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Clinical Activity of Behcet's Disease Associated with SARS-CoV-2 and Herpes Simplex Virus: Insights from Three Case Reports

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Introduction: The Behçet's Disease Current Activity Form (BDCAF) is crucial for monitoring the progression and treatment efficacy of Behçet's Disease (BD), an autoimmune disorder that can be triggered or exacerbated by viral infections. Herpes simplex virus type 1 (HSV-1) has long been recognized as a potential trigger for BD, as it can induce systemic inflammation and exacerbate symptoms. In contrast, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has recently emerged and may also initiate or worsen BD symptoms. This report examines three BD cases with oral manifestations specifically triggered by HSV-1 and SARS-CoV-2, comparing their clinical activity and treatment responses.

Case: Three female patients, aged 29, 24, and 41 years, presented to the Oral Medicine Department with complaints of canker sores, along with genital and skin lesions and red eyes. Intraoral examination showed ulcerative, erosive, and white plaque lesions throughout the oral mucosa. The first patient was confirmed to have COVID-19 by the SARS-CoV-2 RNA test. The second and third patients had a two-year history of recurrent oral ulcerations with reactive IgG anti-HSV-1 tests. All patients were diagnosed with BD according to the International Criteria for Behcet's Disease. The BDCAF measurements were conducted, showing a BD activity index score of 4 for the COVID-19-positive patient, while scores of 6 and 7 were recorded for the other two patients with seropositive HSV-1.

Case Management: Medications provided include corticosteroid, antimetabolite, analgesic, antiviral, antifungal, antiseptic mouthwash, and multivitamin. All patients showed good clinical improvement after treatment.

Conclusion: The BD activity index scores of a BD patient with COVID-19 were lower than those with HSV-1 infection. This difference may be due to the recent SARS-CoV-2 infection in the patient, whereas reactivation of chronic latent HSV-1 in the other patients likely contributed to a longer history of clinical manifestations, resulting in increased disease activity.

Keywords: autoimmune disease, Behcet's disease, SARS-CoV-2, HSV-1

Introduction

Behcet's disease (BD) was named after a Turkish dermatologist, Hûlusi Behçet, in 1937.[1,2] BD is a rare systemic vasculitis disorder, with a worldwide prevalence ranging from 3.3 to 31.8 cases per 100,000 people.[3] The incidence is highest along the ancient silk route connecting Europe and Asia, with Turkey being the epicenter. BD commonly occurs between the ages of 20 and 40, and the clinical features are generally more severe in young male patients.[1] The hallmark of BD is a self-limiting inflammation with relapses and remissions. Recurrent oral and genital ulceration, skin lesions (erythema nodosum and acneiform pustular lesions), uveitis, arthritis, and gastrointestinal, neurological, and cardiovascular involvement are clinical features of this disease.[1,2,4]

The etiology of BD remains unclear.[3,5] The pathogenesis of BD is often described as a genetic disease provoked by an infectious agent or trauma. This condition activates the immune system, resulting in inflammation and clinical symptoms.[1]

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Several studies have found that the HLA-B51 gene is linked to the occurrence of BD in different populations.[6] This relationship between genetic susceptibility and environmental factors suggests that BD may reflect a range of immune-mediated disorders driven by particular antigens. Recent breakthroughs in virology and immunology have identified various types of viral DNA from BD patients, including the herpes simplex virus (HSV), which has been recognized as a potential contributing factor due to its ability to alter immune function. Research indicates that BD patients exhibit elevated levels of HSV-1 DNA and antibodies compared to healthy controls, suggesting a significant association between HSV infection and disease activity. However, the mechanisms by which HSV and other viral infections may trigger or exacerbate BD remain poorly understood.[3,7–9] Additionally, SARS-CoV-2, the virus responsible for Coronavirus disease 2019 (COVID-19), which has rapidly developed into a pandemic in many countries, has also been suspected of triggering autoimmune diseases, including BD.[10–12] The interplay between viral infections and genetic predisposition in the context of BD underscores the need for further research to elucidate the underlying mechanisms and potential therapeutic targets.

The diagnosis of BD was made based on clinical criteria due to the absence of pathognomonic diagnostics. Therefore, reliance on clinical presentation requires a comprehensive evaluation of the patient's symptoms and medical history. The International Team for Revision of International Criteria proposed a new set of criteria known as the International Criteria for Behcet's Disease (ICBD) in 2014 by giving two points for ocular lesions, oral aphthous, and genital ulcers, and one point for skin lesions, neurological manifestations, vascular manifestations, and a positive pathergy test. Patients with a total score of four points are considered to have BD. The ICBD has shown high diagnostic accuracy, with a sensitivity of 96.1% and specificity of 88.7% in adult patients. These data demonstrate the reliability of the criteria in differentiating BD from other conditions that may have similar symptoms. By using these standardized criteria, healthcare providers can improve early detection and ensure timely treatment of BD, ultimately resulting in better patient outcomes and a more consistent treatment approach.[1,9,13]

Behcet's disease cannot be cured, but it can be treated.[13] Measuring the clinical activity of the disease is an important part of BD management. The Behcet's Disease Current Activity Form (BDCAF) was used for this assessment. This instrument examines the history and clinical symptoms caused by BD in the last four weeks using the following 12 components: headache, oral aphthous, genital ulcers, skin erythema, skin pustules, arthralgia, arthritis, nausea/vomiting/abdominal pain, diarrhea with altered/frank blood per rectum, eyes, central nervous system, and major blood vessels. Each component is given a score of absent (0) or present (1). The BD activity index (BDCAF) is calculated by adding the scores of each component, with a maximum score of 12. A total score ≥ 2 is defined as active BD, whereas < 2 is defined as inactive BD.[2,14–16] These measurements can monitor the history and effect of therapeutic interventions in BD.[2,17] Dentists have an essential role in the detection, diagnosis, treatment, and follow-up of BD patients.[18] This report aimed to compare the clinical activity of three Behcet's Disease (BD) cases affecting the oral cavity, triggered by SARS-CoV-2 and HSV-1, to highlight the potential impact of viral infections on the progression and clinical management of the disease.

Case Presentation

Case 1

A 29-year-old woman came to the Oral Medicine Clinic with chief complaints of having a widespread white coating on her tongue and redness on her palate, which had caused her difficulty swallowing and eating for three days before her visit. These symptoms were accompanied by genital sores and redness in her eyes. The patient was a COVID-19 survivor. Intraoral examination revealed yellowish-white plaques that could be scraped off, leaving erythematous areas covering the entire dorsal surface of the tongue. Additionally, there were multiple ulcers ranging from 1 to 3 mm in diameter, surrounded by an erythematous halo, spreading across most of the dorsal surface of the tongue and the left and right buccal mucosa. Erosive lesions, multiple ulcers, and white plaques that could be scraped off, leaving erythematous areas, were also found from the palate to the oropharynx (Figure 1).

Based on the anamnesis and clinical examination, the working diagnoses were suspected BD post-COVID-19 and acute pseudomembranous candidiasis. The patient was referred to the Department of Dermatology and Venerology for a fungal smear examination and an ANA test. The result of the ANA Ro-06 dsDNA test was positive (homogenous weak positive), and the tongue smear showed positive gram-negative rods, gram-positive cocci, and yeast. The result of the pathergy test from the Department of Dermatology and Venereology was negative. The ICBD examination score was 6,

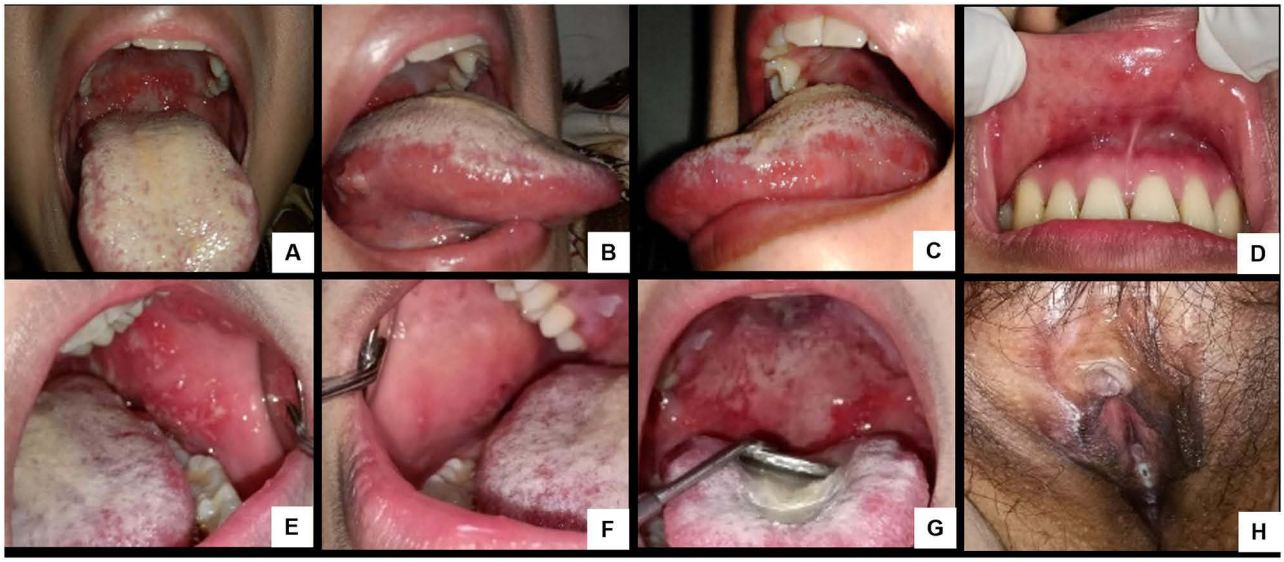

Figure 1 The clinical presentation of Behcet's disease in a 29-year-old woman during the initial visit. (**A**) White plaques and multiple ulcers on the dorsum of the tongue, also diffuse erythema affecting the soft palate and tonsillar area. (**B–F**) Multiple ulcers and erosive lesions on the lateral side of the tongue, upper labial mucosa, and buccal mucosa. (**G**) White plaques and erythematous lesions on the hard palate extended to the oropharynx. (**H**) Ulcers on the genital area.

which included 2 points for ocular lesions, 2 points for oral aphthous ulcers, and 2 points for genital ulcers. The definitive diagnosis of BD was established. The patient underwent multidisciplinary treatment by Oral Medicine Specialists and Dermatology and Venerology Specialists. The pharmacological therapy included methylprednisolone, calos 500 mg, vitamin B12, folic acid, nystatin oral suspension (100,000 IU), and povidone-iodine mouthwash. The patient was also educated to maintain oral hygiene, including brushing her teeth and tongue with a soft-bristled toothbrush.

After the first two weeks of follow-up, the patient reported a reduction in oral cavity complaints. Intra-oral examination still showed erythema throughout almost the entire oral cavity, but the white plaques on the palate had resolved. The previous therapy was continued. Significant progress was observed during the second and third follow-ups, eight weeks following the initial visit. Intra-oral examination showed the lesions had healed across nearly the entire oral cavity, although new ulcers had developed on the tongue. Genital lesions also showed improvement as well. The previous treatment was maintained. Two weeks after the last visit, the intraoral ulcers were nearly completely healed, as illustrated in Figure 2. The patient was advised to continue the medications, including methylprednisolone (tapering off), calos 500 mg, vitamin B12, and folic acid.

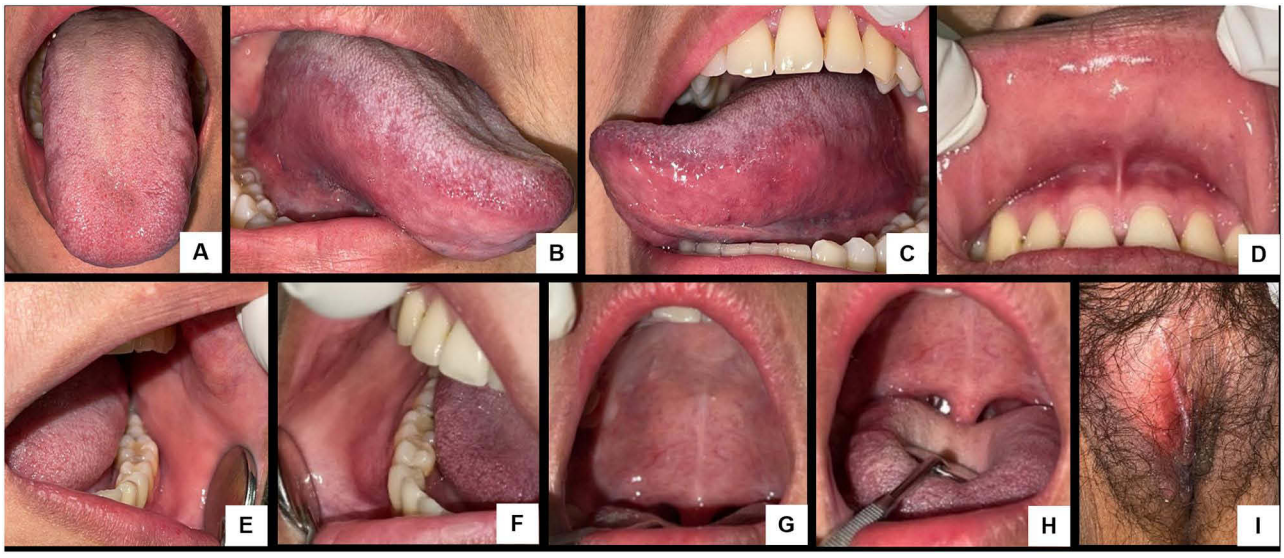

Figure 2 The clinical presentation after three months of treatment. (**A–I**) The oral mucosal lesions showed significant improvement and completely healed.

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The assessment of BD clinical activity was conducted using the BDCAF instrument following the establishment of the BD diagnosis. Scores for oral aphthous, genital ulcers, arthralgia, and eyes were all 1, while scores for headache, skin erythema, skin pustules, arthritis, nausea/vomiting/abdominal discomfort, diarrhea with altered or frank blood per rectum, central nervous system, and major vessels were all 0. The total BDCAF score was 4, indicating active BD. The patient provided written informed consent for the publication of this case report, including any accompanying images.

Case 2

A 24-year-old woman presented at the Oral Medicine Clinic with recurrent small, multiple, and intensely painful canker sores in her oral cavity. She also reported a widespread white coating on her tongue, leading to difficulty in eating over the past three days. Additionally, she experienced genital sores, dry and painful eyes when blinking, and skin ulcers that had persisted for the past two years. She has been taking dexamethasone at erratic doses during that time. Intraoral examination revealed multiple ulcers with yellowish-white bases, measuring 0.1 to 0.3 cm in diameter and of shallow depth, surrounded by an erythematous halo that spread across the dorsal surface of the tongue, as well as on the buccal and labial mucosa. Yellowish-white plaques that could be scraped off, leaving areas of erythema on the dorsal surface of the tongue, were also observed (Figure 3). The lateral and ventral sides of the tongue were difficult to assess.

Based on the anamnesis and clinical examination, the working diagnoses included suspected BD, recurrent intraoral herpes (RIH), and acute pseudomembranous candidiasis. The patient was advised to undergo a comprehensive laboratory examination, including a hematology test, human immunodeficiency virus (HIV) viral load test, IgG anti-HSV-1 test, vitamin D test, serum glutamic oxaloacetic transaminase (SGOT) test, serum glutamic pyruvic transaminase (SGPT) test, antinuclear antibody (ANA) test, and a pathergy test. A referral was made to the Department of Dermatology and Venereology to treat genital sores, and the patient's eye complaints were referred to the Eye Hospital for further evaluation.

Laboratory examination revealed increased levels of erythrocytes, leukocytes, monocytes, SGOT, and SGPT. The result of the HIV viral load test was not detected, the ANA test was non-reactive, and the IgG anti-HSV-1 was reactive at 163.3 U/mL. Additionally, the patient exhibited vitamin D deficiency, with a level of 4 ng/mL. The diagnosis from the

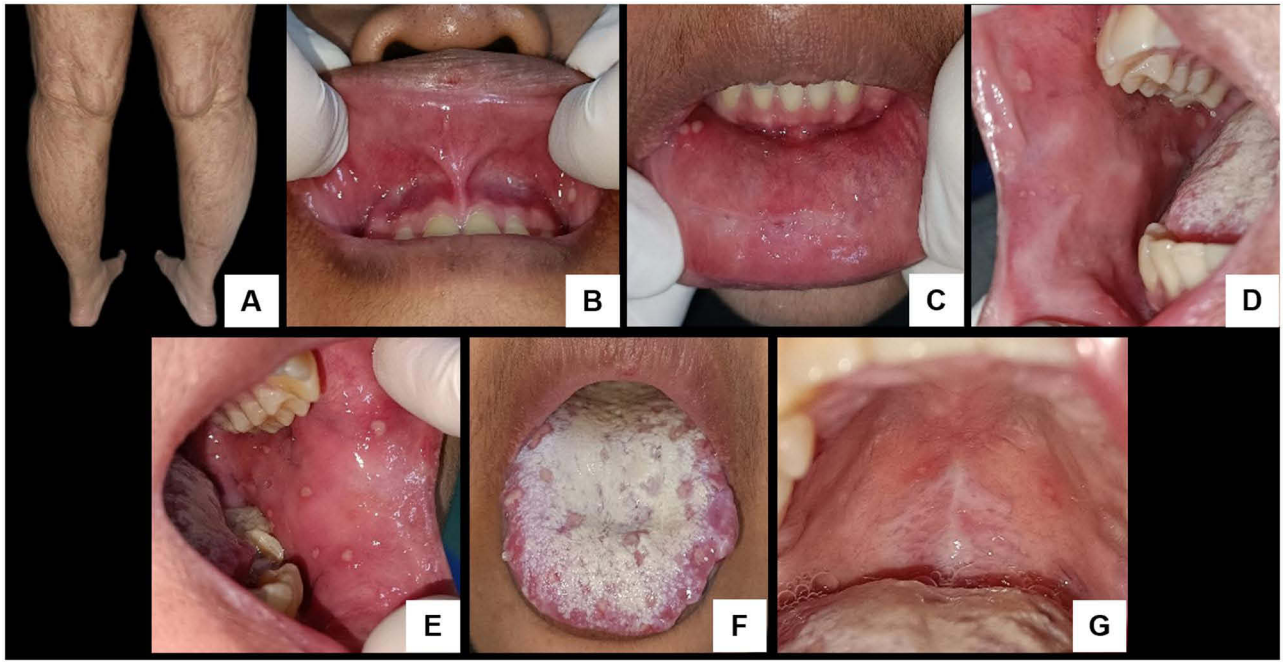

Figure 3 The initial visit presented the clinical manifestation of Behcet's disease in a 24-year-old woman. (**A**) Stretch marks on the skin of the legs due to long-term use of steroids. (**B–E**) Multiple ulcers on the upper labial, lower labial, right buccal, and left buccal. (**F**) White plaques and multiple ulcers on the dorsum of the tongue. (**G**) Multiple ulcers on the palate.

Eye Hospital indicated another cataract, suspected to be steroid-induced or a steroid responder. A clinical examination from the Department of Dermatology and Venereology resulted in an ICBD score of 7, with points allocated as follows: 2 for ocular lesions, 2 for oral aphthous ulcers, 2 for genital lesions, and 1 for skin lesions. The patient was prescribed methotrexate, beginning with a dose of 5 mg per week, which was later increased to 7.5 mg per week, and folic acid 500 mg, as directed by the Dermatology and Venereology Specialist. Treatment from the Department of Oral Medicine included povidone-iodine mouthwash, nystatin oral suspension (100,000 IU), vitamin D (5000 IU), multivitamins, oral acyclovir 400 mg, benzydamine hydrochloride lozenges, and instructions for maintaining oral hygiene.

After one week of follow-up, the patient still reported painful swallowing. An intraoral examination revealed ulcers throughout the oral cavity, although the white plaque on the dorsum of the tongue had improved. The previous treatments were continued, and paracetamol 500 mg was prescribed to manage the pain while swallowing. Noticeable improvement was observed at the second follow-up, one week after the initial visit, with most intraoral ulcers almost completely healed. However, new ulcers were found on the lateral side of the tongue, so treatments were maintained. Two weeks after the second visit, the intraoral ulcers were completely healed (Figure 4). The patient was advised to continue taking vitamin D (5000 IU) and multivitamins.

BD clinical activity was evaluated using the BDCAF instrument after the diagnosis of BD was confirmed. Scores of 1 were noted for headache, oral aphthous ulcers, genital ulcers, skin pustules, arthralgia, nausea/vomiting/abdominal pain, and eye involvement. The scores for skin erythema, arthritis, and diarrhea with altered or frank blood per rectum, central nervous system, and blood vessels were all 0. The total clinical activity index BD (BDCAF) score was 7, indicating active BD. The patient provided her informed consent for both the treatment and the publication of this case, including any accompanying images.

Case 3

A 41-year-old woman visited the Oral Medicine Clinic with a chief complaint of recurrent canker sores that had persisted for the past two years. The ulcers were accompanied by a skin rash characterized by fluid-filled blisters that were itchy and subsequently burst, leaving black marks. Additionally, she reported a sore wound in the vagina, blurred vision, and

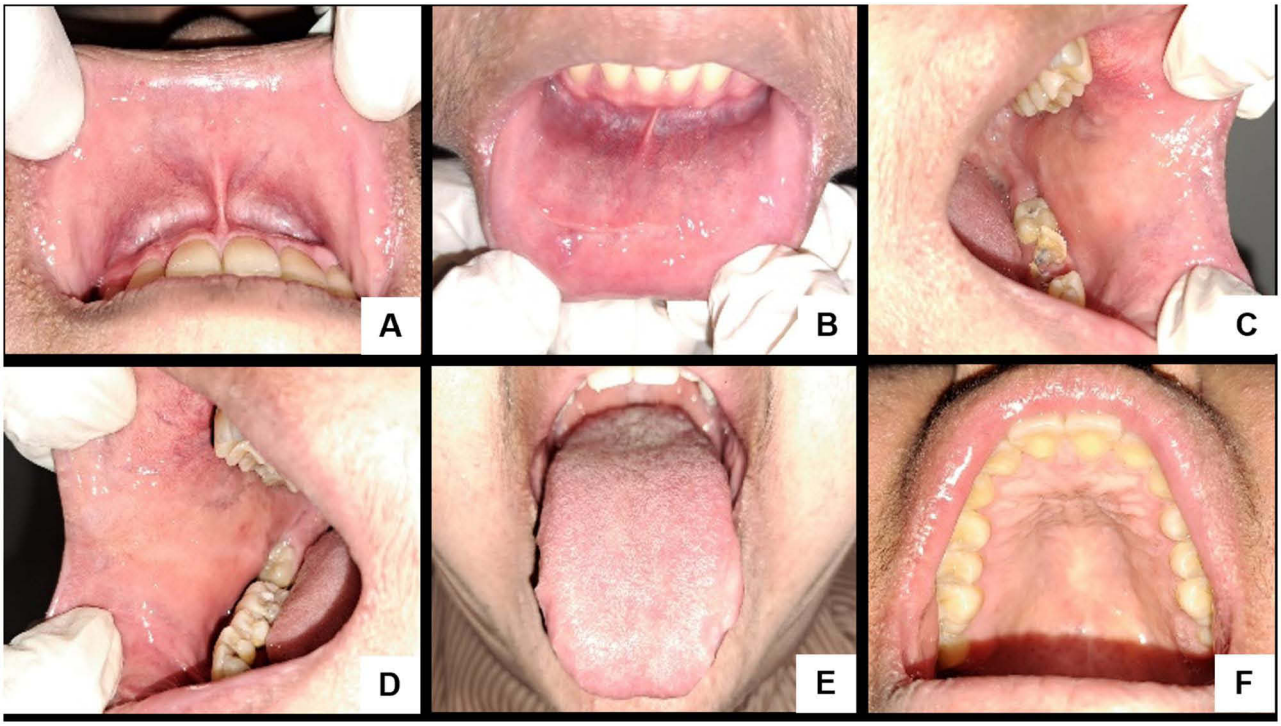

Figure 4 The clinical presentation at the last visit following one month of treatment. (**A–F**) The lesions observed throughout the oral mucosa showed significant healing, indicating a positive response to treatment.

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joint pain in the feet and hands. The extraoral examination revealed pale conjunctiva and scleral hyperemia in the left eye. Submandibular lymph nodes were palpable and sore, and the lips were dry and exfoliative. Furthermore, the intraoral examination showed multiple ulcers covered with a yellowish-white pseudomembrane, surrounded by erythematous areas on the dorsal and lateral sides of the tongue, hard palate, and lower labial mucosa (Figure 5).

Based on the anamnesis and clinical examination, the patient was diagnosed with suspected BD. The patient was referred for a complete hematology examination and tests for anti-HSV-1 IgG, anti-HSV-2 IgG, anti-HIV, and ANA panel. The patient was also referred to the Department of Dermatology and Venereology for joint management. The prescribed treatment from the Department of Oral Medicine included chlorhexidine digluconate 0.12% spray, triamcinolone acetonide in orabase 0.1%, and petroleum jelly. Additionally, the patient received instructions for maintaining oral hygiene. One week after the previous visit (Figure 6), marked improvement of the lesions was observed, with no new ulcers appearing. Hematology examination

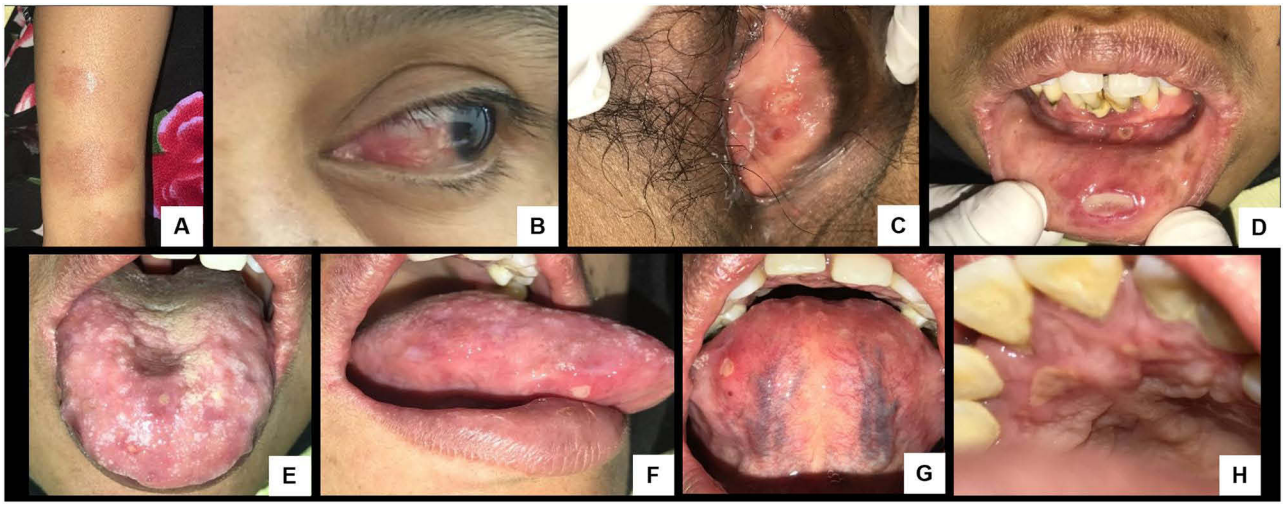

Figure 5 Clinical presentation of Behcet's disease in a 41-year-old female patient at the initial visit. (**A**) Skin lesions on the arm. (**B**) Scleral hyperemia and redness in the left eye indicate ocular involvement. (**C**) Painful genital ulcers. (**D–H**) Multiple ulcers affect the oral mucosa, including the lower labial mucosa, dorsum, lateral, and ventral sides of the tongue, as well as the palate.

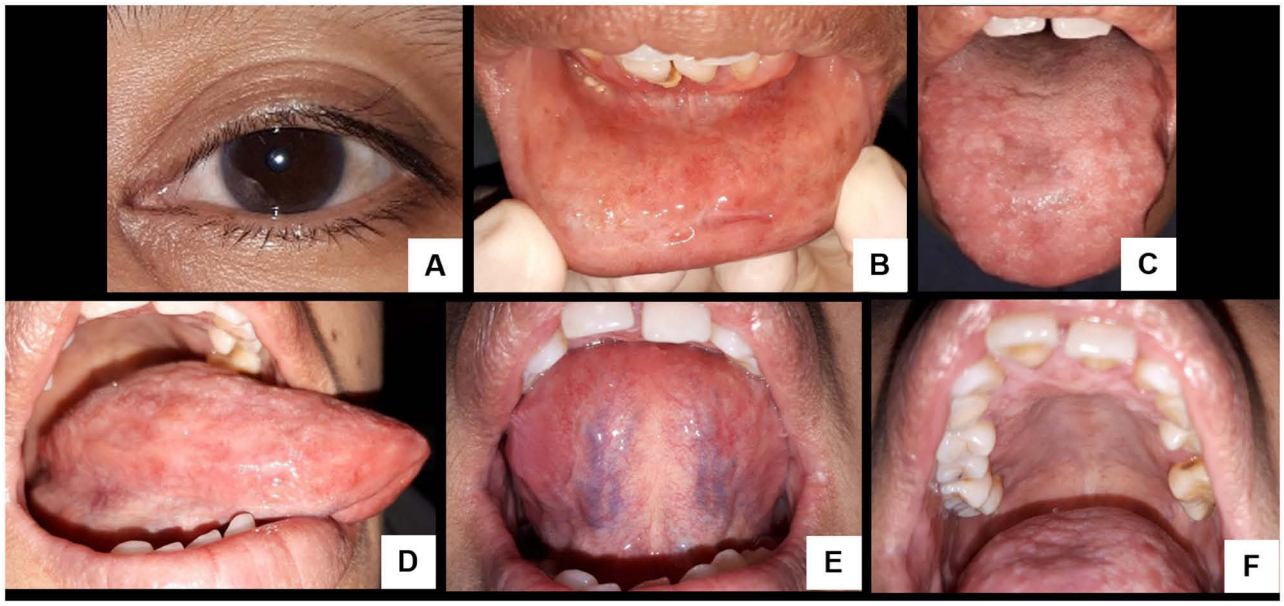

Figure 6 Physical examination findings after three weeks of treatment. (**A–F**) All lesions had completely resolved.

revealed no abnormalities. The results of laboratory tests of anti-HIV, anti-HSV-2, and ANA test were non-reactive but anti-HSV-1 reactive. The ICBD score of 7 included 2 points for ocular lesions, 2 points for oral aphthous ulcers, 2 points for genital lesions, and 1 point for skin lesions. The definitive diagnosis from the Department of Dermatology and Venereology confirmed BD, and the patient was prescribed methylprednisolone 8 mg and ranitidine 150 mg. The treatment prescribed by the Oral Medicine Specialist was continued.

BD clinical activity was assessed using the BDCAF instrument following the diagnosis of BD was confirmed. Scores of 1 were recorded for oral aphthous ulcers, genital ulcers, skin erythema, skin pustules, arthralgia, and ocular symptoms, while scores for headache, arthritis, nausea/vomiting/abdominal pain, bloody diarrhea, central nervous system involvement, and major vessels were all 0. The total clinical activity index BD (BDCAF) score was 6, indicating active BD. Written informed consent was obtained from the patient for the publication of this case and accompanying image.

A detailed comparison of the Clinical Activity Assessment of Behcet's Disease in each case is summarized in Table 1.

Discussion

Recurrent oral ulcers have been reported as the earliest disease manifestation in 47–86% of BD patients. The lesions typically have a disciform appearance, sharp, rounded erythematous margins, and a yellowish fibrinous base covered by a grayish-white pseudomembrane. The ulcers rapidly develop into deep wounds, which may appear as single or multiple lesions and can heal with or without scarring. Common locations include the gingival mucosa, buccal mucosa, tongue, and lips. Lesions may also appear on the hard palate, soft palate, pharynx, and tonsils.[9,19] The most common clinical manifestations of oral ulcers in BD patients include three patterns, which are minor ulcers, major ulcers, or herpetiform ulcers.[5] Minor ulcers, the most common form, are less than 1 cm in diameter, have a shallow depth, occur in groups of 1–5 ulcers, cause moderate pain, and heal without scarring within 4–14 days. Major ulcers, which are less common, are more than 1 cm in diameter, more painful, and heal with scarring within 2–6 weeks. Herpetiform ulcers, the rarest form, are multiple, have a diameter of 0.2–0.3 cm, are very painful, and may appear confluent. The prognosis for oral lesions is generally good.[9,19] Oral ulcers were observed in all three cases of BD reported here. Two cases presented with a herpetiform ulcer pattern, while one case had a major ulcer pattern that healed with scarring.

The association between COVID-19 and autoimmune diseases, such as BD, is increasingly recognized. However, research specifically linking BD to SARS-CoV-2 infection remains limited. A case reported by Shahram et al described a 57-year-old man who developed BD following a COVID-19 infection. The patient's symptoms included fever, sore throat, nasal congestion, cough, fatigue, and myalgia. He later experienced mild dyspnea, diarrhea, anosmia, illusion, and restlessness. He had a history of type 2 diabetes and was taking glibenclamide. COVID-19 was diagnosed clinically without PCR confirmation, and he was treated at home with azithromycin and symptomatic management. After four weeks, all symptoms resolved. Three months later, the patient developed recurrent oral and genital ulcers, arthralgia, and constitutional symptoms. HLA typing indicated a positive result for B51, confirming the diagnosis of BD and leading to colchicine treatment initiation. This case suggests that COVID-19 may act as a trigger for the onset of BD symptoms. The disruption of immune tolerance due to SARS-CoV-2 infection potentially induces autoimmune responses, raising concerns about the virus's role in the onset or exacerbation of clinical autoimmunity.[20] Ozcifci et al reported that 43.5% of BD patients experienced flares after a median of 45 days following COVID-19 infection. This flare-up was significantly associated with the discontinuation of immunosuppressive drugs. For patients with BD or other autoimmune diseases, discontinuing immunosuppressive drugs can lead to an increased risk of disease flares, as it can reduce the immune system's control over inflammatory responses. Immunosuppressive medications help to control the abnormal immune response characteristic of autoimmune diseases, and their withdrawal can lead to increased immune reactivity, potentially resulting in worsening symptoms or flare-ups.[21]

Cytokine pathways and immune signaling disturbances have been implicated in the pathogenesis of BD and COVID-19 infections. In both conditions, an increased production of inflammatory cytokines leads to deregulation of the immune system and immunopathology. Cytokine storm syndrome in COVID-19 patients may contribute to the development of various disorders, including BD. The prolonged cytokines production can lead to a loss of tolerance to self-antigens and exacerbate BD.[10,22,23] Autoimmune patients with higher levels of the inflammatory cytokines IL-17, IFN-γ, and IL-23 are one of the risk factors for developing ulcers in the oral mucosa and complications of opportunistic infections.[12] IL-17 mediates tissue damage

Table 1 Assessment of Clinical Activity of Behcet's Disease

Case	Behcet's Disease Current Activity Form (BDCAF)												The Total clinical activity index BD
	Headache	Oral aphthous ulcers	Genital ulcers	Skin Lesions		Joint		Gastrointestinal		Eyes	Central nervous system	Major vessels	
				Skin Erythema	Skin Pustules	Arthralgia	Arthritis	Nausea/ Vomiting/ Abdominal Discomfort	Diarrhea with Altered/ Frank Blood per Rectum				
Case 1	0	1	1	0	0	1	0	0	0	1	0	0	4
Case 2	1	1	1	0	1	1	0	1	0	1	0	0	7
Case 3	0	1	1	1	1	1	0	0	0	1	0	0	6

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and plays a role in granulopoiesis and neutrophil production. Th17 induces IL-17 differentiation, which plays a role in adaptive immunity in epithelial cells in the formation of opportunistic infections. These findings can be useful in identifying disease pathogenesis in COVID-19 patients.[6] In this case series, the condition of the oral cavity with opportunistic infections accompanied by ulcers spread to almost the entire patient's oral cavity.

Both SARS-CoV-2 and BD play a role in regulating serum amyloid A (SAA) and fibrinogen production, which serve as the acute phase markers of inflammation. Increased SAA due to inflammation and infection by inducing the expression of various cytokines. Among inflammatory mediators, angiotensin II has an important role in both conditions.[10,24] The high-affinity binding of SARS-CoV-2 to ACE2 via the spike receptor binding domains (RBD) protein can induce a propagating immune response to the self-component involved in this cell entry complex. This long-term complication of COVID-19 can induce autoimmune diseases caused by an immune response.[11] Understanding the overlapping pathogenesis of COVID-19 and autoimmune diseases could provide insights into viral mechanisms and guide therapeutic development.[10]

HSV is one of the main candidates that has a potentially key role in the pathogenesis of BD.[7] The role of HSV infection in the pathogenesis of this disease has been studied for many years, with growing evidence linking HSV-1 to immune dysregulation in BD patients.[1,3,7] Cell-mediated immune responses to HSV have been implicated in the pathogenesis of various inflammatory diseases, including BD, but it remains unclear whether the pathological changes in skin lesions are caused by the virus itself or by secondary immunological reactions against viral antigens. In vitro studies with human dermal microvascular endothelial cells (HDMECs) exposed to HSV-1 revealed increased T cell binding and expression of cell adhesion molecules, such as CD54 (intercellular adhesion molecule-1 [ICAM-1]), vascular adhesion molecule 1 (VCAM-1), and E-selectin, which may drive BD immunopathogenesis. Similarly, incubation of HSV-infected peripheral blood mononuclear cells with uninfected HDMEC induced upregulation of CD54 and major histocompatibility complex class I molecules. The binding of T cells to HDMECs is inhibited by anti-CD54, anti-interleukin (IL-1), or tumor necrosis factor-alpha (TNF)-α, which may contribute to BD immunopathogenesis. Clinical similarities between herpetiform ulcers in BD and ulcers due to HSV infection support an etiological role of HSV in BD. Several studies have shown that the amount of HSV-1 DNA in leukocytes, blood, and saliva samples, and anti-HSV-1 antibodies in serum samples of BD patients showed significantly higher levels compared to the control group.[3,7,8] In this report, we conducted routine serological examinations and found that HSV antibodies were only detected in peripheral blood. However, we did not perform testing for HSV in mucosal tissues, as such testing is not typically part of routine practice. This raises important questions about the systemic versus localized effects of the virus in BD.

BD is characterized by episodes of relapse and remission. Monitoring tools that measure disease activity are necessary for the effective management of BD. BDCAF is the most widely used instrument for measuring disease activity in BD. This measurement is easy to implement in routine clinical practice and a reliable method for assessing and documenting clinical activity in BD patients. The BDCAF is based on the history and clinical features present for the month before the date of assessment. The results of this measurement are useful for monitoring the history of the disease, the effects of interventions, and determining the further management needed to obtain a good prognosis in BD patients.[2,16] In this report, all three BD cases presented active conditions. BDCAF scores were 4 for a patient with suspected SARS-CoV-2-triggered BD, while scores for patients with suspected HSV-1-triggered BD were 7 and 6. These higher scores in HSV-1 cases possibly because reactivation of chronic latent HSV-1 in BD patients led to more extensive immune reactivation and increased disease activity compared to the relatively recent SARS-CoV-2 infection.

This case report offers a perspective emphasizing the necessity for ongoing and potentially intensified drug therapy related to Behçet's disease (BD) during virus-induced flare-ups, such as those triggered by SARS-CoV-2 or HSV-1. This approach challenges the traditional practice of pausing immunosuppressive therapies during infections due to concerns about immune suppression. However, our report suggests that continuing therapy may more effectively manage BD-related inflammation, even in the presence of viral infections. This perspective is supported by existing literature, underscoring the importance of continuous management of BD despite viral triggers. Recent studies have shown that a tailored approach to BD treatment, including maintaining immunosuppressive therapy, can be particularly beneficial when addressing conditions exacerbated by viral infections.[25]

Recurrent BD-related mucosal ulcers were managed with a combination of low-dose systemic corticosteroids and topical treatments, along with antiviral therapy (acyclovir) for HSV-1 infection. Additionally, antiseptics with antiviral and antibacterial properties, such as chlorhexidine, were used to support a balanced oral environment and promote ulcer healing. This approach effectively balanced control of localized and systemic inflammation while minimizing side effects.[26] Topical therapies provided symptomatic relief, while low-dose systemic corticosteroids ensured broader inflammation management, particularly in cases where viral infections (HSV-1 and SARS-CoV-2) could exacerbate BD-related inflammation.

The management of BD requires a multidisciplinary approach tailored to the specific organs and severity of symptoms.[9] Treatment is empiric and focuses on relieving symptoms, managing inflammation, limiting tissue damage, reducing recurrence, frequency, and severity, and preventing life-threatening complications. Currently, there is no single curative therapeutic agent for BD. Treatment generally depends on the clinical manifestations of each patient.[7] Some evidence suggests that corticosteroids may help prevent neurological complications, while immunosuppressants like methotrexate have shown promise in recent studies.[13] Treatment of COVID-19 disease is also carried out to relieve clinical symptoms and signs, as definitive treatment options for the virus itself remain limited.[10,19] The involvement of HSV in the pathogenesis of BD led to treatment strategies targeting HSV infection or associated immunological pathways.[5] Although various therapeutic agents have been used for BD, treatment outcomes vary widely among individuals.[7]

Oral Medicine Specialists play a crucial role in the early detection and management of oral manifestations of BD. Topical therapy can reduce dysbiosis and stabilize the oral environment, promoting ulcer healing and reducing disease activity.[19] Instructions for maintaining oral hygiene and managing foci of infection are also essential. However, active BD patients should avoid dental treatment that may trigger exacerbation. Treatment of oral lesions significantly improves the quality of life of BD patients. Multidisciplinary care and regular follow-up support a successful healing process and a better prognosis.[18,19,27]

This report has several limitations, however, emphasizing the value of its findings may serve as a foundation for further research. First, the small sample size of three cases limits the generalizability of these conclusions to a broader population of BD patients. Nevertheless, this study provides valuable insights into a potential link between viral infections and BD activity. Future studies with larger subjects and more diverse cohorts could help confirm these findings and enhance our understanding. Second, the short follow-up period is another limitation, as a longer follow-up was not feasible within the scope of this report. Future studies with extended follow-up could explore the sustained effects of SARS-CoV-2 and HSV-1 on BD activity. Third, this report utilized routine tests to confirm viral infections, including serological confirmation of HSV-1 and SARS-CoV-2 infections. Therefore, future studies could enhance these findings by incorporating molecular data to clarify the role of active viral replication or reactivation, providing more precise insights into BD progression.

Conclusion

This report underscores the importance of understanding viral triggers in BD activity, particularly SARS-CoV-2 and HSV-1. Patients with SARS-CoV-2-triggered BD tend to exhibit lower disease activity than those with HSV-1 infections. This difference in disease activity may result from the fact that COVID-19 is typically a new infection, whereas HSV-1 is often reactivated from a latent state, leading to recurrent clinical manifestations and higher disease activity. Regular follow-ups are essential for monitoring the clinical progression of BD in patients, allowing treatment to be appropriately adjusted to their current condition. In addition, a more comprehensive understanding of these associations may contribute to developing targeted therapeutic approaches and improving disease management and patient outcomes.

Consent Statements

All patients provided written consent for the publication of their clinical information and accompanying images. The institution has also approved the publication of this work.

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Disclosure

The authors declare no conflicts of interest in this work.

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