A Japanese Case of Familial Mediterranean Fever with Homozygosity for the Pyrin E148Q Mutation

Key words: familial Mediterranean fever, pyrin/marenostrin, MEFV gene, E148Q

Familial Mediterranean fever (FMF) is an autosomal recessive inflammatory disease occurring mainly in Mediterranean and Middle Eastern populations. FMF is characterized by periodic fever, polyserositis of the chest, abdomen and joints and is frequently complicated with reactive AA systemic amyloidosis (1). Recently, mutations of the MEFV gene, which encodes the neutrophil protein pyrin (marenostrin), were shown to be responsible for the disease. The first Japanese case of FMF with a pyrin mutation was reported in 2002 (2) and, subsequently, about 20 more cases have been described. Here, we report a Japanese case of FMF with homozygosity for the pyrin E148Q mutation.

The patient is a 25-year-old Japanese male. He has had periodic episodes of high fever, usually lasting for less than 3 days, at 1 to 3 month intervals since the age of 20 years. The fever is often accompanied by diarrhea and abdominal pain. In one severe attack, he was admitted to a nearby hospital and diagnosed as having acute enterocolitis. He had an appendectomy (because of appendicitis) at the age of 24 years. There is no family history of periodic fevers. His parents are not consanguineous.

On May 5, 2003 he suffered a high fever with severe abdominal pain and diarrhea and, the next day he was admitted to hospital. His body temperature was 38.6°C, blood pressure 118/98 mmHg, pulse rate 72 beats/min and regular. Heart and lung functions were normal. Severe tenderness was observed in the whole abdomen and bowel sound was increased. He also had neck pain, but did not have any oral symptoms or any eye or skin effects. There was no lymphadenopathy or joint swelling. Laboratory examinations showed elevation of C reactive protein (4.38 mg/dl), white blood cell count (10,600/µl), erythrocyte sedimentation rate (27 mm/h) and serum amyloid A protein (988 µg/ml; normal <8); other laboratory data, including immunological examination, did not present any abnormalities. A fecal occult blood test was negative, and no pathogens were recovered from feces. An abdominal X-ray showed no abnormality.

Although an infectious disease was suspected, the occurrence of periodic episodes with the same symptoms was not compatible with this diagnosis. Autoimmune disorders, including Behçet’s disease, were also excluded because of the absence of both detectable abnormalities in immunological examinations and typical symptoms. The patient declined to undergo colonoscopy and consequently inflammatory bowel diseases such as ulcerative colitis or Crohn’s disease could not be ruled out. The symptomatic occurrence of periodic fevers with spontaneous improvement within three days, suggested a possible alternative diagnosis of familial Mediterranean fever (FMF).

After obtaining informed consent, we extracted genomic
DNA from peripheral lymphocytes of the patient and screened the *MEFV* gene. We found homozygosity for a mutation, GAG to CAG in codon 148 of exon 2, of the *MEFV* gene. This mutation (E148Q) results in the substitution of glutamic acid by glutamine in the pyrin protein (Fig. 1). Homozygosity for the pyrin E148Q mutation has previously been found to be associated with FMF (1). However, the significance of pyrin E148Q is somewhat controversial; pyrin E148Q has been considered to be a normal variant by some (3, 4); whilst others have pointed to the significantly higher frequency of pyrin E148Q in patients with AA amyloidosis or unknown chronic fever and suggested this relationship is causal (5). On the basis that the patient displayed the typical symptoms and course of FMF and also had a homozygous mutation in the *MEFV* gene, we concluded that he was indeed suffering from FMF. After making the gene diagnosis, we suggested to the patient that he should take colchicine to prevent further attacks, but we could not obtain his consent for treatment because of his concerns over the drug’s side effects.

In conclusion, we suggest that cases of FMF in Japan may previously have been overlooked and misdiagnosed as infectious diseases or autoimmune disorders. Accordingly, we recommend that whenever a patient presents with recurrent fever or abdominal pain, FMF should also be considered as a possible diagnosis.

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