

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

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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

(Intern Med 53: 2381-2384, 2014)

(DOI: 10.2169/internalmedicine.53.2872)

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 diag-

nosed 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-

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Received for publication March 12, 2014; Accepted for publication March 27, 2014

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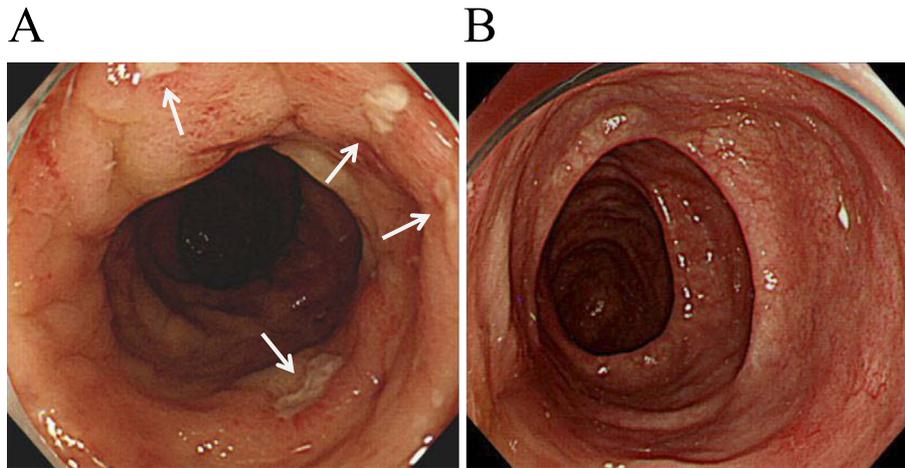


Figure 1. Colonoscopy findings of a 57-year-old woman with entero-BD. Deep punched-out ulcers with clear margins were observed in the terminal ileum (A). The ulcers improved remarkably six weeks after the start of treatment (B). The white arrows indicate punched-out ulcers.

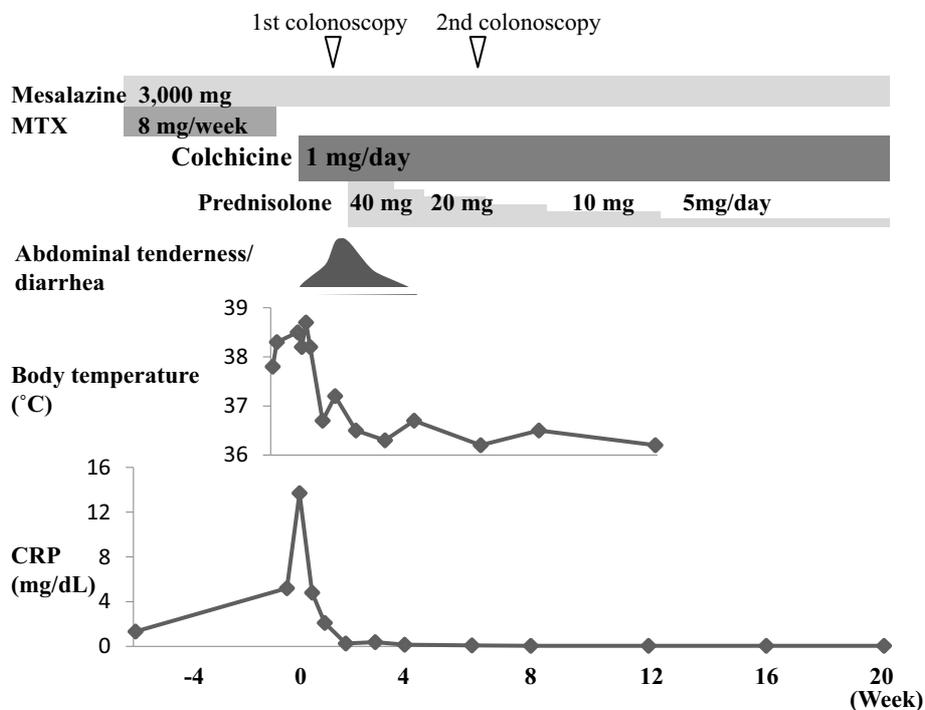


Figure 2. The patient's clinical course

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-1 β 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 Tasliyurt 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). Tasliyurt et al. also reported that the frequency of uveitis 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) α antagonists, is used empirically to treat entero-BD. Colchicine is useful for treating arthritis, genital 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.

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

Financial Support

This work was supported by a Grant-in-Aid for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare of Japan.

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