Periodic Peritonitis due to Familial Mediterranean Fever in a Patient with Systemic Lupus Erythematosus

Masayuki Matsuda, Dai Kishida, Ayako Tsuchiya-Suzuki, Kazuhiro Fukushima, Yasuhiro Shimojima, Masahide Yazaki and Shu-ichi Ikeda

Abstract

We report a patient with systemic lupus erythematosus (SLE) who showed periodic peritonitis with spontaneous remission. She showed compound heterozygous mutations in the MEFV gene, leading to the diagnosis of familial Mediterranean fever (FMF). Oral colchicine successfully reduced the severity and frequency of her peritonitis. SLE occasionally manifests abdominal symptoms, but in cases with periodic peritonitis, associated FMF should be considered as a possible cause.

Key words: systemic lupus erythematosus, familial Mediterranean fever, MEFV gene, colchicine, peritonitis


Introduction

Systemic lupus erythematosus (SLE) sometimes manifests peritonitis (lupus peritonitis), which is indistinguishable from that due to other causes with regard to clinical symptoms and elevated inflammatory reactions (1). Because this type of peritonitis develops in parallel with an increase in disease activity of SLE, corticosteroid is usually employed for treatment (1). Here, we describe an SLE patient with periodic peritonitis unresponsive to corticosteroid treatment. She was diagnosed as having familial Mediterranean fever (FMF) based on clinical symptoms and compound heterozygous mutations in the MEFV gene, and colchicine successfully reduced the frequency and severity of peritonitis. This is the first case report of a Japanese patient with FMF associated with SLE. We discuss the differential diagnosis of periodic peritonitis in young SLE patients, and focus upon the clinical importance of MEFV gene analysis.

Case Report

A 19-year-old Japanese woman developed high fever and painful lymphadenopathy in the bilateral neck with no obvious precipitating cause or significant family history. She was diagnosed as having SLE in our hospital based on butterfly rash in the face, photosensitivity, non-erosive polyarthritis, bicytopenia (WBC 2,210/μL, normal 3,040-8,720/μL; platelet 12.6×10^4/μL, normal 13.7-37.8×10^4/μL) with lymphopenia (440/μL, normal 900-2,980/μL) and elevated levels of the anti-double-stranded (ds) DNA antibody (36.5 IU/mL, normal <10 IU/mL) and anti-nuclear antibody (×320, normal <×40) in serum (2). The anti-Sm antibody was negative. After starting oral prednisolone at a dose of 30 mg/day, clinical symptoms quickly improved with normalization of laboratory data (WBC 5,570/μL; platelet 29.2×10^4/μL, anti-dsDNA antibody 6.0 IU/mL), but Raynaud’s phenomenon and/or slight fever with polyarthritis and skin lesions, such as butterfly rash, sometimes appeared while tapering this drug. At age 23 she was admitted to a neighboring hospital because of sudden-onset severe epigastralgia with slight fever, which occurred approximately 1.5 years after cessation of corticosteroid treatment at her request. She had no diarrhea or vomiting. Laboratory tests demonstrated marked increases in inflammatory reactions (C-reactive protein, CRP 11.2 mg/dL, normal <0.1 mg/dL; WBC 19,930/μL). Despite administration of antibiotics, epigastralgia persisted with the appearance of rebound tenderness, and she was transferred to our hospital 1 week after the onset of abdominal symptoms.

On admission, the patient complained of severe abdominal pain, and physical examination showed rebound tender-
Figure 1. Computed tomography demonstrated dilatation of the intestine with fluid retention during an attack of abdominal pain.

ness mainly in the epigastric region. Body temperature was 36.5°C, and she had no skin lesions or tender joints suggestive of active SLE. Routine laboratory tests demonstrated slight anemia (hemoglobin 10.2 g/dL, normal 10.7-15.3 g/dL) with increases in CRP (4.64 mg/dL), erythrocyte sedimentation rate (ESR, 100 mm/hour, normal 3-15 mm/hour), 50% hemolytic unit of complement (CH50, 69.7 IU/mL, normal 30-53 IU/mL) and IgG (2,469 mg/dL, normal 870-1,700 mg/dL). WBC was within normal limits (7,960/μL). No abnormal findings were seen in either liver and renal indices or on urinalysis. The anti-dsDNA antibody had been normal (9.1 IU/mL) 2 months before the appearance of abdominal pain, but it was slightly elevated on admission to our hospital (23.6 IU/mL). The anti-cardiolipin IgG antibody, anti-cardiolipin-β2GPI antibody and lupus anticoagulant were undetectable, and other autoantibodies, including rheumatoid factor, were all negative. There were no significant increases in serum antibodies against infectious agents, such as Chlamydia trachomatis. Abdominal computed tomography (CT) demonstrated dilatation of the intestine with fluid retention suggestive of subileus due to peritonitis (Fig. 1).

Intravenous administration of minocyclin was started soon after admission, and her abdominal symptoms quickly improved in parallel with a decrease in CRP and ESR. No significant lesions were detectable on endoscopy of either the upper gastrointestinal tract or colon. Two weeks after admission she was discharged from our hospital. Nevertheless, the abdominal pain frequently recurred with no fever approximately every month. These attacks showed clinical symptoms and signs suggestive of peritonitis usually in the epigastric region and sometimes in the lower abdomen, marked increases in inflammatory reactions and persistence for 1 to 2 weeks with spontaneous remission. The clinical effectiveness of antibiotics, including minocyclin, was unclear, and oral administration of prednisolone at a dose of 20 mg/day (0.44 mg/kg) failed to reduce the frequency and severity of the abdominal pain. Non-narcotic analgesics, such as pentazocine, were often given in order to relieve her severe abdominal pain. Based on the MEFV gene analysis showing 4 compound heterozygous mutations (E148Q, R202Q, P369S and R408Q) in exons 2 and 3 (Fig. 2), we decided to use colchicine. Shortly after starting this drug, the interval between attacks was lengthened from 1 month to 3 or 4 months, and the duration of abdominal pain was reduced from at least 1 week to at most 3 days. She has since been in good general health at a dose of 1 mg/day of colchicine even after cessation of oral prednisolone, although abdominal pain sometimes still occurs under psychic or physical stress. The butterfly rash and Raynaud’s phenomenon with necrosis on the toe (Fig. 3) appear occasionally, but visceral organ involvement ascribable to SLE has not yet been confirmed.

Discussion

The present patient showed recurrent attacks of severe abdominal pain suggestive of peritonitis, though no apparent cause was detectable on either endoscopy or radiological examinations, including CT. As for the cause of her peritonitis there are three possibilities worth consideration. The first is infection, particularly due to Chlamydia trachomatis, which sometimes causes acute peritonitis in young women designated as Fitz-Hugh-Curtis syndrome (3). In the present patient, however, this possibility is quite low because antibiotics, including minocyclin, were ineffective for abdominal pain since the time of her second attack in addition to the
Upon the peritonitis (8). Clinical symptoms of FMF usually depend on the presence of FMF with regard to colchicine-responsive recurrent attacks of high fever, polyserositis, and/or arthritis, and genetically by autosomal recessive inheritance (6, 7). Despite the lack of high fever and significant family history, she fulfilled the clinical diagnosis criteria of FMF with regard to colchicine-responsive recurrent peritonitis (8). Clinical symptoms of FMF usually depend on the MEFV genotype (7). FMF patients with a mutation in codon 694 have been reported to show typical attacks with high fever and serositis, while in those with other types of mutations, including E148Q, the clinical symptoms are relatively mild as shown in our previous report (9) as well as another report (7). A recent report has demonstrated that P369S/R408Q substitutions are infrequently associated with typical FMF symptoms (10). The MEFV gene analysis of the present patient showed P369S/R408Q in addition to R202Q and E148Q, and this uncommon heterozygous mutation pattern may have contributed to her peculiar FMF phenotype with periodic peritonitis alone.

FMF predominantly affects populations from the Mediterranean basin, but in our previous nationwide questionnaire survey a larger than expected number of patients was found also in Japan (9). This disease may be overlooked or misdiagnosed in patients with periodic fever and/or serositis, particularly when inflammatory diseases, such as SLE, are concurrent as seen in the present patient (11). According to a recent report on FMF patients complicated by SLE, clinical symptoms tend to be milder than in patients with the latter disease alone, although the precise mechanisms remain unclear (12). In the present patient also, SLE symptoms were not so severe with regard to the absence of visceral organ involvement. The MEFV gene mutations responsible for FMF may have produced some effects on the autoimmune inflammatory mechanism, resulting in a reduction of the clinical severity of SLE in the present patient.

In summary, FMF is occasionally associated with other inflammatory disorders, and may modify the clinical manifestations. When patients with collagen vascular disorders, such as SLE, show unexpected clinical symptoms ascribable to periodic inflammation, a concurrence of FMF should actively be considered as a possible cause.

Acknowledgement
This work was supported by a grant from Neuroimmunological Disease Division, the Ministry of Public Health, Labor and Welfare, Japan.

References

