscopy (EGD) revealed multiple linear erosions in the gastric corpus (Fig. 1C) and circular erosions in the duodenal second portion. Although none of the biopsy specimens from these erosions, ulcerative lesions and normal-appearing mucosa revealed any evidence of

epithelioid cell granulomas (Fig. 1D), we clinically diagnosed the patient as having CD, and intravenous administration of infliximab 5 mg/kg was started. However, his symptoms of fever and abdominal pain recurred 5 days after the start of infliximab. Both WBC count (38,800/μL and serum CRP level (6.56 mg/dL) further increased.

Thereafter, we suspected the possibility of FMF because his symptoms met the Tel-Hashomer major criteria of 3 recurrent typical attacks.<sup>[1]</sup> The patient was subsequently given 0.5 mg of colchicine per day. His fever and abdominal pain promptly subsided. We subsequently searched for mutations in exons 1–3, 5, and 10 in *MEFV*. As a result, he was found to have compound heterozygous mutations of E148Q/L110P in exon 2 of *MEFV*. Based on these findings, we finally made a definitive diagnosis of FMF in this patient. Oral administration of colchicine was continued, whereas infliximab was discontinued after 4 times administration (0, 2, 6, 14 weeks). Follow-up colonoscopy 6 months later demonstrated that both the longitudinal ulcers in the terminal ileum and aphthous lesions in the colorectum had completely disappeared (Fig. 2A, B).

### 3. Discussion

In patients with FMF, the mutations in *MEFV* result in loss of pyrin-mediated regulation of apoptosis-associated speck-like protein containing caspase recruitment domain and caspase 1 activity in the inflammasome and in systemic increase in IL-1β.<sup>[3]</sup> In Japanese patients with FMF, major mutations in *MEFV* have been found at E148Q in exon 2 and M694I in exon 10.<sup>[4,5]</sup> In our present case, compound heterozygous mutations of E148Q/



**Figure 2.** Colonoscopic images showing healed ulcer scars in terminal ileum (A) and normal-appearing mucosa in the cecum (B).

L110P in exon 2 was detected. It has been shown that the compound heterozygous mutation of *MEFV* were found in 8.4% of Japanese patients with FMF.<sup>[5]</sup>

There have been several publications regarding the endoscopic findings of gastrointestinal lesions in patients with FMF. Arasawa et al<sup>[6]</sup> first reported a case of FMF who had the circumferentially erythematous mucosa with erosion in the cecum and longitudinal erosions with pseudopolypoid-like lesions in the right side of the colon, and they suggested a similarity in the intestinal lesions between CD and FMF. Subsequently, Takahashi et al<sup>[7]</sup> reported another case of FMF with multiple nonspecific ulcers in the terminal ileum, which apparently suggested a diagnosis of intestinal BD. In a study by Beser et al,<sup>[8]</sup> 12 of 20 (60%) pediatric FMF patients with abdominal pain, diarrhea, or bloody stool were endoscopically diagnosed as having IBD of any form (11 patients mimicking UC and 1 CD). In another study of 10 patients with FMF,<sup>[9]</sup> colonoscopy revealed findings compatible with IBD including hyperemia, fragility, and patchy ulcerations (n=5); aphthous ulcers (n=3); and follicular lymphoid hyperplasia (n=2). Matsumoto et al,<sup>[10]</sup> reported a case of FMF in which CD was suspected because of the wall thickening and increased density of mesenteric adipose tissue in the jejunum, but oral double-balloon endoscopy revealed only mild edema of the jejunum.

More recently, small bowel lesions in FMF have been rigorously investigated by enteroscopy. Demir et al,<sup>[11]</sup> examined 41 patients with FMF by capsule endoscopy and found mucosal defects (erosions or ulcers) in the small bowel in 44% of patients. Kitade et al<sup>[12]</sup> reported a case of FMF with multiple jejunoileal lesions of petal-shaped redness and white hemming detected by capsule endoscopy and double-balloon endoscopy. Thus, patients with FMF are presumed to have variable small bowel lesions. In our present case, colonoscopy revealed longitudinal ulcers in the terminal ileum and multiple aphthous erosions in all areas of the colorectal mucosa, which resembled CD. In contrast, we presume that EGD findings of our case, namely multiple linear erosions in the gastric corpus and circular erosions in the duodenal second portion, are distinctive of those in CD.

Colchicine is recommended to be the first choice medication for treatment of FMF, as it is highly effective.<sup>[13,14]</sup> Also in our patient, fever and abdominal pain subsided immediately after administration of colchicine. It is of interest that ileal longitudinal ulcers and aphthous erosions in the colorectum also disappeared after taking colchicine. In patients with FMF, who are resistant to colchicine, anti-IL-1 $\beta$  monoclonal antibody canakinumab is effective.<sup>[15]</sup>

#### 4. Conclusion

We presented detailed endoscopic findings in a case of FMF, which was initially diagnosed as CD. It should be noted that there are considerable overlaps in clinical symptoms and in gastrointestinal lesions in FMF and CD.

#### References

- [1] Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997;40:1879–85.
- [2] Chae JJ, Komarow HD, Cheng J, et al. Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis. *Mol Cell* 2003;11:591–604.
- [3] Masters SL, Simon A, Aksentjevich I, et al. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. *Annu Rev Immunol* 2009;27:621–68.
- [4] Tomiyama N, Higashiuesato Y, Oda T, et al. *MEFV* mutation analysis of familial Mediterranean fever in Japan. *Clin Exp Rheumatol* 2008;26:13–7.
- [5] Migita K, Agematsu K, Yazaki M, et al. Familial Mediterranean fever: genotype-phenotype correlations in Japanese patients. *Medicine* 2014;93:158–64.
- [6] Arasawa S, Nakase H, Ozaki Y, et al. Mediterranean mimicker. *Lancet* 2012;380:2052.
- [7] Takahashi T, Tsukuda H, Itoh H, et al. An atypical familial Mediterranean fever patient who developed ulcers in the terminal ileum and recurrent abscess-like lesions in multiple organs. *Intern Med* 2012; 51:2239–44.
- [8] Beser OF, Kasapçopur O, Cokugras FC, et al. Association of inflammatory bowel disease with familial Mediterranean fever in Turkish children. *J Pediatr Gastroenterol Nutr* 2013;56:498–502.
- [9] Gurkan OE, Dalgic B. Gastrointestinal mucosal involvement without amyloidosis in children with familial Mediterranean fever. *J Pediatr Gastroenterol Nutr* 2013;57:319–23.
- [10] Matsumoto S, Urayoshi S, Yoshida Y. Familial Mediterranean fever in which Crohn disease was suspected: a case report. *BMC Res Notes* 2014;7:678.
- [11] Demir A, Akyüz F, Göktürk S, et al. Small bowel mucosal damage in familial Mediterranean fever: results of capsule endoscopy screening. *Scand J Gastroenterol* 2014;49:1414–8.
- [12] Kitade T, Horiki N, Katsurahara M, et al. Usefulness of small intestinal endoscopy in a case of adult-onset familial Mediterranean fever associated with jejunoileitis. *Intern Med* 2015;54:1343–7.
- [13] Demirkaya E, Erer B, Ozen S, et al. Efficacy and safety of treatments in Familial Mediterranean fever: a systematic review. *Rheumatol Int* 2016;36: 325–31.
- [14] Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. *Ann Rheum Dis* 2016; 75:644–51.
- [15] Gül A, Ozdogan H, Erer B, et al. Efficacy and safety of canakinumab in adolescents and adults with colchicine-resistant familial Mediterranean fever. *Arthritis Res Ther* 2015;17:243.