Mediterranean fever (MEFV) Variant P369S/R408Q in a Patient with Entero-Behçet’s Disease who Successfully Responded to Treatment with Colchicine

Keita Fujikawa¹, Kiyoshi Migita², Akio Nagasato¹, Toshiaki Tsukada¹, Atsushi Kawakami³ and Katsumi Eguchi⁴

Abstract

A 57-year-old Japanese woman who had been diagnosed as having entero-Behçet’s disease nine years earlier was admitted with a persistent high-grade fever. An Mediterranean fever (MEFV) gene analysis revealed the compound heterozygous P369S-R408Q variant. She was treated with colchicine, and her symptoms immediately improved. Prednisolone (PSL) was added to treat the punched-out ulcers in the terminal ileum, leading to remission. There has been no relapse since the PSL was discontinued. In Behçet’s disease patients with MEFV variants, the use of colchicine should therefore be considered in such patients as well as immunosuppressive therapy.

Key words: MEFV, P369S/R408Q, entero-Behçet’s disease, auto-inflammatory disease, colchicine

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Introduction

Behçet’s disease (BD) is a rare immune-mediated systemic disease characterized by recurrent oral aphthous ulcers, genital ulcers, skin lesions and uveitis. Occasionally, BD also involves visceral organs, such as those of the gastrointestinal, vascular and neurological systems (1). Several research groups have suggested that the familial Mediterranean fever (MEFV) gene is linked to susceptibility to BD and may be the modifier gene in patients with BD (2-6). We herein present the case of a patient with entero-Behçet’s disease who had a rare MEFV variant and for whom colchicine had beneficial effects.

Case Report

In 2004, a 48-year-old Japanese woman presented with a fever, oral aphthous ulcers, genital ulcers, erythema nodosum and hemorrhagic stools. She was subsequently diagnosed with entero-BD based on the findings of multiple colon ulcers on colonoscopy. For the prior two years, she had been in good condition, taking oral mesalazine and methotrexate (MTX). In 2013, at 57 years of age, she was referred to our hospital with a high fever that had persisted for the prior week. Initially, she showed no symptoms other than fever upon hospitalization, including ocular involvement, and the origin of the fever was not identified. The laboratory data revealed an elevated level of C-reactive protein (13.7 mg/dL; normal range: 0-0.1 mg/dL), although the levels of white blood cells, antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, complement and IgD were within the normal ranges. The patient’s Human Leukocyte Antigen (HLA) typing B51 was negative. The wall of the ascending colon was observed to be edematous on abdominal computed tomography (CT), thus suggesting colitis. An MEFV gene analysis revealed the compound heterozygous P369S-R408Q variant. We therefore initiated treatment with colchicine at a dose of 1 mg/day. The patient’s fever promptly disappeared, and the level of C-
reactive protein decreased from 13.7 to 2.1 mg/dL within several days. After the start of the colchicine treatment, abdominal symptoms, including tenderness and diarrhea, became obvious. On colonoscopy, deep punched-out ulcers with clear margins were observed in the terminal ileum through the ascending colon (Fig. 1A). A histological examination revealed ulceration with infiltration of inflammatory cells, including neutrophils. The patient was given prednisolone (PSL) at a dose of 40 mg/day (0.8 mg/kg) for the active intestinal lesions. Her abdominal symptoms immediately improved, and the multiple ulcers demonstrated remarkable improvements on colonoscopy performed six weeks after the initiation of treatment (Fig. 1B). The dose of PSL was thus tapered and discontinued after 20 weeks of treatment (Fig. 2). The patient had no episodes of recurrence during the six-month follow-up period.

**Discussion**

BD is a chronic systemic inflammatory disorder whose etiology has not been fully established. This condition has long been regarded to be a Th1-type autoimmune disease due to its association with HLA-B51 (7) and hyperactivity against streptococcal antigens (8). Entero-BD is characterized by the presence of deep and round punched-out ulcers in the terminal ileum. In severe cases of entero-BD, perfora-
tion of the intestines may occur, resulting in life-threatening complications. The frequency of gastrointestinal manifestations in patients with BD is more common in Japan (13-25%) than in Turkey (5%) (1). The frequency of eye involvement and the rate of positive HLA-B51 are significantly lower in patients with gastrointestinal involvement (9).

It has recently been demonstrated that BD and auto-inflammatory diseases share several clinical features. For example, familial Mediterranean fever (FMF) has much in common with BD in terms of clinical findings and treatment, as well as geographic and ethnic co-occurrence. FMF is an autosomal-recessive inherited auto-inflammatory disorder that causes MEFV gene mutation. Pyrin proteins coded by the MEFV gene regulate IL-1β processing (10). The frequency of the MEFV variants of P369S and R408Q is 6.1% and 5.2%, respectively, in Japanese BD patients (5).

Touitou et al., Imirzalioglu et al., Esmaeili et al., Kirino et al. and Tasiyiurt et al. reported that the frequency of MEFV mutations is higher in BD patients (2-6). Atagunduz et al. and Rabinovich et al. reported that MEFV mutations are associated with an increased risk of venous thrombosis (11, 12). In contrast, some studies have reported that the frequency of MEFV mutations is not significantly higher in patients with BD (13-15). Tasiyiurt et al. also reported that the frequency of uvitis is significantly lower in patients with MEFV mutations, particularly the P369S mutation (6). Therefore, a consensus regarding the relevance of the MEFV gene and BD has not been obtained. However, the MEFV gene has also been suggested to be associated with Crohn’s disease, ulcerative colitis (16), multiple sclerosis (17) and polyarteritis nodosa (18). These findings indicate that the MEFV gene is a susceptibility and modifier gene of various inflammatory disorders, rather than being specific for BD.

No evidenced-based treatment strategy is currently recommended for the management of gastrointestinal involvement in patients with BD (19). Immunosuppressive therapy, such as corticosteroids, azathioprine and tumor necrosis factor (TNF) antagonists, is used empirically to treat entero-BD. Colchicine is useful for treating arthritis, genitai ulcers and erythema nodosum, which may present in BD patients (20); however, there are few reports showing the usefulness of colchicine in cases of gastrointestinal involvement (21). Colchicine acts by mediating the assembly of the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome via the inhibition of microtubules (22) and has been reported to be effective in over 90% of FMF patients (23). Kuloğlu et al. documented the case of a patient with severe refractory Crohn’s disease and a homozygous MEFV mutation who responded dramatically to colchicine (24). In the present case, colchicine had beneficial effects on the patient’s fever, although corticosteroid therapy was required to treat intestinal manifestations. Acquired immune responses, such as those involving IL10 and IL23R, also play a crucial role in the pathogenesis of BD (25). Therefore, it is thought that immunosuppressive therapy is required to treat such conditions.

In conclusion, we herein presented the case of a patient with Entero-BD who possessed the MEFV P369S/R408Q variant and responded to colchicine. We suspect that the pathogenesis of BD is associated with both acquired and innate immunity. Colchicine, as well as immunosuppressive therapy, should therefore be considered as a treatment option in BD patients with MEFV mutations.

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References