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Running title: infliximab and thalidomide for entero-Behcet’s disease

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Abstract

Background: Behcet's disease (BD) is a systemic inflammatory disease with the histopathological features of leukocytoclastic vasculitis that affects nearly all organs and systems. When it involves the intestine, it is called entero-Behcet's disease or gastrointestinal Behcet's disease.

Case presentation: Here we described a patient with entero-BD refractory to conventional therapies, who responded well to the combination therapy of infliximab, an anti-tumor-necrosis-factor (TNF)-alpha antibody, and thalidomide.

Conclusion: The combination therapy of infliximab and thalidomide showed that it appears to be clinically effective in a patient with refractory entero-Behcet's disease. However, further studies need to be performed to evaluate the efficacy of this combination therapy.

Keywords: entero-Behcet's disease, infliximab, thalidomide
Introduction

Behcet's disease (BD) is a systemic inflammatory disease with the histopathological features of leukocytoclastic vasculitis that affects nearly all organs and systems [1]. Entero-Behcet's disease is characterized by intestinal inflammation with round and oval ulcers typically in the ileocaecum and is associated with gastrointestinal symptoms, which are often uncontrollable, relapsing, and can cause acute intestinal bleeding or perforation [2, 3]. Gastrointestinal involvement has been reported in 3%–26% of patients with BD [4] and is most common in countries along the ancient Silk Route. The etiology of Behcet's disease is still unknown, but tissue damage that occurs in BD patients is believed to be caused by oxygen radicals, which are generated by proinflammatory cytokines and arachidonic acid metabolites [5, 6]. Although corticosteroids, 5-aminosalicylic acid derivatives, immunosuppressive agents, and immunomodulators have been used to treat BD patients with varying degrees of success, BD is still associated with severe morbidity and considerable mortality. Tumor necrosis factor (TNF)-alpha plays an important role in this T helper cell type 1 (Th1)-mediated disease [7]. Infliximab, a monoclonal antibody to TNF-alpha, which neutralizes TNF-alpha and down-regulates the expression of GM-CSF (granulocyte-macrophage colony-stimulating factor) has been demonstrated to be an effective therapy for Crohn's disease, rheumatoid arthritis and other Th1-mediated disorders [8].

Thalidomide selectively inhibits the production of tumor necrosis factor alpha (TNF-alpha) in monocytes and reduces its activity by a mechanism distinct from infliximab [9, 10]. Because the single use of infliximab is not efficient in all BD patients [11, 12], we utilized a combination therapy of infliximab and thalidomide and showed that it appears to be clinically
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effective in a patient with refractory entero-Behcet's disease.

Case report

A 23-year-old man was admitted to our hospital because he had recurrent abdominal pain and fever for more than 2 years. The patient began to have a burning pain in the epigastrium in October 2008, which mostly occurred at night and when he was hungry. The pain occurred once every 1 to 2 months, each time lasting for 1 to 2 days, accompanied by fever, with temperature fluctuating between 38-39°C, which would alleviate by itself. The patient did not have diarrhea, night sweats or other symptoms. Laboratory examination in the local hospital revealed white blood cell (WBC) 10.0×10^9/L (normal 3.6-9.7×10^9/L), neutrophil rate (NEU%) 79.2% (normal 50-70%), hemoglobin (HGB) 116g/L (normal 120-160 g/L) and c-reactive protein (CRP) 87.7mg/L(normal 0-5mg/L). Erythrocyte sedimentation rate (ESR) was 27.0mm/h (normal 0-15 mm/h), and occult blood test (OBT) was positive. The patient was a non-smoker with no family history of inflammatory bowel disease. Gastroscopy revealed duodenal bulb ulcers. Although acid inhibitors and antipyretics were used in the local hospital, his symptoms did not improve. He was referred to our department for further evaluation. On admission, a physical examination found an enlarged submental lymph node which was soft and removable without pressing pain. After admission, laboratory examination indicated that WBC, OB, CRP, and ESR were normal. The patient tested negative for autoantibodies to nuclear antigen (ANA), double-stranded deoxyribonucleic acid (dsDNA), nuclear ribonucleoprotein (RNP), anti-saccharomces cerevisiae antibodies (ASCA) and anti-neutrophil cytoplasmic antibodies (ANCA). In addition, Pathergy and Widal tests were
both negative. Gastroscopy and double balloon enteroscopy revealed duodenal bulb ulcers and scattered round small ulcers in the jejunum with no evidence of Helicobacter Pylori (HP) infection (Figure 1A、1B).

Biopsy of a deeply ulcerated area of jejunum revealed nonspecific mucosal inflammation without granulomata (Figure 1C). Positron emission tomography/computed tomography (PET/CT) found multiple and flake concentration around the jejunum and ileum. Inflammatory and hyperplastic lymph nodes without increased metabolism were found in the abdominal, retroperitoneal and mesenteric region (Figure 2).

Although various test had been conducted, the diagnosis of the patient remained unresolved. Because the patient’s medical history was long, and PET-CT did not reveal abnormal concentrations nor increased metabolism, the possibility of intestinal lymphoma was excluded, however Crohn’s disease, tuberculosis of the intestines and Behcet’s disease were difficult to differentiate from each other and remained possible causative conditions. After discharge, the patient still suffered from recurrent abdominal pain. He returned to our department with recurrent abdominal pain and fever in March 2012. On further investigation it was discovered that the patient had had recurrent oral ulcers, genital ulcers and occasional blurred vision since childhood. Capsule endoscopy was carried out and revealed multiple ulcers in the small intestine, mainly located in the jejunum (Figure 3A、3B). Behcet’s disease has no accepted laboratory test and is diagnosed based on clinical evaluation. Thus, our patient was diagnosed with entero-Behcet's disease based on the International Criteria for Behcet’s Disease (ICBD). However, although he had been treated with prednisone, mesalazine, cyclophosphamide and colchicines in the local hospital, his symptoms had not
improved. After discussion with the patient, a combination therapy including infliximab (5mg/kg), thalidomide (100mg,qd) and prednisone (15mg/day) was prescribed. Infliximab was infused at weeks 0, 2, 6, 14, 22 and 30 according to instructions. No medication-related adverse reactions were observed and the prednisone dose was gradually tapered during the treatment. After the first infusion with infliximab the patient’s abdominal pain and fever disappeared despite complete withdrawal of steroids. CRP decreased from 87.7mg/L to 0.7mg/L and ESR decreased from 27.0mm/h to 4mm/h. Because most of his symptoms were gastrointestinal, the Crohn's Disease Activity Index (CDAI) was selected as an objective measure of response to the therapy. The CDAI score decreased from 344 points to 52 points during therapeutic period (Table 1). Meanwhile, his body weight increased from 53kg to 64kg. Capsule endoscopy performed 10 weeks after the last infusion showed marked endoscopic improvement and the patient's multiple ulcers had healed well (Figure 3C, 3D).

**Discussion**

Behcet's disease is a chronic relapsing vasculitis characterized by recurrent oral and genital ulcerations with uveitis and is more prevalent around the Mediterranean and the Far East [13]. Although oral ulceration, genital ulceration and eye disease are classical symptoms of the disease, the cardiovascular, gastrointestinal, musculoskeletal and central nervous systems can also be affected. The pathogenesis of BD remains unknown but major determinants involving genetic and immune system abnormalities have been recently reported [14].

In intestinal BD, deep ulcers develop in the gastrointestinal tract, typically in the ileocaecum. However, the endoscopic manifestations of this patient were scattered small ulcers, mainly in
the jejunum. In addition, the pathergy test was negative, which complicated the diagnosis. After collecting a detailed medical history, the diagnosis was eventually established based on the International Criteria for Behcet’s Disease (ICBD).

Entero-Behcet’s disease is often difficult to manage by conventional therapies such as corticosteroids, 5-aminosalicylic acid derivatives and immunosuppressive agents. Recently, off-label use of anti-tumor necrosis factor (TNF) agents for Behcet's disease (BD) has increased, suggesting that TNF blockade represents an important therapeutic approach for patients with severe and resistant Behcet's disease, but randomized controlled trials are lacking [3, 15-18]. Infliximab has been reported to have rapid and excellent efficacy in patients with refractory entero-BD [16, 19-22]. Although 91% of BD patients responded to infliximab, some patients responded poorly to the treatment of infliximab [12, 15]. Considering the possibility that the patient with refractory entero-Behcet's disease described in this report may respond poorly to infliximab alone, we decided to treat him with a combination therapy of infliximab and thalidomide, which may synergize due to a complete blockade of TNF-α.

To our knowledge, this is the first report of a treatment regime using the combination therapy of infliximab and thalidomide. The good response of the patient to this combination therapy is likely a result of a complete TNF-α blockade by the two agents. Although our report describes only one case, the improvement in symptoms of the patient supports evidence that increased levels of TNF-α play a critical role in the inflammatory process associated with BD.
In view of limitations of the present treatment for intestinal BD, combination therapy with infliximab and thalidomide appears to be an effective approach for the treatment of entero-Behcet's disease and perhaps other manifestations of BD. However, further studies need to be performed to evaluate the efficacy of this combination therapy.

We declare that we have no competing interests.

Authors' contributions

Yue Li designed and drafted the manuscript. Zelong Han participated in the design of the study. Yue Li and Zelong Han contributed equally to this paper. Zhihui Mo and Xianfei Wang performed the data collecting of this case. Side Liu conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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Consent statement:
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.
References


**Figure Legends**

**Figure 1:** Gastroscopy revealed a scar (arrow) left on the anterior wall of the duodenum from a healed ulcer (A). Double balloon enteroscopy revealed a round ulcer (arrow) characterized by hyperemia and erosion (B). Biopsy specimens from the jejunum revealed chronic inflammatory infiltrate consisting of a mixture of neutrophils, lymphocytes and plasma cells (C).

**Figure 2:** PET-CT revealed multiple enlarged lymph nodes (arrow) in the abdominal and mesenteric region without abnormal concentration of 18F-fluorodeoxyglucose (18F-FDG).

**Figure 3:** Before infusion, capsule endoscopy showed multiple oval ulcers with purplish red color change and thin fur attached on the surface. Congestion and edema of the mucosa can be seen around the ulcers which were widely distributed in the small intestine (A,B). Repeated capsule endoscopy showed improvement in ulcerations and inflammation 10 weeks after the last infusion (C,D). Most of the ulcers had healed, leaving a small sheet of erosion (arrow).
Table 1: A CDAI score <150 points is considered clinical remission in a patient with CD. After the first infusion, the patient noticed great improvement in symptoms, and his CDAI score declined dramatically from 344 points to 100 points, which indicated clinical remission.
Abbreviations used in this paper:

BD, Behcet's disease

TNF, tumor necrosis factor

WBC, white blood cell

NEU, neutrophil

HGB, hemoglobin

CRP, C-reactive protein

ESR, erythrocyte sedimentation rate

OB, occult blood test

PET-CT, positron emission tomography/computed tomography

ICBD, the International Criteria for Behcet’s Disease

CDAI, the Crohn's Disease Activity Index