Combination Therapy With Infliximab and Methotrexate in Recalcitrant Mucocutaneous Behçet Disease

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Behçet disease is a multisystem inflammatory disease with features of vasculitis. It undergoes periods of spontaneous remission and relapse. It often affects the skin, blood vessels, central nervous system, joints, gastrointestinal system, eyes, mucous membrane, and other systems, and it can cause substantial morbidity and mortality. The etiology of Behçet disease remains unknown. Current treatment of Behçet disease involves symptomatic relief with prevention of relapse.

We describe the treatment of a recalcitrant case of Behçet disease with infliximab and methotrexate. The patient is a 40-year-old Korean woman with tender lesions on the lower extremities of 1.5 years' duration and intermittent oral and genital ulcerations that failed multiple conventional therapies. The patient was placed on a trial of infliximab. She reported resolution of the tender lower extremity lesions and the oral and vaginal ulcerations shortly after the initiation of the anti–tumor necrosis factor agent. The patient was symptom free for 2 years following the initiation of infliximab. She subsequently reported mild breakthrough oral ulcers and joint pain. The treatment regimen was modified by adding methotrexate 7.5 mg weekly, prednisone 5 mg daily, and a shortened treatment interval of infliximab infusion that resulted in resolution of her symptoms.

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Case Report

A 40-year-old Korean woman presented with intermittent episodes of pruritic and erythematous papules under the breasts, painful lesions on the lower extremities, and painful ulcers on the oral and vaginal mucosa of 1.5 years' duration. The patient stated the pruritic papules initially developed on the thighs and calves before involving the inframammary area. The lesions were sensitive to touch and also had a burning sensation. She expressed that this condition has substantially affected her quality of life. Her medical history included rheumatoid arthritis involving the knees and hypercholesterolemia. She denied any family history of skin disease or autoimmune disease. Her only medication was acetaminophen. She denied any drug allergies.

On physical examination, the patient had multiple erythematous, indurated, palpable nodules on the bilateral lower extremities. Oral or genital mucosal ulcers were not present at the time. A 4-mm punch biopsy was performed on the right lateral lower extremity. Microscopic examination of a specimen stained with hematoxylin and eosin revealed superficial and deep perivascular and interstitial dermatitis with mixed infiltrates (Figure 1). Heavy neutrophilic infiltrate with leukocytoclasis was noted in the subcutis without any evidence of leukocytoclastic vasculitis in multiple levels (Figure 2). The histology resembled lobular panniculitis.

Laboratory workup included infectious, autoimmune, and inflammatory etiologies. Antinuclear antibody, anti–double-stranded DNA antibodies, and Lyme disease antibody were negative. Hepatitis A, B, and C panel and rapid plasma reagin test were nonreactive. C-reactive protein and rheumatoid factor were within reference range. (See the Table for a full list of laboratory test results.)

A second 4-mm punch biopsy was performed on the left pretibial tender nodule that showed differential diagnoses of ruptured folliculitis/cyst and erythema nodosum with slightly widened subcutaneous fibrous septa. Periodic acid–Schiff, Giemsa, acid-fast

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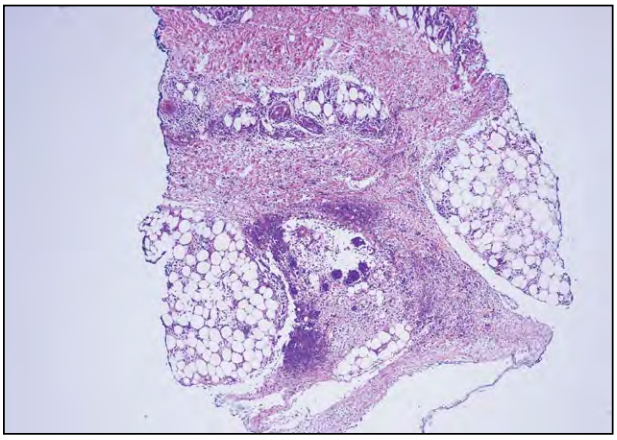

Figure 1. A biopsy specimen obtained from the right lateral lower extremity revealed superficial and deep perivascular and interstitial dermatitis with mixed infiltrates (H&E, original magnification ×20).

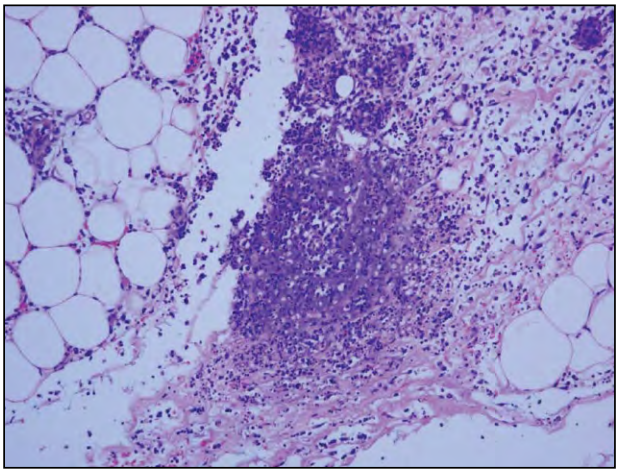

Figure 2. Heavy neutrophilic infiltrate with leukocytoclasis was noted in the subcutis without any evidence of leukocytoclastic vasculitis (H&E, original magnification ×100).

bacillus, Alcian blue, and hematoxylin and eosin stains were all negative for microorganism.

A diagnosis of Behçet disease was made based on the International Study Group criteria.[1] The patient had intermittent oral ulcers more than 3 times in 12 months, recurrent genital ulcers, and painful cutaneous nodules on the bilateral lower extremities resembling erythema nodosum. She initially was treated with colchicine 0.6 mg 3 times daily and valacyclovir 1 g daily for prophylactic treatment of orogenital herpes reactivation. She was referred for ophthalmologic evaluation for possible ocular involvement. On her subsequent visits over the following 9 months, she reported less frequent episodes of oral mucosal ulcerations; however, she continued to experience new painful and sensitive lesions on the bilateral lower extremities.

After a discussion with her rheumatologist and confirmation of negative purified protein derivative (tuberculin) status, the patient initially was started on prednisone 10 mg daily and cyclosporine A 50 mg daily. The dosages were increased incrementally to prednisone 20 mg daily and cyclosporine A 150 mg daily. Serum urea nitrogen and creatinine level with basic metabolic panel and complete blood cell count were monitored monthly and were reported within reference range. Blood pressure also was monitored monthly. The lesions on the patient's lower extremities considerably improved on this regimen; however, she developed frequent flares of oral and vaginal ulcerations. The patient also developed hypertension, change in vision, and an episode of left eye edema 3 months following the initiation of prednisone and cyclosporine A therapy. The patient received an ophthalmologic evaluation and was instructed by the ophthalmologist to decrease the prednisone dosage. The patient was maintained on cyclosporine A 150 mg daily and felodipine 5 mg was initiated. Prednisone was discontiued and prednisolone was started at 8 mg daily. With the adjusted oral corticosteroid dosage, the patient experienced uncontrolled oral and vaginal ulcerations and painful sensitive lower extremity lesions bilaterally. Therefore, the use of infliximab was considered. After discussing with the patient the risks and benefits of infliximab and consulting with her rheumatologist, she was started on infliximab 5 mg/kg intravenous infusion at weeks 0, 2, and 6, and every 8 weeks thereafter. The patient reported rapid improvement of the lower extremity lesions and disappearance of both the oral and vaginal ulcerations shortly after the initiation of infliximab. She remained free of tender lesions of the lower extremity and with occasional mild breakthrough oral ulcerations for the first 2 years. Subsequently, she developed more frequent oral ulcerations with arthritis. She was started on methotrexate 7.5 mg weekly, prednisone 5 mg daily, and the frequency of infliximab was changed from every 8 weeks to every 6 weeks with resolution of joint pain and oral ulcerations.

Comment

Behçet disease is a chronic recurrent inflammatory disease with multisystemic concerns including orogenital ulceration; skin lesions; intraocular inflammation with uveitis and retinal vasculitis; and less commonly symptoms involving the skeletal, vascular, gastrointestinal, central nervous, pulmonary, and cardiovascular systems. Oral ulcers usually are the initial symptom of this disease. Ocular involvement has been found in approximately 50% to 70% of patients with Behçet disease, which has led to blindness in 20% to 25% of

Lists of Laboratory Workup to Identify Possible Infectious, Autoimmune, and Inflammatory Etiologies

Laboratory Test	Value	Reference Range
Comprehensive metabolic panel	All within reference range	
Complete blood cell counts	All within reference range, except mildly elevated PLT of $457\times10^3/\mu L$	PLT, $140–400\times10^3/\mu L$
Antinuclear antibody	Negative	Negative
Rheumatoid factor	9 IU/mL	<14 IU/mL
C-reactive protein	0.2 mg/dL	<0.8 mg/L
Ferritin	14 ng/mL	10–154 ng/mL
DNA antibodies (double stranded)	<30	Interpretation: <30, negative; 30–60, low positive; 61–200, positive; >200, strong positive
Rapid plasma reagin test	Nonreactive	Nonreactive
SS-A antibody	≤1.00	Interpretation: ≤1.00, negative
SS-B antibody	≤1.00	Interpretation: ≤1.00, negative
Cardiolipin antibody (IgA)	<10 APL	Interpretation: <10 APL, negative
Cardiolipin antibody (IgG)	<10 GPL	Interpretation: <10 GPL, negative
Cardiolipin antibody (IgM)	<10 MPL	Interpretation: <10 MPL, negative
Lyme disease antibody	0.57 LIV	Interpretation: 0.00–0.99 LIV, negative
Smith antibody, EIA	≤1.00	Interpretation: ≤1.00, negative
Smith/ribonucleoprotein antibodies	≤1.00	Interpretation: ≤1.00, negative
Antimyeloperoxidase antibody	<6 U/mL	Interpretation: <6 U/mL, negative
Antiproteinase-3 antibody	<6 U/mL	Interpretation: <6 U/mL, negative
Thyrotropin	1.96 mIU/L	0.4–5.5 mIU/L
Hepatitis A IgM viral antibody	Nonreactive	Nonreactive
Hepatitis B surface antigen	Nonreactive	Nonreactive
Hepatitis B core IgM antibody	Nonreactive	Nonreactive
Hepatitis C viral antibody	Nonreactive	Nonreactive
Serum electrophoresis (protein)	Normal protein pattern	
Albumin	4.14 g/dL	3.5–4.7 g/dL
α_1-Globulin	0.19 g/dL	0.1–0.3 g/dL
α_2-Globulin	0.70 g/dL	0.5–1.0 g/dL

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Table (continued)

Laboratory Test	Value	Reference Range
Serum electrophoresis (protein)(continued)		
β-Globulin	1.06 g/dL	0.8–1.4 g/dL
γ-Globulin	1.42 g/dL	0.6–1.6 g/dL
Serum immunoglobulins		
IgG	1191 mg/dL	694–1618 mg/dL
IgA	308 mg/dL	81–463 mg/dL
IgM	248 mg/dL	48–271 mg/dL

Abbreviations: PLT, platelet count; SS-A, Sjögren syndrome antigen A; SS-B, Sjögren syndrome antigen B; APL, IgA phospholipid units; GPL, IgG phospholipid units; MPL, IgM phospholipid units; LIV, lyme index value; EIA, enzyme immunoassay.

affected patients.[2] The management of patients with Behçet disease involves various subspecialty care.

This condition is strongly linked to the HLA-B51 allele that is found predominantly in patients from countries along the ancient Silk Road, from Japan to the Middle East and the Mediterranean basin. The incidence of Behçet disease is greater in women in Japan and Korea. However, in the Middle East the incidence is higher in men compared to women. The peak age is in the second and third decades of life.[3]

The etiology of Behçet disease remains unknown. An infectious process (viral [eg, herpes simplex virus, hepatitis C virus, *Parvovirus* B19] or bacterial [eg, streptococcus]) initially was considered, but subsequent evidence failed to support this assumption.[4] Environmental factors also may be of etiologic relevance. In genetically predisposed individuals, there is evidence suggesting that microbial heat shock protein produced by normal flora of the mucosal tract (eg, *Streptococcus sanguis*) cross-reacts with the oral mucosal antigen, upregulates the expression of γδ T cells, and induces an immunologic hyperreactivity reaction.[5-7]

Vascular injuries, neutrophil hyperactivity, and autoimmune responses are characteristics of Behçet disease.[8] The pathogenesis appears to be linked to various cytokines derived from helper T cell T_H1, either via spontaneous and/or induced overexpression of tumor necrosis factor α (TNF-α) and various interleukins.[9] The elevated cytokine level activates neutrophils. Neutrophils interact with the circulating immune complex and trigger an autoimmune response that corresponds to the inflammatory reaction and various vascular injuries.[8]

There is no specific diagnostic test for Behçet disease; diagnosis is based on clinical impression of multiple systemic symptoms matching the criteria described in International Study Group guidelines, and exclusion of other possibilities. The criteria include recurrent oral ulcers observed at least 3 times in 12 months, plus any 2 of the following: (1) recurrent genital ulcers; (2) ophthalmologic involvement including anterior or posterior uveitis, cells in the vitreous fluid on slit lamp examination, or retinal vasculitis; (3) cutaneous lesions such as erythema nodosum or pseudofolliculitis; or (4) positive pathergy test as interpreted by the physician.[1]

In the course of Behçet disease, painful oral ulcerations frequently are the initial clinical finding. Oral ulcerations can sometimes precede other manifestations over a number of years. Lesions appear with well-defined, round, erythematous borders with an ulcerated surface covered with fibrinous pseudomembrane. The lesions heal in 10 to 14 days without scarring. Lesions in the genital area are similar to the oral type but usually have larger, deeper, and irregular margins with scar formation after resolution.

Ocular involvement affecting the anterior segment includes iridocyclitis, uveitis, cataract, and glaucoma, and posterior segment involvement includes vasculitis, vitreitis, retinitis, panuveitis, retinal edema, macular degeneration, venous or arterial occlusion, disk edema, and retinal detachment.[10] Patients with ocular manifestations frequently report blurry vision, excessive lacrimation, eye pain, photophobia, and periglobal hyperemia. Anterior uveitis generally subsides spontaneously, but recurrent episodes lead to irreversible

structural changes including deformity of the iris and secondary glaucoma. Recurrent explosive involvement of vascular occlusive disease of the retina may lead to blindness. During the acute phase of ocular manifestation, an ophthalmologic evaluation in the posterior segment can reveal hemorrhagic and exudative retinal lesions and a cellular infiltration in the vitreous humor. Fluorescein angiography can be used to identify retinal vascular damage, even during remission.

Erythema nodosum–like lesions often occur on the anterior aspects of the lower extremities and are commonly seen in female patients. Painful lesions on the lower extremities, sometimes with ulceration, usually spontaneously resolve but may result in hyperpigmentation. In male patients, pseudofolliculitis and acneform nodules are observed with involvement on the back, face, neck, and the hairline, especially in patients who are not taking glucocorticoids.[8]

Vasculitis is the major pathologic process in Behçet disease with the involvement of either veins or arteries, or both in approximately 7% to 38% of patients. Superficial thrombophlebitis and deep vein thrombosis are characteristic venous manifestations affecting the lower extremities.[11] Occlusion of major veins and arteries from thrombosis often causes bleeding, infarction, organ failure, and restricted movement of the arms and legs. Aneurysms may develop with potentially fatal consequences. Behçet disease can be distinguished from vasculitis-associated diseases such as systemic lupus erythematosus and polyarteritis nodosa. Serologically, most patients are negative for antinuclear antibody, antineutrophil cytoplasmic antibodies, and antiphospholipid antibody.[12]

Arthritis develops in 1 or more joints in approximately 50% of Behçet patients. Knee joints are the most frequently affected, followed by the wrists, ankles, and elbows.

Gastrointestinal tract involvement may affect the ileocecal region and less commonly the large intestines, causing abdominal pain, diarrhea, melena, and sometimes perforation. A positive pathergy test can rule out Crohn disease or inflammatory bowel disease.

Neurologic involvement in Behçet disease is rare but can lead to serious manifestations such as central nervous system neuro-Behçet syndrome, intra-axial neuro-Behçet syndrome, or cerebral venous sinus thrombosis. Younger patients usually are affected and present with acute or subacute brainstem syndrome or hemiparesis. Complications from treatment of Behçet disease with cyclosporine A can cause central nervous system neurotoxicity. Neuropathy may develop from treatment with thalidomide.[13]

Management of Behçet disease predominately consists of symptomatic relief and prevention of irreversible vital organ damage. Therapeutic agents such as colchicine and thalidomide are used to treat mucocutaneous lesions.[14,15] Systemic immunosuppressive agents such as azathioprine, methotrexate, cyclosporine A, cyclophosphamide, mycophenolate mofetil, and chlorambucil are used as monotherapy or combined with corticosteroids when there are frequent flares or vital organ involvement is suspected.[16] Interferon alfa or tumor necrosis factor inhibitors such as etanercept and infliximab also are used for recalcitrant disease that is unresponsive to systemic immunosuppressive agents or if adverse effects to the initial treatment regimen develop.[17,18]

Because of the elevated levels of circulating serum TNF-α in patients with Behçet disease and its essential role in inflammatory reaction, therapeutic agents targeting TNF-α activity may be effective in moderating disease severity.[18,19]

Infliximab, an anti–tumor necrosis factor agent, is a chimeric IgG monoclonal antibody that directly binds to soluble and cell-associated TNF-α. It inhibits proinflammatory cytokine IL-1 and IL-6 production by monocytes and macrophages. The decreased circulating level of IL-1 and TNF-α limits the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) present on the membrane surface of the leukocytes and endothelial cell.[20] The low concentration of ICAM-1 and VCAM-1 reduces the binding of leukocytes to endothelial cells and transmigration of leukocytes into the tissues. Infliximab has been used with success to treat other T_H1-mediated disorders such as rheumatoid arthritis, ankylosing spondylitis, and Crohn disease.

Several case reports have documented patients receiving infliximab treatment of conditions associated with Behçet disease such as uveitis, intractable orogenital ulceration, and/or cutaneous lesions (off-label use).[21,22] Infliximab also has been used when patients are refractory to other immunosuppressive therapy such as cyclosporine A or etanercept.[21,23] Patients usually respond rapidly soon after the initiation of therapy and undergo remission of various manifestations of Behçet disease. These publications have supported the role TNF-α plays in the inflammatory process of Behçet disease.

Our case is another example of treatment failure with conventional therapy as well as a combination of corticosteroid and an immunosuppressive agent (cyclosporine A) in a recalcitrant Behçet patient. She became symptom free for the first 2 years soon after receiving infliximab. She subsequently started to develop arthritis and painful oral ulcerations. Several studies have demonstrated a decrease in clinical efficacy with the long-term use of infliximab, which may be due to the production of anti-infliximab antibodies or an increased systemic clearance.[24-26] The infliximab trough is lowered in

patients who have detectable anti-infliximab antibodies before the next infliximab treatment. The breakthrough oral ulcers and worsening joint pain our patient experienced probably were the result of the production of anti-infliximab antibodies and/or a decrease in the level of available infliximab circulating in the system. Multiple studies have indicated that the suboptimal clinical response can be overcome by either increasing the treatment dose of infliximab, decreasing the dosage interval, or adding low-dose methotrexate concomitantly with the use of infliximab.[24-27] The combination of infliximab and methotrexate appears to reduce inflammatory disease activity as well as promote immunologic tolerance to infliximab.[27]

Infliximab should be considered as a possible therapeutic option in the management of refractory Behçet disease, especially when conventional immunosuppressive therapy fails to keep this disease under control. Combination therapies with infliximab and methotrexate should be considered when clinical efficacy of infliximab monotherapy declines.

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