

CASE REPORT

## 발열과 두드러기를 동반한 반복적 복통 1예

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### A Case of Recurrent Abdominal Pain with Fever and Urticarial Eruption

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Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent episodes of fever and serosal, synovial, or cutaneous inflammation, caused by a dysfunction of pyrin as a result of mutation within the *MEFV* gene. It occurs mainly among Mediterranean and Middle Eastern populations, including Jews, Arabs, and Turks. However, FMF cases have been reported outside the Mediterranean and Middle Eastern countries in recent years. Although FMF has been relatively rare in Korea until now, proper recognition of FMF might lead to more frequent diagnoses of FMF. We experienced an interesting case, a 31-year-old Korean man who presented with recurrent abdominal pain with fever and urticarial eruption for 10 years. DNA analysis showed complex mutations (p.Leu110Pro, p.Glu148Gln) in the *MEFV* gene. To date, three cases have been reported, and this case of FMF with skin conditions is the first case in Korea. (*Korean J Gastroenterol* 2014;64:40-44)

**Key Words:** Familial Mediterranean fever; Abdominal pain; Urticaria

#### INTRODUCTION

Familial Mediterranean fever (FMF) is an inherited disease characterized by recurrent inflammatory polyserositis. The disease is associated with a number of mutations of the *MEFV* gene.<sup>1</sup> FMF is typically expected only in the Middle East population; however, recently, this disease has been increasingly reported in non-Mediterranean regions.<sup>2</sup>

Recurrent abdominal pain is a common symptom of FMF, being observed in approximately 90% of patients.<sup>3</sup> However, FMF is typically not familiar to clinicians in non-endemic areas and conventional diagnostic evaluations typically fail to detect FMF. Thus, it might be misdiagnosed as another gastrointestinal disease.<sup>4</sup>

Various cutaneous features can also be seen during the course of FMF.<sup>5,6</sup> Erysipelas like erythema is the well-known skin lesion.<sup>5</sup> On the other hand, FMF presenting as a urticarial eruption is rare.<sup>6</sup> We report on a case of FMF, which showed recurrent urticarial eruption and peripheral eosinophilia.

#### CASE REPORT

A 31-year-old male visited our hospital due to a 10-year history of recurrent, cramping abdominal pain, fever, and urticarial eruption. There was no family history of recurrent fever attack and abdominal pain. Typically, the abdominal pain, fever, and urticarial eruption had lasted for approximately three

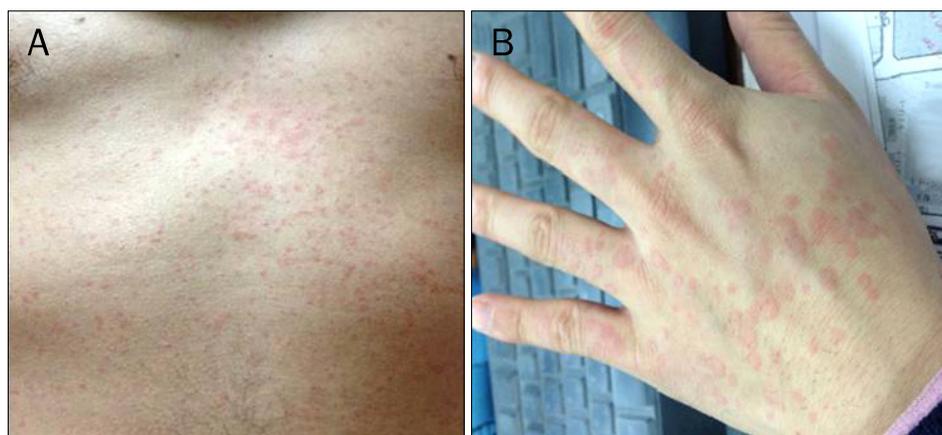
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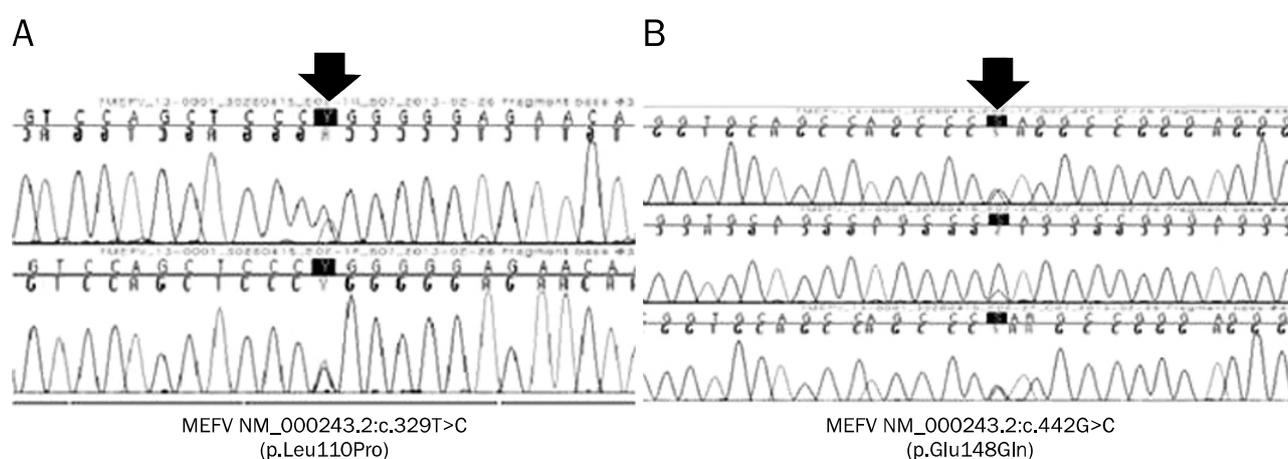
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**Fig. 1.** Urticarial eruption. Numerous small wheal-like lesions are found on the anterior trunk (A) and hand (B).



**Fig. 2.** Results of DNA analysis of the *MEFV* gene. DNA sequencing shows (A) the p.Leu110Pro mutation (arrow) and (B) p.Glu148Gln mutation (arrow).

days and then resolved simultaneously and spontaneously. Similar attacks occurred every year or every other year. He had already undergone repetitive full blood tests, endoscopy, and abdominal computed tomography in other hospitals, which had not determined the cause of the symptoms.

At admission, his blood pressure was 120/80 mmHg, pulse rate was 100 beats/min, respiratory rate was 24/min, and rectal temperature was 38.8°C. Mild tenderness in the epigastric area and hypoactive bowel sound on the whole abdomen were observed during examination. Laboratory findings showed leukocyte count 4,430/ $\mu$ L (neutrophils 1,993/ $\mu$ L [45.1%], eosinophils 708/ $\mu$ L [16.5%]), hemoglobin 14.3 g/dL, and platelet 288,000/ $\mu$ L. Elevation of C-reactive protein (3.47 mg/dL; reference range, 0-0.5 mg/dL) and erythrocyte sedimentation rate (13 mm/hr; reference range, 0-9 mm/hr) were found. Markers for autoimmune disease, including an anti-nuclear antibody and anti-neutrophil

cytoplasmic antibody were negative. A peripheral blood cell morphology smear found no clues of other periodic fever diseases, such as malaria. Urinalysis was negative for protein and bacteria. The urticarial eruption broke out on the face, abdomen, back, and trunk and disappeared when fever and abdominal pain had subsided (Fig. 1).

We performed multiple biopsies in antrum, body, and fundus of gastric mucosa and ascending, transverse and descending colon as well as the rectum to rule out eosinophilic gastroenteritis. There was an elevated eosinophil count (up to 16 per high power field) in a degree that did not satisfy the diagnostic criteria for eosinophilic gastroenteritis. We also performed several tests to find any cause of peripheral eosinophilia, including stool parasite exam, multiple allergen screen test, peripheral blood cell morphology smear, and chest radiography. However, we failed to find any such cause of peripheral eosinophilia.

**Table 1.** Four Cases of Familial Mediterranean Fever (FMF) in Korea

Author	Gender	Onset age (yr)	Symptoms	Gene mutation	Complication	Family history of FMF
Joo, et al. <sup>9</sup>	Male	2	Fever, arthralgia	p.Glu148Gln p.Pro369Ser p.Arg408Gln	Extensive thrombosis	None
Lim, et al. <sup>10</sup>	Male	29	Fever, vomiting abdominal pain	p.Glu148Gln p.Leu110Pro	None	None
Koo, et al. <sup>11</sup>	Male	7	Fever, edema, scrotal swelling	p.Pro369Ser p.Arg408Gln	Renal amyloidosis	None
Current case	Male	21	Fever, urticaria abdominal pain	p.Glu148Gln p.Leu110Pro	None	None

Based on the findings of the history, physical examination, laboratory tests, and radiologic imaging, infection, malignancy, and collagen vascular disease were also ruled out.

Considering the patient's fever pattern and other clinical manifestations, periodic fever syndromes, such as FMF, hyperimmunoglobulinemia D (HIDS), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), or Muckle-Wells syndrome were suspected. We first highly suspected FMF because one major criterion (fever and abdominal attack due to peritonitis) and one minor criterion (recurrent episodes of fever) of the Tel-Hashomer criteria were fulfilled. In addition, short duration and self-limited fever attack were also satisfied typical clinical features of FMF. We requested DNA analysis of the *MEFV* gene to an outside specialized institution and two point mutations, p.Leu110Pro and p.Glu148Gln, were detected in exon 2 (Fig. 2). We finally diagnosed this case as FMF by clinical manifestation and DNA analysis of the *MEFV* gene. The patient is now taking colchicine doses of 1.2 mg/day. During the follow-up period of more than one year, he had no recurrence.

## DISCUSSION

In 1960, Fox and Morrelli<sup>7</sup> described the first case of FMF in a patient of non-Mediterranean ethnic origin. Since then, more cases of FMF have been reported outside Mediterranean or Middle Eastern countries.<sup>2</sup> In Japan, more than 80 cases of various features of adult FMF have been reported.<sup>8</sup> Recently, in Korea, two cases of adult<sup>9,10</sup> and one case of child FMF<sup>11</sup> were reported (Table 1). However, this case is the first FMF case in a Korean patient manifesting as skin involvement.

In non-endemic areas, diagnosis of FMF is not easy. The typical manifestations of this disease are recurrent attacks

of abdominal pain due to serositis and a fever that lasts 1-3 days and then resolves spontaneously.<sup>4,12</sup> It can be diagnosed by verifying the mutation of the *MEFV* gene.<sup>13</sup> It maps to chromosome 16p13.3, which encodes a 781 amino acid protein termed pyrin (or marenostin).<sup>13</sup> Lack of normal pyrin (or marenostin) activity in FMF is considered to be the cause of excess cytokines and subsequent spontaneous inflammatory attack.<sup>14</sup>

Major clinical manifestations of FMF are recurrent periodic fever accompanied by pain in the abdomen, chest, or joints.<sup>2</sup> In general, FMF suffering begins before the twentieth year of life.<sup>1,15</sup> However, FMF begins after the twentieth year of life in approximately 14% of FMF cases and after 40 in 0.5%.<sup>1,15</sup> Complications, such as amyloid nephropathy and chronic arthritis were less common, and a mild clinical course was observed in FMF with adult-onset.<sup>1,15</sup> Several sets of criteria have been proposed for the diagnosis of FMF. Highly sensitive and specific criteria for FMF were established in 1997.<sup>3</sup> The diagnosis of FMF was based on the observation of at least one major criterion. FMF was diagnosed as recurrent ( $\geq 3$  of the same type), febrile (rectal temperature of 38°C or higher), or short-duration (lasting between 12 hours and three days).<sup>3</sup> This particular case could be described as that with typical symptoms, including recurrent, febrile, and short-duration.

Although this case satisfies the typical attack of FMF, it is necessary to differentiate from other periodic fever syndromes such as TRAPS or Muckle-Wells syndrome and HIDS. TRAPS and Muckle-Wells syndrome are inherited with an autosomal dominant pattern, therefore, parents, sibling, or relatives of each syndrome should have similar symptoms. Through investigation of family history, we can exclude the possibility of TRAPS or Muckle-Wells syndrome.<sup>16</sup> Patients with HIDS by definition have elevations of the serum im-

munoglobulin D level ( $> 100$  IU/mL); however, 13% of FMF patients also have modest increases in immunoglobulin D level, thus, the serologic test is not always helpful. There are clinical differences between FMF and HIDS, such as week-long fever (generally over five days) in HIDS.<sup>16</sup> Decisively, patients with HIDS do not show linkage to chromosome 16p.<sup>16</sup>

Because this case also showed elevated eosinophil count, hypereosinophilic syndrome or eosinophilic enteritis can be considered. However, hypereosinophilic syndrome is a disease characterized by a persistently elevated eosinophil count ( $\geq 1,500$  eosinophils/mm<sup>3</sup>) in the blood for at least six months. This case showed transient hypereosinophilia in serum only during fever and abdominal attack. When his symptoms were waning, peripheral eosinophilia showed spontaneous resolution. We can rule out eosinophilic gastroenteritis thorough random biopsy, which was performed at the stomach and colorectal mucosa. Although there was a mildly elevated eosinophil count in some tissue, eosinophil count did not satisfy the diagnostic criteria for eosinophilic gastroenteritis.<sup>17</sup>

FMF with peripheral eosinophilia is not a common finding. According to one previous report, active FMF patients showed an elevated eosinophil cationic protein level.<sup>18</sup> This finding suggests that eosinophil mediated inflammation and Th<sub>2</sub> cells may play an important role in FMF pathogenesis.<sup>18</sup> In addition, one case report of *MEFV* gene mutations combined with eosinophilic gastritis has been reported.<sup>19</sup> In general, peripheral eosinophilia can be accompanied by parasitic infection, allergic reaction to drug, microscopic colitis, inflammatory bowel disease, and malignant lymphoma. In this case, we could exclude all of these diseases with history, physical examination, and several tests. Therefore, we assumed that peripheral eosinophilia in our patient may be associated with several lines of inflammatory cascade in active FMF.

In the current case, two complex mutations of p.Leu110Pro and p.Glu148Gln were noted. In previous studies, mutation of p.Leu110Pro was found mainly combined with p.Glu148Gln mutation.<sup>8,10,20</sup> According to one Japanese study, these types of mutations have been reported in 11.3% of FMF patients.<sup>8</sup> In addition, the same two point mutations were reported as FMF in Korea in 2012.<sup>10</sup> Although we could not confirm the inheritance pattern of the two mutant alleles due to the lack

of family gene data, these Japanese data and Korean case suggested that our mutations are sufficient to express the typical symptoms of FMF.

Typical cutaneous lesion of FMF was characterized by warm, tender erysipelas-like erythema with well-defined borders located on the lower legs, medial malleolus, or the dorsum of the foot.<sup>6</sup> However, in this case, the eruption was found over the entire body and displayed wheal-like features. In this case, abdominal pain, fever, and skin rash lasted for around three days and then subsided spontaneously. We consulted a dermatologist to take a biopsy of the skin lesion. However, at the time of biopsy by a dermatologist, the skin rash had disappeared and we unfortunately failed in taking tissue to confirm. Although we did not confirm tissue biopsy, the patient's skin rash expressed typical features of a wheal like urticarial eruption.

DNA analysis of the *MEFV* gene mutation was requested to an outside specialized institution; the final result takes approximately two months. Although FMF was initially suspected, we did not have a trial of colchicine during a short attack because FMF is a very rare disease entity and we had a paucity of clinical experience regarding FMF. Thus, we did not confirm colchicine response in active FMF state. Our patient was recommended to receive oral colchicine (1.2 mg/day) to prevent attack of FMF. His symptoms did not recur for over one year during the follow up period. However, due to the short follow up duration, the protective effects of colchicine against attacks of FMF cannot be confirmed.

In conclusion, we report on an interesting case of a 31-year-old Korean man who manifested with fever, abdominal pain, and urticarial eruption and who was finally diagnosed as FMF through *MEFV* gene analysis. Suspicion and diagnosis of FMF is difficult in non-endemic areas. However, if unexplained recurrent abdominal pain accompanied with fever cannot be elucidated using conventional diagnostic tools, FMF should be considered as a potential cause in a non-endemic area like Korea.

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