An Atypical Familial Mediterranean Fever Patient Who Developed Ulcers in the Terminal Ileum and Recurrent Abscess-like Lesions in Multiple Organs

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Abstract

We herein describe the case of a 25-year-old woman who suffered from atypical familial Mediterranean fever for more than a decade. She presented with a periodic fever, abdominal pain and persistent ulcers in the terminal ileum. Colchicine was effective, and familial Mediterranean fever was diagnosed. A genetic study showed a heterozygous E148Q mutation in the MEFV gene. Multiple, recurrent, abscess-like lesions developed asynchronously in the spleen, liver, and a lung. Infliximab was administered when colchicine treatment became ineffective. However, infliximab treatment soon became ineffective, probably because antibodies were generated against it. Therefore, etanercept treatment was started, and the patient showed an immediate response.

Key words: Familial Mediterranean fever, peritonitis, periodic fever, ulcer of the ileum, splenic abscess, liver abscess

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Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease that is characterized by recurrent fever accompanied by peritonitis, pleuritis, arthritis, or erysipelas-like erythema (1). FMF is caused by mutations in MEFV, which is a 10-exon gene encoded on the short arm of chromosome 16. MEFV codes for pyrin, which is a 781 amino acid protein that is predominantly expressed in polymorphonuclear leukocytes and cytokine-activated monocytes. FMF is observed most frequently in Jewish, Armenian, Arab, Turkish, and Italian people, and it has been thought to be a rare disease in Japan. However, an increasing number of cases of FMF have been reported in Japan (2-13). Unlike typical FMF cases in endemic areas, some cases in Japan have been sporadic and adult-onset cases

We herein describe a case of periodic fever that was associated with peritonitis and that fulfilled the Tel Hashomer criteria for the diagnosis of FMF (14). In addition, the patient had other symptoms, such as ulcers in the terminal ileum and multiple recurrent abscess-like lesions in multiple organs.

Case Report

A 25-year-old woman was referred to us in September 2001 because of a periodic fever that was associated with abdominal pain for 5 months. A high grade fever and severe abdominal pain, which lasted for 3 to 7 days, occurred abruptly and resolved spontaneously without specific treatment. Pleuritis, arthritis, and erythema were not associated with the attacks. The patient had undergone a thyroidectomy for thyroid cancer in 2000, but no other medical history. She also had no remarkable family history, and her parents were non-consanguineous. A physical examination showed no abnormal findings, except for tenderness in the right lower abdomen. The findings from a contrast-enhanced computed tomography (CT) scan indicated local peritonitis. Shallow ulcers in the terminal ileum were detected by colonoscopy.
Results of colonoscopic examination. Shallow ulcers were observed in the terminal ileum in September 2001 (A) and in February 2003 (B).

(Fig. 1A). The pathological examination showed non-specific inflammation. The tuberculin test was negative. Both HLA-B51 and a pathergy skin test were negative. Because the attacks developed during menstruation, ectopic endometriosis was suspected. Treatment with leuprolelin acetate was started, and the attacks were suppressed for a significant period. We lost contact with the patient until February 2003 when she presented with a recurrence of the attacks. The ulcers in the terminal ileum persisted (Fig. 1B). After obtaining informed consent, an exploratory ileocectomy with ileocolostomy was performed. There were no ectopic endometriosis lesions or granulomatous lesions indicating Crohn’s disease or tuberculosis. The pathological findings of the ulcers resembled those of Behçet’s disease (BD).

The attacks persisted after the exploratory surgery (Fig. 2A). In July 2003, the patient developed severe pain under the ribs on the left side, which was associated with a persistent high grade fever and multiple cystic lesions in the spleen were detected by a contrast-enhanced CT scan (Fig. 3). Antibiotics were administered because an infectious abscess in the spleen was suspected, and the lesions thereafter gradually disappeared. However, repeated blood bacterial cultures were negative. Colchicine was started because a diagnosis of FMF was suspected at that time. The attacks were suppressed while the patient was taking colchicine, but they recurred after stopping it. Therefore, a diagnosis of FMF was made according to the Tel Hashomer criteria for the diagnosis of FMF (14).

However, the attacks recurred in 2005, and they became more frequent (once or twice a month) and prolonged (7 to 10 days), even though she continued colchicine treatment. She repeatedly visited our emergency room in order to receive pentazocine injections for the abdominal pain. Abdominal CT scans were performed on several occasions during the attacks, and they showed findings of peritonitis without ascites. Increasing doses of colchicines did not suppress the attacks.

In September 2008, she was started on treatment with infliximab (a chimeric anti-tumor necrosis factor (TNF) -alpha monoclonal antibody), while colchicine was also continued (Fig. 2B). The abdominal pain and fever dramatically disappeared shortly after infusion of the drug. However, she declined to continue the treatment for economic reasons, and the severe attacks recurred two months later. In May 2009 (after an 8 month interval), she decided to take infliximab again, and a complete resolution of the symptoms was observed. However, a severe serum sickness-like adverse reaction developed a week after the third course. Prednisolone and azathiopurine were administered in order to suppress this adverse event, and infliximab was continued. Although the attacks could not be completely suppressed thereafter, the abdominal pain was less severe than before the introduction of infliximab. At that time, sequencing of the whole exon of the MEFV gene was performed (courtesy of Dr.
Ryuta Nishikomori, Department of Pediatrics, Kyoto University Graduate School of Medicine), and a heterozygous E148Q mutation in the MEFV gene was detected.

In September 2009, severe right flank pain that was associated with a persistent high-grade fever developed. As shown in Fig. 3, a contrast-enhanced CT scan disclosed a large cystic mass in the liver. Intravenous antibiotics were administered because an infectious liver abscess was suspected, although repeated blood cultures were negative. Percutaneous needle drainage was performed, and gray viscous fluid without a putrid odor was obtained. No white blood cells or microorganisms were microscopically observed in the fluid. A bacterial culture of the drained specimen was also negative. The fever and inflammatory reaction both gradually resolved thereafter, while the periodic administration of infliximab was continued.

In December 2009, although the patient showed no symptoms, a routine chest X-ray examination showed an abnormal shadow in the left upper lung field. As shown in Fig. 4, a mass measuring 1 cm in diameter with a cavity was ob-
Figure 4. A contrast-enhanced CT scan of the abdomen conducted in September 2009. A large cystic mass in the liver is shown.

Figure 5. Chest CT scan conducted in December 2009. A mass of 1 cm in diameter with a cavity was observed.

served on a chest CT scan. A transbronchial lung biopsy showed no definite pathological findings. The repeated cultures of sputa were negative, and the polymerase chain reaction tests for tuberculosis and atypical mycobacteria were negative. The serum anti-aspergillus test was also negative. The lesion completely disappeared in two months while the patient was taking oral antibiotics.

In February 2010, the splenic cystic lesions developed again. Although repeated blood bacterial cultures were negative, antibiotics were administered because an infectious abscess could not be ruled out. The lesions gradually disappeared. A similar episode occurred in July 2010. The abdominal pain attacks gradually became refractory to infliximab, probably due to the production of neutralizing or blocking antibodies to the drug. In April 2011, the patient was started on adalimumab (a fully humanized monoclonal antibody against human TNF-alpha) to replace the infliximab. Although the frequency and severity of the attacks were suppressed to some extent for a few months, they gradually became refractory to adalimumab, and the splenic lesions recurred once again in March 2012. Etanercept (a fusion protein of soluble TNF receptor joined to an Fc immunoglobulin motif) was started in place of adalimumab, and the disease is currently under control.

Discussion

Periodic fever syndromes should be suspected when a patient presents with recurrent fever that is associated with other inflammatory symptoms. These are classified into FMF, hyper-IgD syndrome (HIDS), tumor necrosis receptor-associated periodic fever syndrome (TRAPS), and cryopyrin-associated periodic syndromes (CAPS) (15). We herein presented the case of a patient who developed a periodic fever and peritonitis at 25 years of age with no particular family history. Colchicine was initially effective for suppressing the attacks, and, FMF was thus diagnosed according to the Tel Hashomer criteria (14). This case’s clinical features, such as the sporadic episodes, longer attack periods, and late onset, were different from those of typical cases in endemic areas. However, a diagnosis of other periodic fever syndromes was ruled out in this case because
HIDS develops in infancy and TRAP and CAPS are inherited as an autosomal dominant trait.

A genetic study of this patient showed a heterozygous E148Q mutation. It remains controversial as to whether the E148Q mutation is a disease-causing mutation or a simple polymorphism because of the high allele frequency found in healthy controls (16, 17). However, a study in Japan showed the allele frequency of E148Q in patients with FMF to be significantly higher than that in healthy individuals, and this mutation is considered to cause FMF, especially when patients are compound heterozygous for E148Q and other MEFV mutations or homozygous for E148Q (18). Although the present patient did not have the compound heterozygous mutation or the homozygous mutation, the diagnosis of FMF was still valid because MEFV mutations are not always found on both alleles, even in typical FMF patients. It is possible that the function of the other allele of the MEFV gene was disrupted by a mechanism other than a mutation in the exons, such as promoter methylation or mutations in the introns.

It is well known that anti-TNF-alpha agents are the choice of treatment for FMF. We used infliximab first because the effectiveness of the drug in a Japanese FMF patient was previously reported (19). Infliximab dramatically alleviated the patient’s symptoms. Although the disease eventually became refractory to infliximab and adalimumab, probably due to the production of neutralizing or blocking antibodies to the drugs, etanercept was still effective for preventing the attacks. The exact role of anti-TNF-alpha agents in FMF remains to be elucidated. However, increased levels of the soluble TNF receptor during FMF attacks have been reported (20). It is also known that the MEFV gene is up-regulated by TNF-alpha (21). Therefore, TNF-alpha might be involved in the process of the FMF attacks through the activation of the cytokine network.

Multiple, recurrent, abscess-like lesions in the spleen, liver, and a lung developed in the present patient. These might have been caused by bacterial infections. However, we could not detect any microorganisms during repeated blood bacterial cultures, sputa cultures, or cultures of drained specimens. It therefore seems likely that the lesions were a result of the autoimmune inflammatory process of FMF. We previously reported on a gout patient who developed an inflammatory pseudotumor (IPT) in the liver with central liquefactive necrosis which was indistinguishable from a liver abscess by imaging studies (22). Like FMF, gout is also a systemic inflammatory disorder. IPTs are benign localized lesions that consist of a fibrous stroma and chronic inflammatory infiltrates. They can involve any organ system and have been most frequently described in the lung. The etiology and pathogenesis of IPTs have not yet been elucidated. It might be possible that the systemic inflammation in the present case triggered abnormal auto-inflammatory reactions in the spleen, liver, and lung, resulting in the formation of the abscess-like lesions.

In addition, the present patient had persistent ulcers in the terminal ileum. The pathological findings of the ulcers resembled those of entero-BD. BD is characterized by oral aphthosis, uveitis, genital ulcers, and skin lesions, such as folliculitis and erythema nodosum (23). Both FMF and BD are chronic relapsing inflammatory disorders. In spite of the distinct clinical features of BD and FMF, they share many common features, such as abnormal neutrophil activation and the effectiveness of colchicine. The MEFV gene mutation that is responsible for FMF has been reported to probably be a susceptibility factor for BD, and both disorders can occur concurrently in a single patient (10, 18, 24, 25). The present patient did not have symptoms of BD other than recurrent fever and the ileal ulcers. HLA-B51, which is found in 60 to 70% of BD patients, was also negative. However, the asynchronous development of multiple inflammatory lesions in the different organs in this patient is reminiscent of BD.

In summary, we herein described a sporadic and late onset atypical FMF patient with a heterozygous E148Q mutation in the MEFV gene. In addition, she developed ulcers in the terminal ileum and multiple, recurrent, abscess-like lesions in the spleen, the liver, and the lung. Anti-TNF-alpha agents were effective for controlling the attacks to some extent after the disease became refractory to colchicine.

The authors state that they have no Conflict of Interest (COI).

References