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【 CASE REPORT 】

Nasal Mucosal Manifestation of Behçet's Disease

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Abstract:
Behçet's disease (BD) is a multisystem inflammatory condition that rarely affects the nasal mucosa. We report the case of a 25-year-old man presenting with prolonged fever, bilateral rhinalgia, and nasal obstruction, who was subsequently diagnosed with nasal ulcers associated with BD. These ulcers resolved along with the systemic symptoms following treatment with colchicine, apremilast, and prednisolone. Although there is no specific treatment strategy for nasal mucosal lesions in BD, standard systemic therapies may be effective. This case highlights nasal mucosal involvement as a rare but important manifestation of BD, emphasizing the importance of thorough evaluation and consideration of nasal symptoms for the diagnosis and treatment.

Key words: Behçet's disease, nasal mucosal manifestation, apremilast, colchicine, prednisolone

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Introduction

Behçet's disease (BD) is a multisystem inflammatory condition characterized by recurrent oral and genital ulcers, cutaneous lesions, and ocular involvement (1). Although BD can affect multiple organs, nasal involvement is not typically considered a feature of this disease. However, a cross-sectional study in Iran reported nasal involvement in 7.8% of patients with BD presenting with symptoms such as dysosmia, nasal obstruction, and ulcers (2). Nasal septum perforation has also been reported as a severe complication (3). These findings suggest that nasal mucosal involvement is uncommon but may be overlooked. Despite advancements in the treatment of systemic and mucocutaneous manifestations, further research is needed to develop targeted therapies, specifically for nasal lesions in patients with BD.

We herein present a rare case involving a patient with BD and nasal mucosal ulcers who demonstrated significant improvement following combination therapy with colchicine, apremilast, and prednisolone. This approach may serve as a potential management option for nasal mucosal manifestations of BD.

Case Report

A 25-year-old Japanese man presented with a one-month history of fever. His illness began with fever, cough, and a sore throat. About two weeks before admission, he developed multiple painful ulcers on his lips and gingiva, followed by the appearance of painful rashes on his trunk and lower legs, and genital ulcers, approximately one week before admission. The patient consulted a local urologist for the genital ulcers. Although sexually transmitted infections were suspected, serological test results were negative for syphilis, herpes simplex virus IgM and IgG, and human immunodeficiency virus (HIV) antibodies.

Five days before admission, the patient experienced bilateral nasal obstruction. The patient visited a local internal medicine clinic because of fever and upper respiratory symptoms. Antigen tests for coronavirus disease 2019 (COVID-19) and influenza were negative, and the patient was treated symptomatically for a presumed upper respiratory tract infection. Despite these interventions, his symp-

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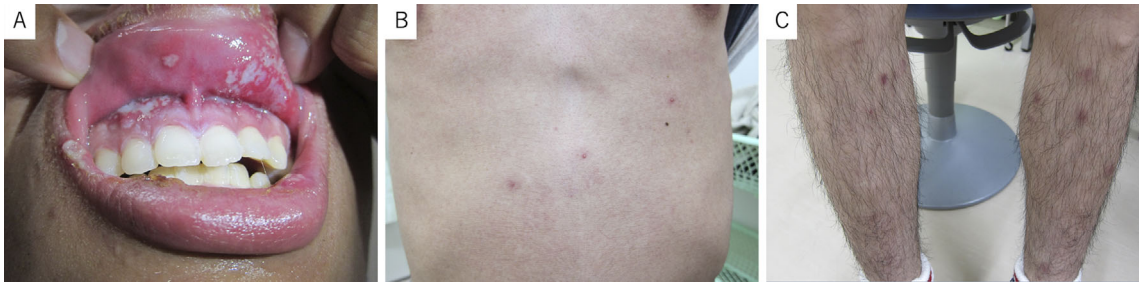

Figure 1. Painful ulcers on the upper and lower lips and gingiva (A), folliculitis-like rashes on the trunk (B), and erythema nodosum on both lower legs (C) observed during physical examination.

toms persisted. Subsequently, the patient visited a general hospital. However, owing to limitations in diagnostic capabilities, he was referred to our institution for further evaluation and management of suspected sexually transmitted infections.

The patient had a medical history of panic disorder and pollen allergies. His family history was unremarkable, with no known hereditary or significant medical conditions. He reported no known allergies to food or medications. His regular medications included sertraline hydrochloride (50 mg) for panic disorder and bepotastine besilate (20 mg) for pollen allergies. He worked as a construction-site supervisor. He reported a history of sexual activity with his partner including protected intercourse and oral sex.

Upon admission, examinations revealed the following: body temperature, 37.7°C; blood pressure, 100/66 mmHg; heart rate, 136 beats/min; respiratory rate, 20 breaths/min; and oxygen saturation, 97% on room air. A physical examination revealed painful ulcers on the upper and lower lips and gingiva (Fig. 1A). Folliculitis-like rashes were observed on the trunk (Fig. 1B). Genital examination revealed painful ulcers on the penis glans and scrotum. Examination of the extremities revealed erythema nodosum in both the lower legs (Fig. 1C). Redness and tenderness were observed in both the lateral malleoli. Tenderness was observed in the metacarpophalangeal joint of the left index finger.

Blood tests revealed elevated levels of inflammatory markers, including white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level (Table). Elevated liver enzyme levels were also observed on admission. Serological testing was negative for antinuclear antibodies, myeloperoxidase-antineutrophil cytoplasmic antibodies, and proteinase 3-antineutrophil cytoplasmic antibodies. Computed tomography (CT) of the neck, chest, abdomen, and pelvis revealed no significant lymphadenopathy. Screening for sexually transmitted infections, including syphilis, herpes, and HIV, yielded negative results, which was consistent with the previous results from the urology clinic. Genetic testing revealed that the patient was positive for human leukocyte antigen (HLA)-A31 and HLA-B51, which are genetic markers associated with BD.

Esophagogastroduodenoscopy (EGD) and a nasal endoscopic examination were performed to evaluate the patient's sore throat and bilateral nasal obstruction. EGD revealed ulcers near the epiglottis in the hypopharynx and at the esophageal entrance. Nasal endoscopic examination revealed multiple ulcers in both nasal vestibules (Fig. 2). Lower gastrointestinal endoscopy revealed no lesions, including ulcers, in the ileocecal region. An ophthalmologic examination revealed no significant findings such as uveitis. Although a formal pathergy test was not performed, erythema was not observed at the venipuncture site. Brain magnetic resonance imaging revealed no abnormalities, and a cerebrospinal fluid analysis revealed a normal cell count and unremarkable interleukin-6 levels. The patient exhibited three major symptoms: recurrent oral ulcerations, skin lesions, and genital ulcerations with no ocular involvement. Based on the International Study Group (ISG) for BD classification (4) and International Criteria for BD (ICBD), the patient was diagnosed with BD (5). Furthermore, his presentation of three major symptoms without ocular lesions fulfilled the Japanese Ministry of Health, Labour and Welfare criteria for incomplete-type BD (6). Although the patient did not report significant fatigue, it was highly likely due to his systemic symptoms. Based on the findings at the time of admission, the Behçet's Disease Current Activity Form (BDCAF) score at admission was 6, indicating high disease activity (7).

Colchicine therapy (1.0 mg/day) was initiated on the first hospitalization day. On the third day, the colchicine dose was increased to 1.5 mg/day. Although colchicine therapy resulted in partial symptomatic improvement, serum levels of inflammatory markers remained elevated. On the 11th day of hospitalization, apremilast was initiated and gradually titrated to 60 mg/day for oral and nasal ulcerations, along with prednisolone at a dose of 10 mg/day to manage joint symptoms. Following these adjustments, the serum levels of the inflammatory markers decreased. The patient was discharged on the 17th day, with follow-up scheduled at our outpatient department. On the 31st day after admission, repeat EGD and nasal endoscopic examinations were performed. EGD showed marked improvements in the ulcers in the hypopharynx and esophageal entrance compared with the initial findings. Similarly, nasal endoscopic examination revealed significant improvement in the ulcers of both nasal vestibules (Fig. 3). Based on the therapeutic effects on nasal lesions, we concluded that the nasal mucosal lesions were associated with BD.

The clinical symptoms identified at admission, including

Table. **Blood Test Results on Admission.**

Laboratory parameters	On admission	Reference range
Complete blood count		
WBC (/μL)	11,580	3,300-8,600
Neutrophil (%)	85.6	40.0-70.0
Lymphocyte (%)	9.6	16.5-49.5
Monocyte (%)	4.2	2.0-10.0
Eosinophil (%)	0.4	0.0-8.5
Basophil (%)	0.1	0.0-2.5
RBC ($\times10^4$/μL)	477	4.35-5.55
Hb (g/dL)	14.9	13.7-16.8
Platelet ($\times10^4$/μL)	25.6	15.8-34.8
ESR (mm/h)	85	2-10
Biochemistry		
Alb (g/dL)	4.4	4.1-5.1
AST (U/L)	75	13-30
ALT (U/L)	49	10-42
LDH (U/L)	176	124-222
Sodium (mmol/L)	139	138-145
Potassium (mmol/L)	4.1	3.6-4.8
Chloride (mmol/L)	98	101-108
BUN (mg/dL)	9.5	8.0-20.0
Cre (mg/dL)	0.82	0.65-1.07
CRP (mg/dL)	8.9	≤0.15
Serological		
sIL-2R (U/mL)	504.2	156.6-474.5
T-SPOT.TB	Negative	
STS	Negative	
TPHA	Negative	
VZV-IgM	Negative	
VZV-IgG	Positive	
HSV-IgM	Negative	
HSV-IgG	Negative	
HIV antibody	Negative	
Antinuclear antibodies	<1:40	<1:40
RF (IU/mL)	<5.0	<16
PR3-ANCA (IU/mL)	<0.60	<2.00
MPO-ANCA (IU/mL)	0.29	<3.50

Alb: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Hb: hemoglobin, HIV antibody: human immunodeficiency virus antibody, HSV-IgG: herpes simplex virus immunoglobulin G, HSV-IgM: herpes simplex virus immunoglobulin M, LDH: lactate dehydrogenase, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3 anti-neutrophil cytoplasmic antibody, RBC: red blood cell, RF: rheumatoid factor, sIL-2R: soluble interleukin-2 receptor, STS: serologic test for syphilis, TPHA: *Treponema pallidum* hemagglutination assay, VZV-IgG: varicella zoster virus immunoglobulin G, VZV-IgM: varicella zoster virus immunoglobulin M, WBC: white blood cell

oral and genital ulcers, skin lesions, and joint manifestations, also improved, with a BDCAF score of 1-2. Liver enzyme levels improved in parallel with the clinical symptoms. On day 49 post-discharge, his alanine aminotransferase (ALT) level normalized to 34 U/L, and his aspartate

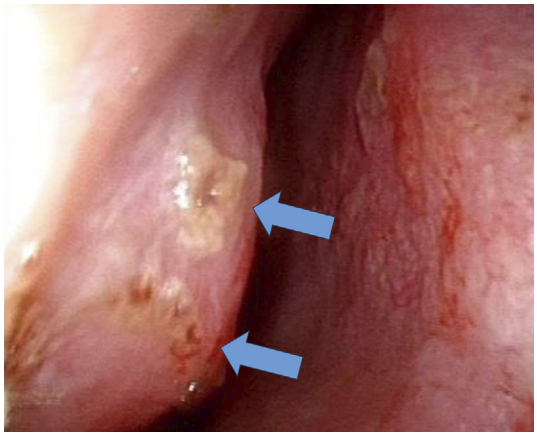

Figure 2. **The nasal endoscopic examination showed multiple ulcers in both nasal vestibules (shown by arrows).**

aminotransferase (AST) level decreased to 48 U/L. At a follow-up visit on day 216 post-discharge, the patient reported a one-month history of loose stool and abdominal pain. Because adverse effects of colchicine were suspected, the dose was reduced to 1.0 mg/day. The gastrointestinal symptoms resolved by day 251. On day 287 post-discharge, laboratory tests showed further improvement, with an ALT level of 21 U/L and AST level of 38 U/L, continuing the trend toward normalization. The AST level remained slightly above the normal range throughout the course. Following discharge, prednisolone was gradually tapered from 10 mg/day to 0 mg/day over the course of approximately 14 months. Apremilast was continued at a dose of 60 mg/day, and no recurrence of nasal mucosal lesions was observed during follow-up. Throughout the maintenance phase with apremilast, the BDCAF score remained stable at 0-1. No major adverse effects were observed with prednisolone or apremilast.

Discussion

BD is characterized by recurrent oral aphthous ulcers and various systemic manifestations, including those affecting the skin, mucosa, and joints, as observed in this case. Gastrointestinal, cardiovascular, and neurological manifestations may also occur (1). Mucocutaneous lesions are the most common symptom upon onset or at any stage of BD, with oral ulcers observed in 92-100% of patients and genital ulcers in 57-93% of patients (8).

Nasal involvement is uncommon, but possible in BD. Dysosmia and nasal obstruction are common; however, only 2 of 400 patients have nasal ulcers (2). Another study showed that approximately half of patients had nasal mucosal manifestations (9). These conflicting results make it difficult to accurately describe the frequency of nasal mucosal manifestations in BD, and these symptoms may not be properly recognized. Previous reports have indicated that nasal manifestations of BD can lead to severe conditions such as nasal septum perforation (3), which can significantly affect the pa-

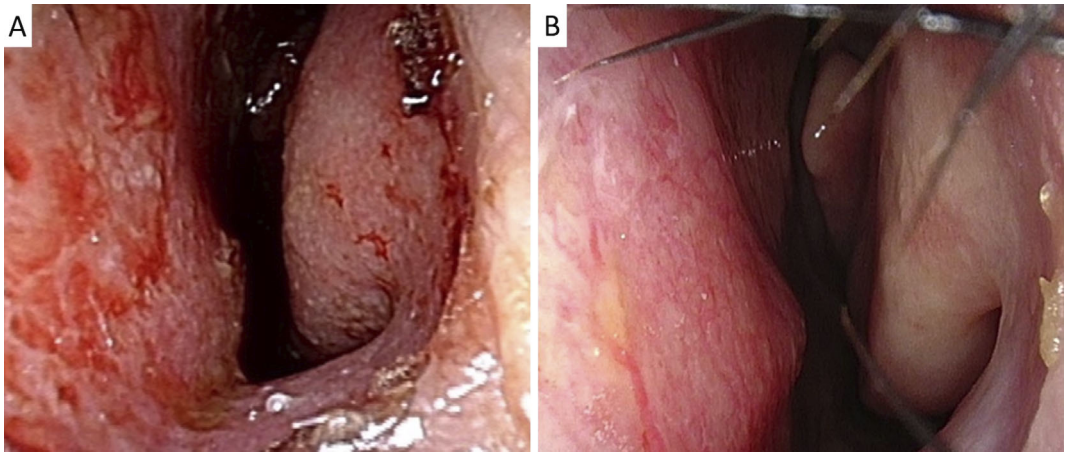

Figure 3. **Nasal mucosal ulcers improved from admission (A) to one month after treatment (B).**

tient's quality of life.

Nasal mucosal manifestations are relatively uncommon and are therefore not included in the diagnostic criteria of the ISG, ICBD, or the Japanese Ministry of Health, Labour and Welfare (4-6), which focuses on more common symptoms. However, nasal mucosal manifestations may be more common in patients with BD than previously believed, suggesting that more detailed examinations should be performed. In patients presenting with nasal symptoms, it is crucial to perform thorough nasal examinations using advanced tools such as nasal endoscopy (10).

A nasal endoscopic examination enables the direct visualization of the nasal mucosa. It allows clinicians to identify subtle abnormalities such as ulcers, crusting, or other signs of inflammation that might otherwise be missed during routine physical examinations. Other differential diagnoses of nasal mucosal manifestations, such as vasculitis (eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis), systemic lupus erythematosus, and lymphoma were excluded (10).

There are no established treatment strategies specifically targeting nasal mucosal involvement in BD, because isolated nasal symptoms are insufficient for the diagnosis and typically occur alongside other systemic or mucocutaneous manifestations. Most therapeutic approaches for BD focus on managing systemic disease manifestations by suppressing the underlying inflammatory processes. The treatment of mucocutaneous lesions in BD requires a personalized and stepwise approach.

Apremilast, a small-molecule phosphodiesterase 4 inhibitor, has been shown to reduce oral ulcers more effectively than placebo, although adverse events, such as diarrhea, nausea, and headache, have been reported in the RELIEF study (11). A reduction in oral ulcers and overall disease activity, along with a favorable safety profile regarding adverse events, has been demonstrated in a Japanese subgroup (12, 13). Considering the clinical course of the present patient, this treatment may also be a viable option for managing patients with nasal mucosal lesions.

In the present case, the disease activity was well controlled after the initiation of apremilast and prednisolone, following a partial response to oral colchicine. However, distinguishing between the individual effects of apremilast and prednisolone when addressing nasal manifestations is difficult. The absence of a relapse in nasal mucosal symptoms, even after tapering prednisolone, suggests that apremilast may be effective in improving the symptoms. It remains challenging to determine whether apremilast is directly effective against nasal manifestations without conducting prospective trials. However, considering that apremilast is a reasonable treatment option for mucosal manifestations, its therapeutic potential should be considered. At the very least, controlling the overall disease activity may lead to the improvement of nasal mucosal lesions. Although pre-onset laboratory data were unavailable, the liver enzyme levels gradually normalized during treatment, suggesting that the elevation was attributable to BD. Persistent mild elevation in AST levels may represent the baseline level of the patient.

In conclusion, this case highlights the importance of recognizing nasal mucosal manifestations as rare but clinically significant symptoms of BD. This underscores the critical need for thorough assessment of nasal symptoms as part of a comprehensive evaluation of systemic diseases. This case suggests that apremilast is potentially useful for the treatment of nasal lesions in BD.

Written informed consent was obtained from the patient for this case report.

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

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