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Familial Mediterranean Fever E148Q/P369S/R408Q Exon 3 Variant with Severe Abdominal Pain and PFAPA-Like Symptoms

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Abstract

Familial Mediterranean fever (FMF) can be classified into typical and incomplete/atypical types. An accompanying of severe abdominal pain by the serotitis is characteristic of typical FMF. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome-like symptoms has been found in atypical type carrying P369S-R408Q mutations in the responsible gene MEFV. FMF with both symptoms is extremely rare. An 8-year-old boy has had recurrent fever accompanied with both of severe abdominal pain and PFAPA like symptoms, carrying heterozygous alterations involving E148Q/P369S/ R408Q. The Corticosteroid resulted in partial benefit, but not clear effect by the colchicine, and persistent cure was not obtained by tonsillectomy.

Keywords: Familial Mediterranean fever; Severe abdominal pain; Colchicine; P369S-R408Q; MEFV mutation; Periodic fever

Introduction

Familial Mediterranean fever (FMF) is an inherited autosomal recessive autoinflammatory disorder characterized by recurrent and self-limited episodes of fever, painful serositis such as peritonitis and pleuritis, arthritis or erysipelas-like skin disease with a marked acute-phase inflammatory response [1]. FMF on Japanese population can be classified into typical and incomplete/atypical types based on clinical findings and genetic screening [1-3]. Whereas intense abdominal pain is the characteristic symptom of typical FMF in addition to chest pain, arthritis, and erysipelas-like exanthema, incomplete FMF attacks, as described in the Tel Hashomer criteria [1], exhibit low-grade fever of less than 38°C, attack duration of 6 hours to 1 week, no signs of peritonitis during abdominal attacks, localized abdominal signs, and atypical distribution of arthritis. Arthritis or osteomyelitis occurs to upper arms in incomplete FMF, whereas arthritis occurs to large joints of lower limbs such as hip joint, knee joint, or ankle joint in typical FMF [4]. Periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome-like symptoms have been reported in patients with atypical FMF as well [2,5]. Regarding the characteristic gene mutations responsible for FMF that are located in the Mediterranean fever (MEFV) gene, typical FMF tends to feature an abnormality in exon 10, particularly the frequently-carried -M694I mutation in Japan [3], while atypical FMF patients predominantly harbor a P369S and R408Q in exon 3, i.e. MEFV exon 3 variants [6]. PFAPA syndrome-like symptoms have also been found in patients carrying the P369S and R408Q [2].

PFAPA represents the most common autoinflammatory fever disorder occurring during childhood [6,7]. The clinical entity is characterized by regular occurrences of high fever (>39°C) that are associated with at least 1 of 3 cardinal clinical signs of aphthous stomatitis, pharyngitis, and cervical adenitis. Additional manifestations, including headache, gastrointestinal symptoms, and sore throat, may be present [5], but are not consistently noted. Disease onset is generally before the age of 5 years, with attacks lasting 2-8 days and recurring every 3-8 weeks. Patients are asymptomatic between episodes and show normal growth and development [8]. Here we describe the first known case of an FMF exon 3 variant that had very rare accompanying symptoms, notably, the combination of PFAPA-like symptoms consistent with atypical FMF and along with the severe abdominal pain characteristic of typical FMF.

Case Report

A 8-year-old Japanese boy suffered from intense abdominal pain and tonsillitis was transferred to our university hospital in December, 2012. His initial symptoms were intense abdominal pain so as to roll over, tonsillitis with fur, and stomatitis, lasting for a few days at 6 years old, then consulted a nearby doctor. There, he had been diagnosed as having mesenteric adenitis, during which his laboratory data included white blood cell count 14,900 /mm^3 and C-reactive protein (CRP) 1.1 mg/dl (normal value is <0.1 mg/dl). He did not show abnormality for urinalysis. He later experienced similar attacks in September, 2010, March, 2011, and May, July and December, 2012. His body temperature was 37.5-38°C. The abnormality was not seen by the examination for a computed tomography scan with contrast, and appendicitis was excluded by the radiological results. Because of above frequent episodes, he was transferred to our hospital. He had a medical history of allergic rhinitis, and his family history was unexceptional apart from ulcerative colitis in his maternal grandmother. There was not the person in a relative who had periodic fever or tonsillectomy. At presentation in December, 2012, the patient had a sore throat, pharyngeal redness, and tonsillitis with fur (Figure 1A), along with a feeling of suffocation. These symptoms were improved after several days of conservative treatment. His fever peaked at 37.5°C, and arthralgia, rash, arthritis, diarrhea, cervical lymphadenitis, chest pain, blood in the stool, nor uveitis were absent. He was not losing weight. He also exhibited allergic rhinitis-like symptoms. Laboratory findings such as IgD level (2.3 mg/dl) and Kidney function tests were normal apart from CRP 0.4 mg/dl, serum amyloid A 488.3 μg/ml (normal value is <8 μg/ml), and erythrocyte sedimentation rate 38 mm/h (normal value is <20 mm/h). He was doing well and CRP and serum amyloid A levels were normal in between the episodes. We could exclude infections and malignancies on the basis of laboratory findings and frequent episodes. Autoimmune

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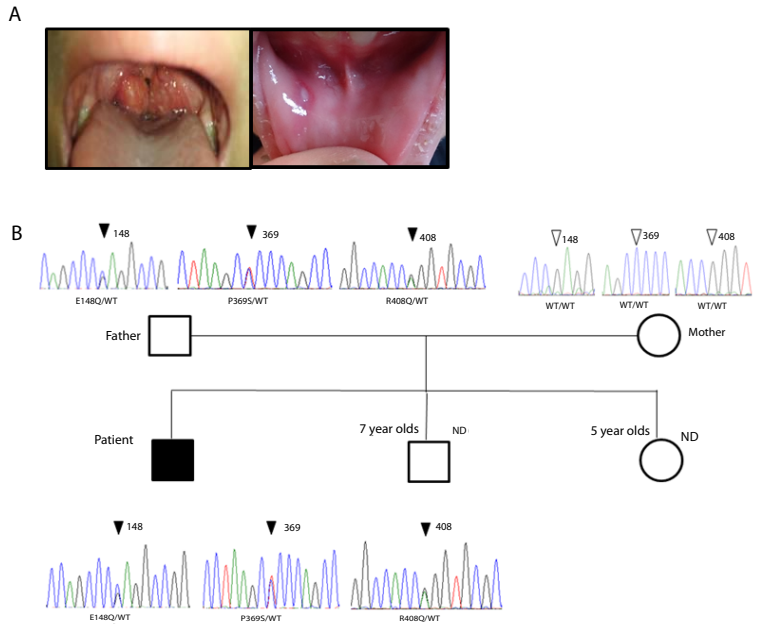

Figure 1: Tonsillitis with fur (left), and stomatitis (right) during the attack (A). Family tree and MEFV mutations. ND: gene analysis not done (B).

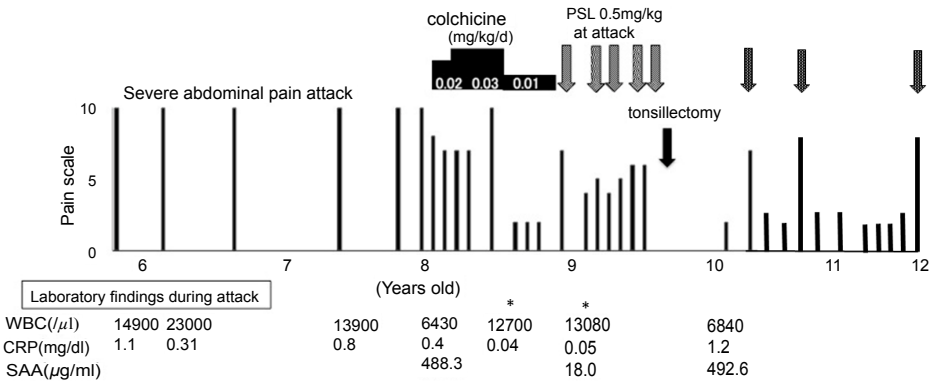

Figure 2: Clinical course of the patient. Pain scale expressed the pain that he felt to be strongest as 10. Laboratory findings reveal during the attack except for those between the episodes which are marked with an asterisk.

disease was also negative from the lack of autoantibodies. We suspected an autoinflammatory disorder, such as atypical FMF, and examined the MEFV gene analysis. Heterozygous germ-line alterations involving E148Q in exon 2, and P369S and R408Q in exon 3 (Figure 1B) were detected. Based on these findings, we made a diagnosis of atypical FMF. Colchicine administration was initiated with the dosage of 0.02 mg/kg, but the frequency of the occurrence of similar symptoms did not decrease, occurring once every 1-2 months. After increasing colchicine dosage to 0.03 mg/kg, the attack frequency did not decrease, but the degree of the abdominal pain decreased a little from 10-7 on a pain scale. We thought that the effect of colchicine is ineffective or partial. We decreased gradually the dosage of colchicine and it was switched to prednisolone orally to be taken as needed at the dosage of 0.5 mg/kg, 1-2 times for one episode. The oral use of prednisolone led to a mild improvement in symptoms. He sometimes complained about a pain of knee and ankle joints during the attack from this time, but the joint swelling was not found. A tonsillectomy was later performed in March 2014 due to increasingly frequent attacks. However, the patient again suffered from relapses of abdominal pain in September and November 2014 after a 6-month asymptomatic period (Figure 2). He has a relatively mild attack once in several months afterwards, but attacks with intense abdominal pain were frequent since in January, 2016. Therefore, we plan to treat with Tocilizumab.

Discussion

A typical FMF attack is defined as an episode lasting from 12 hours to 3 days with fever accompanied by peritonitis, pleuritis, or monoarthritis of the hip, knee or ankle. In particular, the presence of severe abdominal pain is one of hallmarks of typical FMF. Ryan et al. reported on 3 cases of MEFV exon 3 variants displaying PFAPA syndrome-like symptoms. All patients had fever in association with aphthous ulcers, pharyngitis, and cervical lymphadenopathy, but no severe abdominal pain was noted. A single case achieved resolution of symptoms following tonsillectomy, while another did not respond to methotrexate, hydroxychloroquine, montelukast, or etanercept, but was moderately improved by corticosteroid tapering [2]. Our patient also responded partially to colchicine and corticosteroid treatments. In addition to P369S and R408Q, Ryan et al. detected E148Q in 2 of the reported exon 3 variants like our case [2]. This mutation is relatively

rare in healthy Japanese people. P369S and R408Q variant is found in 2%-3% in healthy Japanese people [9]. Father of our patient carried the same MEFV mutation, but never experienced repeated episodes of fever, abdominal pain, or tonsillitis. Gene analysis of our 2 siblings was not possible. We recently described heterozygous alterations involving E148Q/P369S/ R408Q in a mother and 3 daughters, all of whom having experienced repeated fever and/or tonsillectomy for tonsillitis. It suggested a causative role of a heterozygous P369S and R408Q genotype [10]. Kubota et al. reported the clinical findings of a MEFV exon 3 variant presenting only as PFAPA symptoms [5]. The patient received a tonsillectomy at the age of 9 years, but recurrent fever episodes continued at intervals of 2-3 weeks. It is noteworthy that a single dose of oral prednisolone was immediately effective against each attack of periodic fever in this case [5]. FMF exon 3 variants show various reactivity for colchicine and prednisolone.

It is often difficult to distinguish between PFAPA and FMF MEFV exon 3 variants with PFAPA-like symptoms. The effects of corticosteroid and colchicine in our patient were modestly effective in comparison with those seen in typical PFAPA and FMF patients, respectively. This is the first known report of atypical FMF accompanied by periodic fever with tonsillitis and severe abdominal pain. The diagnosis of a FMF MEFV exon 3 variants was made following detection of the MEFV exon 3 mutations, P369S and R408Q in addition to E148Q in exon 2. The colchicine and corticosteroids resulted in partial benefit, and persistent cure was not obtained by tonsillectomy. Thus, this rare type of atypical FMF should be considered during diagnosis since early detection and treatment may enable improvements in patient quality of life.

References

1. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, et al. (1997) Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 40: 1879-1885.
2. Ryan JG, Masters SL, Booty MG, Habal N, Alexander JD, et al. (2010) Clinical features and functional significance of the P369S/R408Q variant in pyrin, the familial Mediterranean fever protein. Ann Rheum Dis 69: 1383-1388.
3. Migita K, Agematsu K, Yazaki M, Nonaka F, Nakamura A, et al. (2014) Familial Mediterranean fever: genotype-phenotype correlations in Japanese patients. Medicine (Baltimore) 93: 158-164.
4. Shimizu M, Tone Y, Toga A, Yokoyama T, Wada T, et al. (2010) Colchicine-responsive chronic recurrent multifocal osteomyelitis with MEFV mutations: a variant of familial Mediterranean fever? Rheumatology (Oxford) 49: 2221-2223.
5. Kubota K, Ohnishi H, Teramoto T, Kawamoto N, Kasahara KT, et al. (2014) Clinical and genetic characterization of Japanese sporadic cases of periodic Fever, aphthous stomatitis, pharyngitis and adenitis syndrome from a single medical center in Japan. J Clin Immunol 34: 584-593.
6. Migita K, Ida H, Moriuchi H, Agematsu K (2012) Clinical relevance of MEFV gene mutations in Japanese patients with unexplained fever. J Rheumatol 39: 875-877.
7. Marshall GS, Edwards KM, Lawton AR (1989) PFAPA syndrome. Pediatr Infect Dis J 8: 658-659.
8. Thomas KT, Feder HM Jr, Lawton AR, Edwards KM (1999) Periodic fever syndrome in children. J Pediatr 135: 15-21.
9. Migita K, Agematsu K, Yazaki M, Nonaka F, Nakamura A, et al. (2014) Familial Mediterranean fever: genotype-phenotype correlations in Japanese patients. Medicine (Baltimore) 93: 158-164.
10. Yamagami KTN, Nakamura R, Hanioka Y, Agematsu K. Familial Mediterranean fever with P369S/R408Q exon3 variant in pyrin presenting as symptoms of PFAPA. Modern Rheumatology in press.