Clinical Case Report

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Infliximab associated with life-threatening lung infection in a patient with Behcet disease with intestinal and hematopoietic system involvement

A case report

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Abstract

Rationale: Tumor necrosis factor (TNF-α) participates in the pathophysiology of Behcet's disease (BD) and myelodysplastic syndrome (MDS). Infliximab is recommaned for the most severe type of BD, however, there is little evidence for its effectiveness in BD associated MDS.

Patient concerns: A 46-year-old female, initially diagnosed with intestinal BD and leukopenia was later diagnosed as MDS. Treatement with infliximab and other immunoregulators lead to life-threatening pneumonia.

Diagnosis: Intestinal BD associated with MDS involving trisomy 8.

Interventions: The patient initially treated with methylprednisolone, thalidomide, cyclosporine A, and infliximab, which lead to severe lung infection. Therefore, the patient was transferred to Intensive Care Unit for life supportive, anti-infection and immune improving therapy.

Outcomes: The patient survived from the lung infection. With combination of methylprednisolone, thalidomide and cyclosporine A, the patient recovered from her intestinal ulceration and MDS manifestations.

Lessons: Infliximab treatment may not benefit a patient with BD associated with MDS but place the patient at risk of infection.

Abbreviations: BD = Behcet disease, C = complement, CH50 = complement hemolysis 50% assay, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Ig = immunoglobulin, MDS = myelodysplastic syndrome, RBC = red blood cell, TNF = tumor necrosis factor, WBC = white blood cell.

Keywords: autoimmune, infection, infliximab, TNF-α, trisomy 8

1. Introduction

Behcet disease (BD) is a systemic autoimmune disorder, characterized by recurrent oral and genital ulceration, eye inflammation, and erythema nodosum. The disease may involve multiple systems: gastrointestinal, neurological, vascular, skeletal, and hematopoietic.[1] Tumor necrosis factor (TNF)-α plays a central role in both the inflammatory and immune responses. Blockade with anti-TNF agents are important tools in the management of a variety of autoimmune disorders. TNF-α appears to participate in the mechanism of BD; however, there is a paucity of adequate clinical trials. Based on case reports and case series, BD is an off-label indication of anti-TNF-α agents.[2] Anti-TNF-α therapy such as infliximab appears to be effective in treatment of severe and refractory BD manifestations.[3]

Infliximab, common to drugs in the class of TNF inhibiting immunosuppressants, has multiple potential adverse effects, some are life threatening. The most severe are serious infections, reactivation of hepatitis B, reactivation of tuberculosis, lethal hepatosplenic T-cell lymphoma, drug-induced lupus erythematosus, and demyelinating central nervous system disorders.[4] We present a rare case of BD with intestinal ulceration, arthritis, and hemocytopenia. The patient experienced a life-threating lung infection during her treatment by infliximab combined with other immunoregulators.

2. Case presentation

A 46-year-old female presented to our institute on 19 December, 2016, complaining of recurrent oral aphthous ulceration of 10 years' duration. She had 2 to 3 attacks per year, lasting 1 to 2 weeks. In the past 2 years, she complained of oral ulcerations almost monthly accompanied with 2 episodes of genital ulceration. The patient also complained of right ankle pain after

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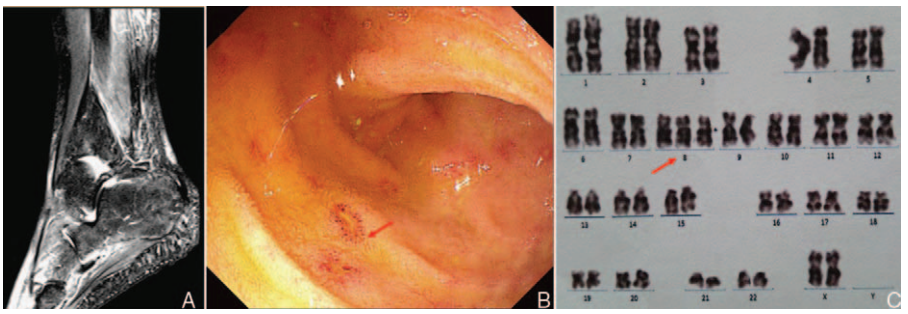

Figure 1. (A) MRI T2WI revealing nonspecific inflammation in right ankle (synovitis, bone edema, and hydrops articuli); (B) endoscopy revealing a 10 mm × 5 mm ulceration in the ileocecal region; (C) karyotype analysis for bone marrow cells revealing 47, XX, +8.

exertion. She had a 1-year history of low white blood cell (WBC) counts. The patient had a reaction pathergy test. BD was diagnosed after ruling out other diagnoses. On admission, her blood examinations were as follows: erythrocyte sedimentation rate (ESR) 80.0 mm/h (normal range 0–20), C-reactive protein (CRP) 104.5 mg/L (normal range < 10), C3 1.83 g/L (normal range 0.9–1.8), C4 0.41 g/L (normal range 0.1–0.4), complement hemolysis 50% assay (CH50) 50.0 U/mL (normal range 23–46), and Immunoglobulin E 325 IU/mL (normal range < 100). These indicated high inflammatory activity. Complete blood count revealed WBC 2.8×10^8/L (normal range 3.5–9.5), red blood cell (RBC) 3.5×10^9/L (normal range 3.8–5.1), hemoglobin 107 g/L (normal range 115–150), and platelet count in normal range. Bone marrow smear revealed mild karyocyte hyperplasia, granulocyte series hyperplasia, mild erythroid colony hyperplasia, mild decreases in megakaryocytes, and scattered clustered and stacked platelets. The overall impression was leukopenia and mild anemia. Karyotype analysis of bone marrow revealed 47, XX, +8 (Fig. 1). The diagnosis of myelodysplastic syndrome (MDS) was considered by a consulting hematologist. Blood tests for hepatic and liver function, blood glucose, cholesterol, coagulation times, microorganisms, cancer markers, and autoantibodies were unrevealing. Magnetic resonance imaging (MRI) of her right ankle revealed mild edema in the lower part of the fibula, calcaneus, navicular, cuboid, cuneiform bone, and metatarsus. There was a mild effusion surrounding a swollen internal ligament of the tarsal sinus, mild effusion in the joint space and postcalcaneal bursa, and plantar fasciitis (Fig. 1A). Endoscopy revealed a 10 mm × 5 mm ulceration in the ileocecal region (Fig. 1B). Histopathology revealed active nonspecific ulceration.

The patient received methylprednisolone 24 mg po daily, thalidomide 50 mg po every night, and cyclosporine A 75 mg po twice daily for intestinal BD, as well as supportive therapy for hemocytopenia and prevention of potential medication side effects. After excluding infectious diseases including tuberculosis, HIV, and HBV, the patient was treated with infliximab 200 mg. The symptoms were all well-controlled and expect for dizziness thought to be caused by thalidomide. This was managed by reducing dosage and treating the patient with mecobalamin. No other side effects were reported. The patient was readmitted to our hospital 2 months later for onset of herpes zoster in her right back. She received a second infliximab infusion.

One week after the second discharge, the patient developed fever, cough, and fatigue. In the emergency department (18 March, 2017), her CRP was 66.66 mg/L. Her WBC was in the high range of normal. Computer tomography (CT) revealed diffuse alveobronchiolitis in both lungs (Fig. 2C and D). Serum lipopolysaccharide was 476.8 pg/mL, and β-1,3-D-glucan was 754.2, suggesting Gram-negative bacterial and fungal infection. Mycoplasma pneumonia and influenza A virus tests were positive. She was treated with panipenem/betamipron, amikacin, and fluconazole (subsequently changed to itraconazole), as well as ganciclovir. These and supportive therapies did not improve her condition. Her condition declined, indicated by blood gas analysis demonstrating acute respiratory failure. A bedside X-ray on 27 March, 2017, and CT on 1 April, 2017 revealed severe lung infection. The patient was transferred to respiratory intensive care unit (RICU) for further therapy. Special attention was paid to increase the patient's immune function by treatment with recombinant human granulocyte colony stimulating factor, thymopentin, leucogen, and immunoglobulin (Ig). A CT scan on 20 April, 2017, revealed substantial improvement in air-space disease. The patient recovered over the course of 1 month.

She continued taking oral methylprednisolone, thalidomide, and cyclosporine, for intestinal BD and hemocytopenia. Follow up in July 2017 revealed less arthritis, clear lungs, and absent intestinal ulceration. Her ESR, CRP, and WBC were normal. Her anemia was improving (Fig. 2).

3. Discussion

We presented a case of BD with joint, intestinal, and hematopoietic system involvement. BD is a chronic multisystem inflammatory disease, first described in the 1930s by Hulusi Behcet. BD is also known as Silk Route disease due to its high incidence in the countries of the eastern Mediterranean and the eastern rim of Asia.[5] However, approximately 2000 years ago, a Chinese doctor named Zhang Zhongjing described very similar symptoms, and named them Huhuo disease in his work *Synopsis of Golden Chamber*.[6]

The incidence of intestinal BD is around 13%. In our institution, 63% of the intestinal ulcers were found in the ileocecum.[7] Although BD and MDS are distinct disease entities, several studies have identified a relationship between them, especially in the context of intestinal BD. Previous reports have also revealed that trisomy 8 appears to play an important role in these disorders.[8,9]

There is evidence that TNF-α inhibition by infliximab is effective for rapid improvement and maintenance of remission in intestinal BD.[10,11] Vallet et al reported that infliximab and adalimumab were effective in treating severe or refractory BD symptoms, including refractory ocular, mucocutaneous, joint, gastrointestinal, central nervous system, and cardiovascular manifestations. These authors claim that anti-TNF-α therapy is appropriate for all severe and refractory BD manifestations.[3] It is unclear if this is the case for BD associated with MDS.

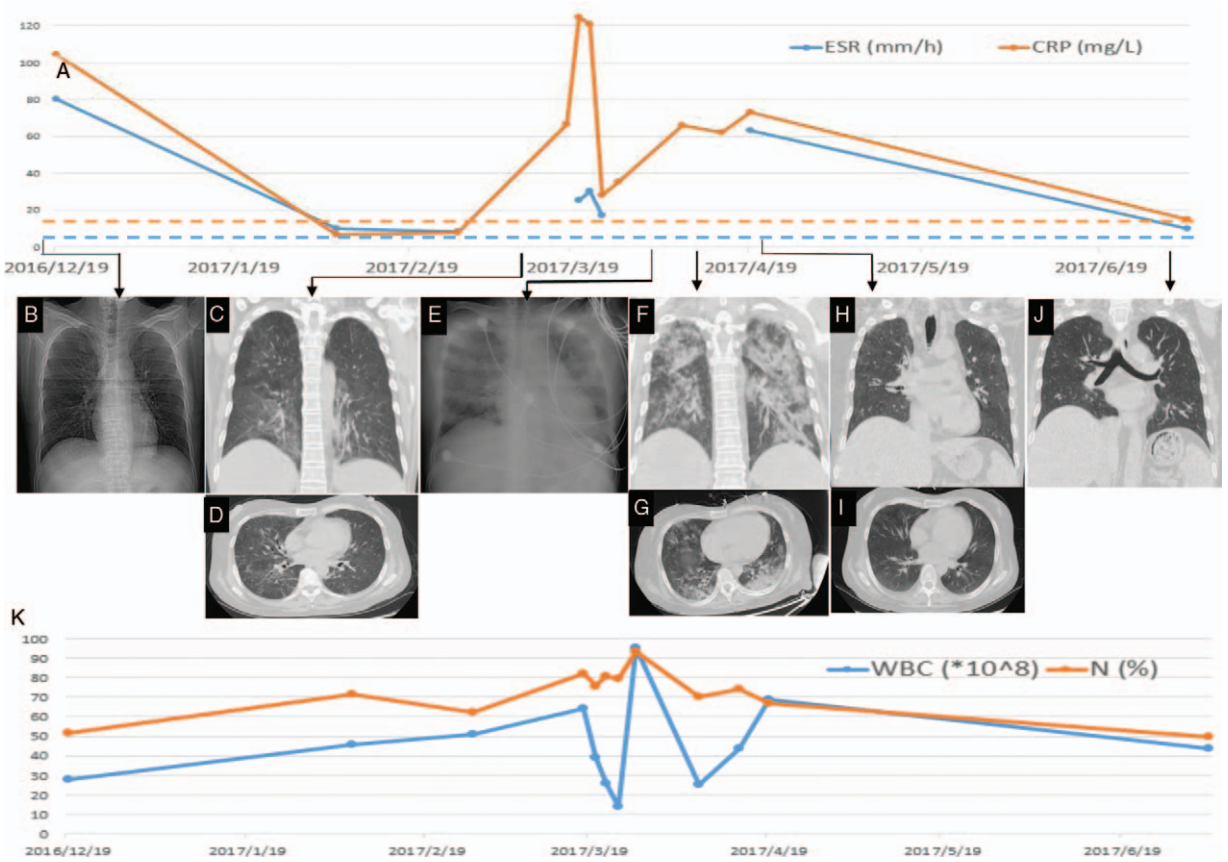

Figure 2. (A) Fluctuation of ESR and CRP before and after infliximab, with subsequent life-threating lung infection. (B) CT scan before infliximab. (C–G) Onset of lung infection after 2 infliximab injections. (H–J) Recovery of lung infection. (K) During lung infection period, WBC count and neutrophil percent were relatively high compared with baseline. Note: Dotted line in red and blue in (A) represent normal upper limit of CRP and ESR, respectively. Dotted line in red and blue in (K) represent baseline of neutrophil percent and WBC count respectively. This patient had an average WBC count of 3.96×10^9/L.

TNF-α is a proinflammatory cytokine that inhibits normal hematopoiesis and induces programmed cell death in both normal total bone marrow cells and normal CD34+ cells. Studies have suggested an important role of TNF-α in the pathophysiology of MDS.[12] Abnormal release of inflammatory cytokines including TNF-α has been reported in cytopenia and disease progression in MDS.[13] The effectiveness of infliximab for treatment of MDS is a matter of dispute.[12,14] Toyonaga et al reported 2 cases of intestinal BD with MDS and trisomy 8 that did not respond to infliximab. In a thorough review of 33 cases, 20 (60.6%) showed temporary improvement of BD symptoms, 10 (30.3%) worsened, and 3 (9.1%) showed no change. Therefore, infliximab might not be effective for treatment of intestinal BD with MDS involving trisomy 8.[9]

Colombel et al evaluated short- and long-term safety of infliximab in 500 Crohn disease patients. Forty-one (8.2%) patients experienced infection attributed to infliximab, of which 20 were serious infections. Two suffered fatal sepsis, 8 had pneumonia (of which 2 cases were fatal), 6 had viral infections, 2 had abdominal abscesses requiring surgery, 1 had arm cellulitis, and 1 had histoplasmosis.[4] MDS is associated with disordered innate immune and inflammatory signaling[15] possibly increasing the risk of infection. However, there are little data to support this.

We report a BD patient with joint and intestinal involvement associated with MDS in the context of trisomy 8. During her treatment with infliximab, she suffered leukopenia and the onset of herpes zoster, suggesting decreased immune function and increased susceptibility to infection. We believe her life-threatening pneumonia could be attributed to infliximab treatment. After 1 month of intensive care, the patient recovered. It hypothesized that MDS is an autoimmune disorder.[13,16] Thalidomide and cyclosporine A have been reported to be effective for MDS.[17] Conventional immunoregulators for intestinal BD might have had favorable effects for MDS in this case.

4. Conclusion

The history of oral and genital ulceration, combined with the positive pathergy test in this case met diagnostic criteria for BD. On endoscopy, the patient was found to have intestinal ulceration. The history of low WBCs, characteristic bone marrow smear, and karyotype analysis suggested the diagnosis of MDS. Although TNF-α plays an important role in the development in MDS, the effectiveness of treatment with infliximab to treat MDS is under dispute. Case reports reveal unfavorable results of anti-TNF-α therapy for BD associated with MDS. Considering the fact that MDS patients have reduced immunity, infliximab might not effect for BD associated with MDS patient, and in fact might place this type of patient at risk of infection.

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