Case Report

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Successful Switch to Adalimumab after Long-Term Thalidomide-Based Maintenance Therapy for Juvenile Onset Intestinal Behçet's Disease: A Case Report

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Abstract

The patient was a 32-year-old woman who had a 20-year history of intestinal Behçet's disease without ocular involvement. At the age of 12, she developed oral aphthosis, genital ulcers, erythema nodosum on the lower limbs, and soon developed lower abdominal pain. Colonoscopic examination revealed a round punched-out ulceration in the ileocecal region. Human leukocyte antigen (HLA)-B51 (B5) antigen was negative. Drug therapies with salazosufapyridine and prednisolone was started. When prednisolone was reduced to 15 mg/d, the ileocecal lesion recurred and in addition, diabetes mellitus developed. The patient had been suffered corticosteroid dependence with severe side effects. Since the induction of thalidomide at the age of 14, partial remission that allowed for outpatient visits was maintained for more than 10 years, but negative C-reactive protein (CRP) and endoscopically mucosal healing of the ileocecal ulcer on colonoscopy were not achieved.

Switch from thalidomide to adalimumab (ADA) was introduced at the age of 26 because of reproductive concern. Since introduction of ADA, no recurrence of genital ulcer or skin lesions had been observed. Negative inflammatory reaction was maintained. Colonoscopy performed after the switch to ADA revealed sustained endoscopic mucosal healing in ileocecal ulcer. ADA may have a more specific anti-inflammatory effect on intestinal BD than thalidomide.

Key words: Intestinal Behçet disease, thalidomide, adalimumab

Introduction

Behçet's disease (BD), originally reported by a Turkish dermatologist Hulisi Behçet in 1937, is an inflammatory disease originally characterized by relapsing oral and genital ulcerations, uveitis, and characteristic skin lesions[1)]. The prevalence of BD is high in areas along the ancient Silk Road from the Mediterranean to East Asia. The incidence of BD in Japan was 15.7 per 100,000 in 2014[2)]. BD is a systemic chronic inflammatory disease characterized by different combinations of lesions and different orders of expression in individual cases. Patients with BD can present with manifestations of ocular, musculoskeletal, vascular, central nervous system, or gastrointestinal involvement. There is a high frequency of intestinal BD in Japanese patients[3)], especially among children[4)]. Gastrointestinal manifestations of BD are of particular importance as they are often associated

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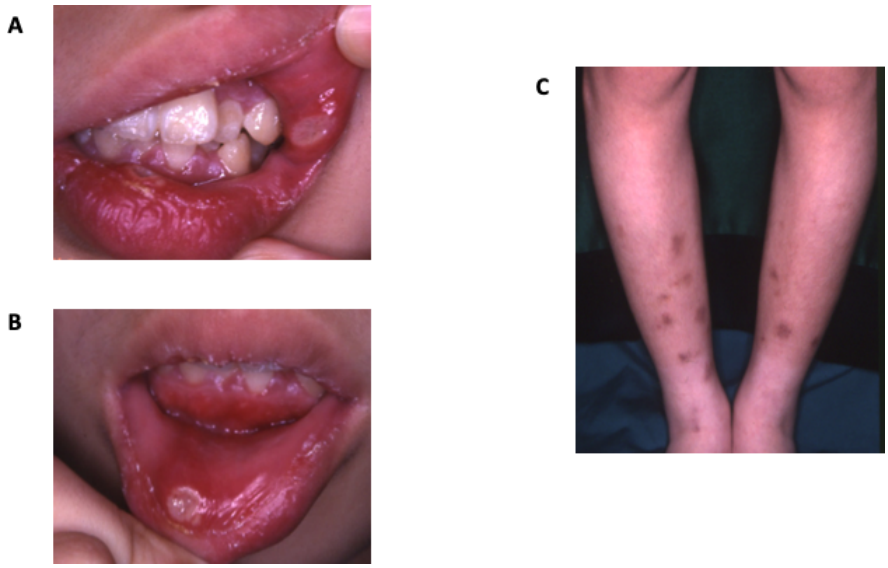

Figure 1. Buccal aphthosis and erythema nodosum on the lower extremities at the first presentation of the patient
Panel **A**, **B** shows multiple aphthous ulcers on the buccal membrane. Panel **C** shows erythema nodosum on the front of the lower extremities.

with significant morbidity and mortality. Ileocecal lesions with round punched-out ulcers are most commonly described. Intestinal BD is often uncontrollable, characterized by recurrence, and can cause gastro-intestinal erosions, ulceration, bleeding or perforation[5]. Here, we report a case of juvenile-onset intestinal BD which had been refractory to treatment with steroids and immunosuppressants, in which clinical remission was maintained for more than 10 years upon initiation of thalidomide therapy and a switch from thalidomide therapy to treatment using the tumor necrosis factor (TNF) -α monoclonal antibody (mAb) adalimumab (ADA) was effective.

Case report

The patient was a 32-year-old woman with a 20-year history of intestinal BD without ocular involvement. The patient began to have symptoms such as recurrent buccal aphthosis and painful erythema on the lower extremities at 12 years of age (**Figure 1**), and consulted a dermatologist. Biopsy of the erythematous skin was performed, and erythema nodosum was diagnosed. Subsequently, she developed genital ulceration and persistent right lower abdominal pain, and endoscopic examination revealed a round punched-out ulceration in the ileocecal region (**Figure 2**). She was diagnosed as BD using the International Study Group for Behçet's Disease 1990 guidelines[6], based on the presence of recurrent oral ulceration, genital ulceration, and skin lesions. Ocular lesions or a positive pathergy test result were not observed. Human leukocyte antigen-B51 (B5) antigen was negative. Therapies with salazosufapyridine and prednisolone (50 mg/d) were initiated. Treatment with cyclosporine and colchicine was also initiated but was ineffective. When the dose of prednisolone was reduced to 15 mg/d, the ileocecal lesion recurred. She developed features of steroid toxicity such as diabetes mellitus and growth retardation and was repeatedly hospitalized. Considering these severe side effects and her dependence on corticosteroid therapy, thalidomide was introduced after the approval by the Ethics Committee of St. Marianna University School of Medicine (Approval no. 572) at the age of 14, resulting in a long-term partial remission (**Figure 3**). The dose of thalidomide was maintained at 50 mg/d. The patient was carefully monitored for possible pregnancy and adverse effect during thalidomide therapy. We reported her case up to the age of 15 in 2003[7]. It was possible to reduce the dose of prednisolone to 2 mg/d for a long period of time. After starting thalidomide therapy, outpatient treatment was possible for as long as 11 years; abdominal pain was under self-control but intermittent, negative C-reactive protein (CRP) and endoscopically mucosal healing of the ileocecal ulcer on colonoscopy were not

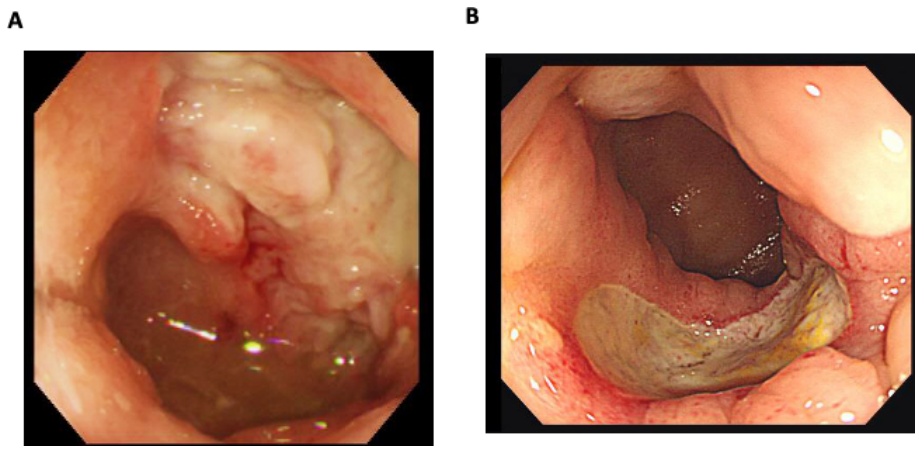

Figure 2. Colonoscopy findings of the patient
Panel **A** shows a large ileocecal ulcer at the time of diagnosis with intestinal Behçet's disease. Panel **B** shows that the Ileocecal ulcer was still present 2 months before initiation of adalimumab therapy.

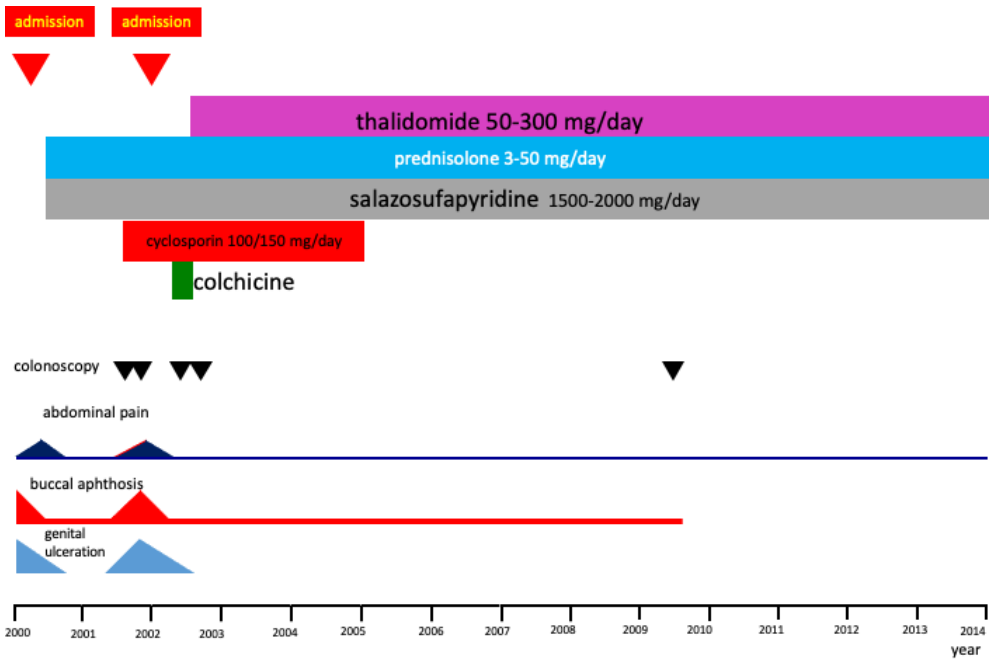

Figure 3. Clinical course from the onset of Behçet's disease to before and during thalidomide therapy

achieved (**Figure 2**). ADA was approved for intestinal BD in Japan in May 2013, and it was administered when she was 26 years old due to reproductive concerns. Blood examination results at the time of ADA initiation showed a normal white blood cell count (6,900/μL). Serum biochemistry analyses revealed a slightly increased CRP level (0.4 mg/dL) and a slightly decreased albumin (3.8 g/dL) level. ADA was started at a dose of 160 mg; the dose was reduced to 80 mg two weeks later and then to 40 mg every other week. Sixty days after the introduction of ADA, CRP became negative, the abdominal pain disappeared, and serum albumin level returned to normal; therefore, thalidomide was discontinued. The administration of prednisolone was also discontinued eight months after initiation of ADA administration (**Fig-**

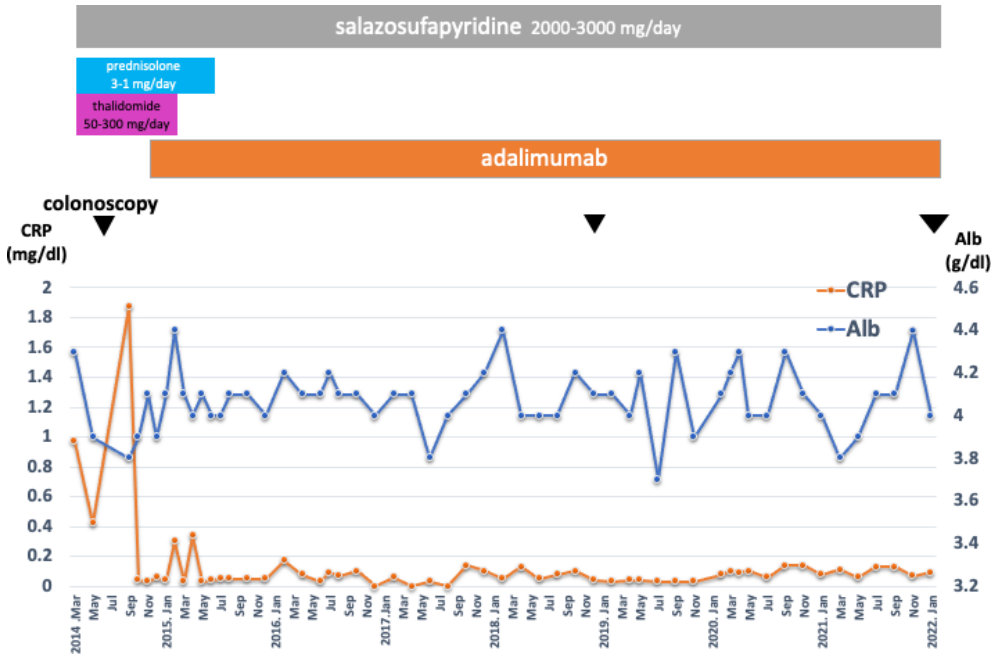

Figure 4. Clinical course before and after the initiation of adalimumab therapy

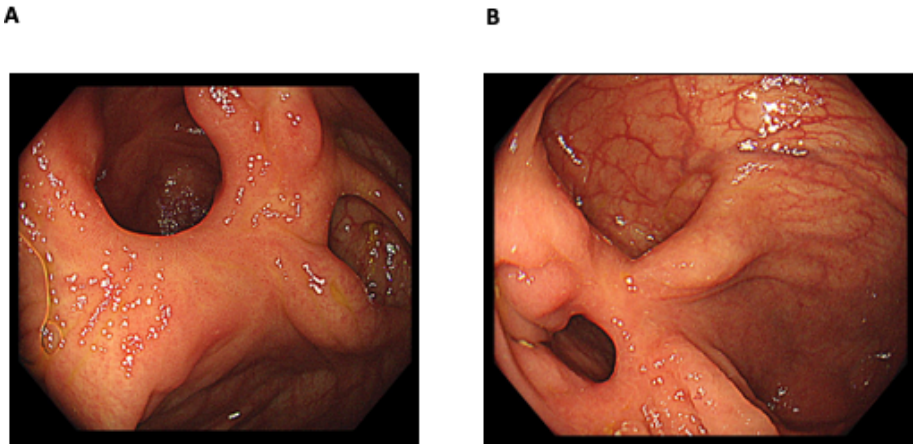

Figure 5. Colonoscopy findings in the patient after initiation of adalimumab therapy
An ileocecal ulcer scar was observed 3 (Panel **A**) and 6 (Panel **B**) years after initiation of adalimumab therapy

ure 4). Since the introduction of ADA, no recurrence of genital ulcers or skin lesions has been reported and CRP < 0.15 mg/dL has been maintained. Colonoscopy performed three and six years after switching to ADA revealed sustained endoscopically mucosal healing of the ileocecal ulcer (**Figure 5**).

Discussion

The present case was juvenile-onset intestinal BD refractory to conventional therapies[3]. The effect of colchicine, the standard drug of BD, was limited. Steroid dependency with severe side effects were observed. At the time of disease onset, anti-TNFα mAb had not yet been developed for intestinal BD, and we decided to introduce thalidomide, whose efficacy for refractory intestinal BD had been reported as described below[8]. While mucosal healing of the ileocecal ulcer and negative CRP was not achieved during

thalidomide therapy, partial remission that allowed for outpatient visits was maintained for more than 10 years.

More than six decades ago, thalidomide was widely prescribed to pregnant women as a tranquilizer, but it was found to be teratogenic, causing newborn babies with multiple severe deformities. Therefore, thalidomide was withdrawn from markets worldwide in the early 1960s[9]. However, since the 1980s, the effectiveness of thalidomide in the medical therapy of mucocutaneous lesions of BD has been reported[9]. A major expansion in the clinical application of thalidomide came in the early 1990s, when *in vitro* studies showed that thalidomide inhibited the TNF-α production in human monocytes[10]. Subsequently, new indications for thalidomide were developed such as treatment of cancer and inflammatory diseases[9]. In a 24-week randomized, double-blind, placebo-controlled trial in patients with BD, thalidomide was effective in treating oral and genital lesions. Complete response occurred in 2 of 32 patients being administered 100 mg/d of thalidomide, 5 of 31 patients being administered 300 mg/d of thalidomide, and none of the 32 patients being administered a placebo. The lesions recurred upon discontinuation of thalidomide[8]. In a case series of seven juvenile-onset intestinal BD cases, clinical improvement and reduction of corticosteroid doses were observed with the administration of thalidomide, and the side effects were well tolerated in all cases[11]. Accordingly, the 2018 update of the European League Against Rheumatism recommended that anti-TNFα mAb and/or thalidomide should be considered for patients with refractory or severe gastrointestinal involvement[12].

In a Japanese clinical trial of ADA for intestinal BD among patients who were refractory to corticosteroid and/or immunomodulatory treatments, the degree of improvement in the colonoscopic evaluation at 52 weeks was as high as 60%[13]. Based on this trial, ADA was approved for the treatment of intestinal BD in 2013. Thus, the Japanese consensus guidelines were revised to recommend ADA as a standard therapy for patients with refractory intestinal BD[14]. In a post-marketing study of ADA among 395 Japanese patients with intestinal BD, overall effectiveness was observed in 324 patients (84.6%) [15]. While a long-term partial remission was maintained by thalidomide, no endoscopic mucosal healing was obtained until after the switch to ADA. Accordingly, specific anti-TNFα activity seems essential for the treatment of mucosal damage in intestinal BD. To the best of our knowledge, the effectiveness of switching from long-term thalidomide therapy to anti-TNFα mAb for intestinal BD has not been reported. In the present case, the CRP has remained negative and healing of the ileocecal ulcer has been maintained for more than 6 years after switching to ADA from thalidomide. Therefore, among the multifaceted biological mechanisms of thalidomide, its anti-TNF-α activity seems to be very important for the therapy of intestinal BD.

In conclusion, we observed a successful switch to ADA after long-term thalidomide-based maintenance therapy for juvenile-onset intestinal BD. Approximately 7 years have passed since the introduction of ADA, and endoscopically mucosal healing of the ileocecal ulcer has been sustained, suggesting that ADA may have a more specific anti-inflammatory effect on intestinal BD than thalidomide. TNF-α activity seems to be the key pathway of mucosal injury in intestinal BD.

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Conflicts of Interest: The authors have no disclosures relevant to this publication.

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