A Case of Intestinal Behçet’s Disease Treated with Infliximab Monotherapy Who Successfully Maintained Clinical Remission and Complete Mucosal Healing for Six Years

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Abstract

Behçet’s disease is a chronic relapsing disease with multiple organ system involvement, including the gastrointestinal tract, which is known as intestinal Behçet’s disease. Intestinal Behçet’s disease is often resistant to empirical treatments such as 5-aminosalicylic acid, immunomodulators and steroids and often causes a perforation, requiring surgical resection. Therefore, intestinal lesions are considered to be a poor prognostic factor in Behçet’s disease. Recently, several reports have demonstrated the efficacy of anti-TNFα monoclonal antibodies, such as infliximab, against intestinal Behçet’s disease, however, it remains unknown whether anti-TNFα therapy can improve the prognosis of patients with intestinal Behçet’s disease. We herein report the case of an adult female patient with intestinal Behçet’s disease who responded well to the induction therapy with infliximab, and has been maintained in remission by scheduled administration of infliximab. Her C-reactive protein level has been sustained at a negative level, and endoscopic findings revealed complete mucosal healing. Therefore, infliximab may have the potential to induce “sustained deep remission” in patients with intestinal Behçet’s disease.

Key words: intestinal Behçet’s disease, infliximab, mucosal healing, sustained deep remission

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Introduction

Behçet’s disease is a chronic relapsing disease with multiple organ system involvement characterized clinically by oral and genital aphthae, cutaneous lesions, and ophthalmological, neurological, or gastrointestinal manifestations (1, 2). About 3-16% of patients with Behçet’s disease have gastrointestinal tract involvement (3). Gastrointestinal disease typically affects the ileocecal area, although involvement of the esophagus and small intestine has been reported (3). The most common gastrointestinal symptoms are abdominal pain, diarrhea, and bleeding. Deep ulcers are responsible for the most common intestinal complications, such as severe bleeding and perforation (4). Various drugs, such as 5-aminosalicylic acid (5-ASA), systemic corticosteroids, and immunosuppressive agents have been used anecdotally to treat intestinal Behçet’s disease. However, the clinical evidence regarding the management of intestinal Behçet’s disease is very limited. Recently, the Japanese Inflammatory Bowel Disease Research Group, supported by the Japanese Ministry of Health, Labour and Welfare, established a consensus for the management of intestinal Behçet’s disease (5). In this consensus, infliximab (IFX) was first described as an optional therapy for intestinal Behçet’s disease. Accumulating evidence of the efficacy of anti-TNFα agents in the management of Crohn’s disease and Behçet uveitis have encouraged the use of anti-TNFα agents for managing intestinal Behçet’s disease. Indeed, several cases of intestinal Behçet’s disease that have been suc-
cessfully treated by anti-TNFα agents have been reported (6-14), although there is insufficient evidence that anti-TNFα agents can improve the long term prognosis of intestinal Behçet’s disease. It is therefore important to determine whether anti-TNFα agents can maintain mucosal healing in patients with intestinal Behçet’s disease, as well as Crohn’s disease. We herein present a case of intestinal Behçet’s disease successfully maintained in clinical remission with mucosal healing for 6 years by IFX monotherapy.

Case Report

In 2003, a 28-year-old Japanese female was admitted in our hospital with a one-year history of oral aphthoid ulcers and pharyngeal ulcers. She was administered 30 mg/day of predonisolone (PSL). Because this patient had severe oral aphthoid and pharyngeal ulcers, taking the tablets was difficult for her. In addition, since PSL therapy had already been started for the treatment of these ulcers, we did not add 5-ASA (Fig. 1). Colonoscopy revealed a round deep punched-out ulcer at the ileocecal region (Fig. 2A). The histopathological findings revealed nonspecific chronic inflammation without granulomas. Upper gastroduodenal endoscopy revealed erosive lesions in the esophagus (Fig. 3A). Small bowel enteroclysis did not reveal other lesions in small intestine except for the ulcers at the ileocecum. Intestinal Behçet’s disease was suspected, and 6-mercaptopurine (6-MP) treatment was started. However, the pharyngeal and oral aphthoid ulcers relapsed, and she presented with a genital ulcer in September 2005.

In March 2006, the patient’s abdominal pain in the right lower quadrant worsened after tapering of the PSL to 5 mg/ day. Colonoscopy revealed active ulcers with inflammation in the ileocecum (Fig. 2B). A CT scan revealed swelling of the ileocecum (Fig. 4). In November 2006, she experienced right hand joint pain. She was diagnosed with Behçet’s disease based on her history of symptoms (recurrent painful oral and pharyngeal ulcers, ileocecal ulcers, genital ulcer, and arthralgia) met the Japanese diagnostic criteria for Behçet’s disease (15).

Since the gastrointestinal lesions were not controlled by several rounds of PSL therapy with 6-MP, we thought that the active deep ulcers in the ileocecum and pharynges were refractory to conventional therapy, so we started IFX therapy (5 mg/kg body weight) in April 2007. IFX was administered at 0, 2, and 6 weeks for induction, followed by administration every 8 weeks as scheduled maintenance therapy. After the third injection of IFX, her symptoms were dramatically improved, and her serum C-reactive protein (CRP) level was decreased to a normal level. The colonoscopy performed after the 3rd injection of IFX showed a dramatic reduction in the size of the ulcers and mucosal swelling (Fig. 2B). Moreover, after 8 months of IFX, the ulcers were completely scarred (Fig. 2C). Since the scheduled administration of IFX could maintain the patient in clinical and serological remission, the PSL was tapered and stopped. Furthermore, because the patient was concerned about the potential adverse effects on pregnancy, 6-MP was discontinued without relapse. The esophageal lesion also improved with mucosal healing (Fig. 3). The colonoscopic findings obtained during...
Figure 2. The colonoscopic findings of the lesions at ICV. A) Before the initiation of IFX therapy. A giant oval ulcer is demonstrated at the ICV. The ICV is inflamed with stenotic changes. B) After the 3rd injection of IFX. C) At 8 months after the initiation of IFX, the ulcers were completely scarred. D) At 20 months after the initiation of IFX. E) Three years after the initiation of IFX. F) The results of the examination performed 4 years and 4 months after the initiation of IFX. G) The results of the examination performed 5 years and 4 months after the initiation of IFX.

Discussion

Since intestinal Behçet’s disease causes perforation of the gastrointestinal tract and massive gastrointestinal bleeding, and it is therefore considered to be a poor prognostic manifestation in Behçet’s disease. The efficacy of empirical therapies, such as 5-ASA, immunosuppressive agents, and steroids have been reported (16), however, no clear therapeutic strategy for intestinal Behçet’s disease has been established. Several essential questions have been raised, including 1) is intestinal Behçet’s disease a progressive disease? 2) have empirical therapies changed the disease prognosis?

A study in Korea showed that 5-ASA/sulfasalazine therapy had a positive effect in maintaining remission in pa-
patients with intestinal BD. However, a younger age (<35 years), higher CRP level, and a higher disease activity were associated with a poor response to 5-ASA/sulfasalazine therapy (17). We also reported that a retrospective analysis of 20 patients that ocular and ileal lesions were a risk factor for a poor outcome from surgery (18). Iida et al. reported that the postoperative recurrence of intestinal ulcers was observed in approximately 80% (7 of 9) of patients with intestinal Behçet’s disease who had undergone a total of 15 operations (19). A retrospective analysis of 72 patients with intestinal Behçet’s disease who underwent surgery in Korea showed that recurrence after surgical treatment was observed in 58.3% of patients, and reoperations were performed in 30.6% of patients. The cumulative recurrence rates after surgical treatment were 29.2% at 2 years and 47.2% at 5 years (20). Considering these reports, intestinal Behçet’s disease, at least in some patients, should be recognized as a progressive disease resulting in severe bowel damage and requiring multiple surgeries. As described, the efficacy of anti-TNFα antibodies for the induction of clinical remission has been reported, however, there is insufficient evidence that anti-TNFα antibodies improve the long term prognosis of patients with intestinal Behçet’s disease.

In this report, although PSL showed efficacy for reducing the clinical symptoms and serum CRP, the patient relapsed several times. In addition, 6MP unfortunately did not prevent clinical relapse. However, after the introduction of IFX therapy, the patient rapidly obtained clinical and serological remission. Scheduled maintenance therapy with IFX successfully maintained the clinical and serological remission. It is also worth mentioning that IFX rapidly induced endoscopic improvement and maintained it. In our case, the giant deep ulcers in the ileocecum were improved and treated led to complete scar formation, so called “mucosal healing”. In addition, after stopping 6MP, the IFX monotherapy has successfully maintained the patient in clinical, serological, and endoscopic remission for 6 years. Recently, it has been reported that Crohn’s disease is a progressive disorder which causes dysfunction of the digestive tract. Therefore, to change the natural history and to improve the long term prognosis of Crohn’s disease, new strategies that not only induce and prolong a clinical remission, but also a serological remission and mucosal healing should be the goal in the management of Crohn’s disease. In the literature, clinical remission with endoscopic mucosal healing is defined as “deep remission” (21). Like Crohn’s disease, intestinal Behçet’s disease is a chronic, relapsing disease with a risk of bowel perforation, leading to a resection and disability. Therefore, the concept of “mucosal healing” may be applicable in intestinal Behçet’s disease as well. To ensure the maximal efficacy of anti-TNFα antibody therapy, the concept of “early Crohn’s disease” has been proposed. This has led to evidence that anti-TNFα antibodies showed maximal efficacy in the patients with Crohn’s disease who had been diagnosed within 2 years before treatment (21). In the presented case, since IFX was started 2 years after the diagnosis, it can be considered “early Behçet’s disease”, and it appears that IFX may successfully induce deep remission in these patients as it does in Crohn’s patients.

Despite anecdotal evidence showing their efficacy, there is controversy surround the use of immunomodulators with an anti-TNFα antibody for maintenance in intestinal Behçet’s disease. Even in Crohn’s disease, it remains unresolved whether anti-TNFα antibodies should be used in combination with immunomodulators (22-24). Only a few cases of such treatment in patients with intestinal Behçet’s disease have been reported previously. A case in which adalimumab monotherapy maintained clinical remission was reported (25). On the other hand, the efficacy of combination therapy with infliximab and methotrexate in refractory intestinal Behçet’s disease was reported (26). Unfortunately, in both reports, mucosal healing was not assessed.

Regarding these issues, our case demonstrated, for the first time, that early intervention using an anti-TNFα antibody induced a dramatic clinical and endoscopic remission, and successfully maintained mucosal healing in intestinal Behçet’s disease. Our case suggests that early intervention using anti-TNFα treatment can induce and maintain mucosal healing, and may improve the long term prognosis of patients with intestinal Behçet’s disease.

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

References