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CASE REPORT

Identifying the Multifactorial Triggers of Monthly Recurrent HSV-1 Reactivation: A Case Report

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Background: Herpes simplex virus 1 (HSV-1) causes recurrent oral lesions with reactivation triggered by factors such as stress, hormones, and nutrition. Immune suppression caused by these factors plays an important role in HSV-1 reactivation and requires comprehensive management.

Purpose: This case report aims to analyze the relationship between triggering factors and recurrent HSV-1 infection and to achieve therapy to prevent recurrence.

Case Presentation: A 39-year-old woman came with recurrent ulcers every month during her menstrual cycle. The results of the anamnesis showed other factors such as malnutrition and stress. Clinical examination showed ulcers on the lips, labial mucosa, and gingiva. A hemogram (complete blood count) examination revealed normal results, IgG anti-HSV-1 with reactive results, and IgM anti-HSV-1 non-reactive. The diagnosis was Herpes Labialis and Recurrent Intraoral Herpes (RIH).

Case Management: Pharmacological therapy was acyclovir cream, chlorine dioxide mouthwash, acyclovir tablets, and vitamins. Non-pharmacological therapy includes improving oral hygiene, stress management (evaluation using the Depression Anxiety Stress Scale-21/DASS-21), and improving nutrition. By the third visit, ulcers on the labial mucosa and lip commissures showed improvement, however, a new ulcer developed on the lower labial mucosa. The use of oral acyclovir tablets, hyaluronic acid gel, and stress management monitored using DASS-21 resulted in complete ulcer healing by the fifth visit.

Conclusion: The multifactorial triggers for recurrent HSV-1 infection in this case are stress, hormonal, and nutritional. Pharmacological therapy in the form of acyclovir and chlorhexidine requires comprehensive management that combines antiviral therapy, stress management, and lifestyle changes by improving nutrition to overcome recurrent HSV-1 infections in the future.

Keywords: acyclovir, DASS-21, herpes labialis, hormone, recurrent HSV-1 infection

Introduction

Herpes simplex virus 1 (HSV-1) is a highly contagious neurotropic pathogen of the Alphaherpesvirinae subfamily of the Herpesviridae family, which primarily causes oropharyngeal and recurrent oral lesions.[1] HSV-1 is predominantly associated with oral and perioral disease, whereas HSV-2 is known to cause anogenital infections but can occasionally affect the orofacial region. The pathogenesis of HSV-1 involves two life cycles: a lytic phase, characterized by active viral replication, and a latent phase, in which the virus remains dormant in ganglia such as the trigeminal nerve. HSV-1 reactivation is influenced by internal and external factors such as ultraviolet light, trauma, hormonal changes, immunosuppression, and stress, which can trigger the transition of the virus from latency to active replication.[1–3]

Recurrent HSV infections are very common worldwide. Approximately 3.7 billion people under the age of 50 (67%) are infected with HSV-1 globally. In the United States, the prevalence of HSV-1 among adults ranges from 57% to 80%, while in Asia, the prevalence is as high as 75% for adults, especially those of low socioeconomic backgrounds. Recurrent HSV infections are estimated to affect approximately one-third of the US population, with some individuals experiencing up to six episodes per year. The average incidence of recurrent HSV is approximately 1.6 per 1000 patients per year, with a prevalence of 2.5 per 1000 patients, although this figure varies between countries and communities.[4]

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Recurrent intraoral herpes (RIH) is a manifestation of HSV-1 reactivation, characterized by painful vesicles on the oral mucosa. These lesions progress from pruritus to macules, papules, vesicles, and finally ulcers that heal within 72–96 hours without leaving scarring. These lesions usually resolve spontaneously in healthy individuals; severe symptoms can occur in those with compromised immune systems.[5,6] This case report concerns a 39-year-old woman with symptomatic Recurrent Intraoral Herpes (RIH). The report discusses the multifactorial triggers, including stress, hormonal fluctuations, and nutritional imbalances, that contribute to chronic HSV-1 reactivation. The report also details the comprehensive treatment, which focused on symptomatic management, improved oral hygiene, nutritional supplementation, and antiviral therapy, emphasizing the importance of comprehensive management in managing recurrent HSV-related conditions. The novelty of this case report is the unique interplay of multiple systemic and lifestyle factors triggering recurrent HSV-1 infection.

Case Report

A 39-year-old woman came to the Department of Oral Medicine on November 8, 2024, with complaints of recurrent oral ulcers that occurred before or after menstruation. This condition worsens with mechanical trauma. The Body Mass Index was below normal (18), suggesting inadequate nutrition. She reported that the recurrent ulcer condition had been present for the past few months. The ulcer last occurred one week ago, coinciding with her menstrual cycle. Four days before the visit, she had a fever. Additional complaints included lesions on the lower lip, which initially appeared as vesicles and then burst after prolonged use of a mask. The ulcers also increased on the inner upper lip two days before the visit. The patient's lifestyle history included drinking 2 L of water per day and inadequate fruit and vegetable intake. She denied any systemic disease, family history of similar conditions, smoking, or alcohol consumption. The patient had an allergy to the antibiotic cefotaxime. Vital signs were within normal limits.

On clinical examination, the patient was conscious and in good general condition. The results of the DASS-21 (Depression Anxiety Stress Scale-21) examination were moderate depression (score 14), normal anxiety (score 2), and mild stress (score 8). Extraoral examination included dry and exfoliative lips with a 4 mm erosive lesion on the lower right lip that was painful and bled easily. Intraoral examination of the gingiva showed shallow ulcers in the region of tooth 17 (3 mm) and in the mucobuccal fold of tooth 14 (1 mm), as well as irregular lesions 3×5 mm on the upper labial mucosa in the region of tooth 23, as seen in Figure 1. The working diagnosis included exfoliative cheilitis, coated tongue

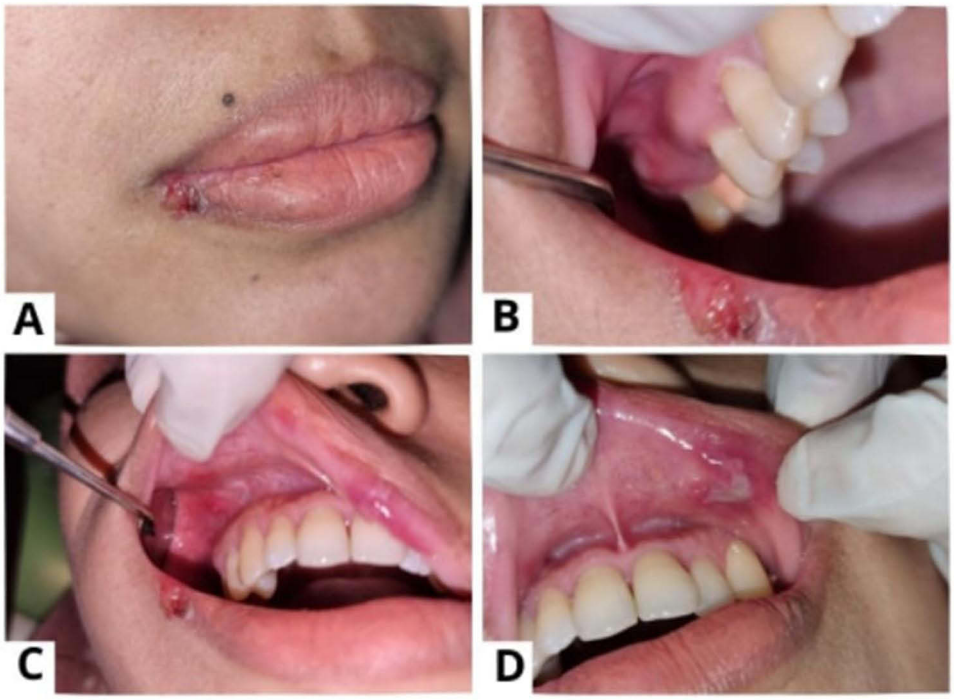

Figure 1 Erosive lesion with erythematous border on the right lower lip (**A**), gingival lesion in the region of tooth 17 (**B**), lesion in the mucobuccal fold in the region of tooth 14 (**C**), ulcer on the upper labial mucosa in the region of tooth 23 (**D**).

(Miyazaki scale 3), suspected Recurrent Intraoral Herpes (RIH), and suspected herpes labialis with a differential diagnosis of Recurrent Aphthous Stomatitis and traumatic ulcers.

Treatment focuses on curing symptoms, improving oral hygiene, and addressing nutritional deficiencies. Non-pharmacological therapy includes instructions for maintaining oral hygiene (OHI), including the use of a soft-bristled toothbrush with fluoride toothpaste twice daily, along with cleaning the tongue. Pharmacological therapy includes topical treatment, including application of 5% acyclovir cream to the lip lesions three times daily for seven days and petroleum jelly to the lips three times daily. Patients were also given 0.2% chlorine dioxide mouthwash (10 mL, twice daily for 1 minute) along with vitamin B12 (twice daily) and folic acid (once daily). Supporting examinations were performed for IgM, IgG anti-HSV-1, and hemogram (complete blood count) examinations. Patients were scheduled for a checkup in the next seven days to monitor progress.

At the second visit (a week after the first visit), the patient no longer complained of mouth ulcers. The prescribed acyclovir and chlorine dioxide creams were used as directed. The patient had managed stress effectively and maintained consistent fruit and vegetable intake. The DASS-21 evaluation showed improvement, indicating moderate depression (score 14), normal stress (score 6), and normal anxiety (score 2). Her vital signs were within normal limits. Intraoral examination showed improvement in the previous ulcers without additional ulcers, as seen in Figure 2. Laboratory results showed an increase in ESR (erythrocyte sedimentation rate 37 mm/hour) and positive anti-HSV-1 IgG levels (54.8), while the results of the anti-HSV-1 IgM examination showed negative results. It indicates that elevated anti-HSV-1 IgG and lack of IgM supported a previous infection, but did not verify current reactivation. The diagnosis was based on clinical findings, including characteristic lesions and symptoms. Previous non-pharmacological and pharmacological therapies were continued.

On the third visit (two weeks after the second visit), which was conducted two weeks after the previous visit, the patient complained of a new ulcer on the inner lower lip. At that time, the patient was menstruating. The use of acyclovir cream for the lower lip has been stopped, while chlorine dioxide and vitamins have been used as directed. The patient continues to manage stress effectively and maintains a consistent intake of fruits and vegetables. The patient also experienced fever and mouth ulcers almost every month during menstruation for the past three years, with a significant increase in frequency this year. Differential diagnoses such as Crohn's disease or Behçet's disease may be considered given the high recurrence rate. However, we found no genital ulcers, ocular mucosal involvement, gastrointestinal symptoms, other systemic manifestations, and a positive response to antiviral therapy, making HSV-1 reactivation the most likely diagnosis. The DASS-21 evaluation showed mild depression (score 12), normal stress (score 6), and normal anxiety (score 1). Vital signs were within normal limits. Intraoral examination found a new irregular ulcer on the lower labial mucosa in the region of tooth 32, measuring 4×4 mm, appearing yellowish white, shallow, with erythematous edges and clear boundaries. The previous ulcer showed significant improvement, as seen in Figure 3. The pharmacological therapy given was acyclovir tablets (400 mg) taken 5 times a day for 5 days. Chlorhexidine gluconate 0.2% compresses (5 minutes, twice daily) are prescribed for ulcers along with vitamin C and D supplements (once daily).

At the fourth visit (a week after the third visit), the patient reported no pain in the lower lip ulcer and showed improvement, although the ulcer had not completely healed. Prescribed medications and vitamins were used as directed.

Figure 2 Ulcers that have undergone repair on the lower right lip (**A**), in the region of teeth 17 and 14 (**B**), and tooth 23 (**C**).

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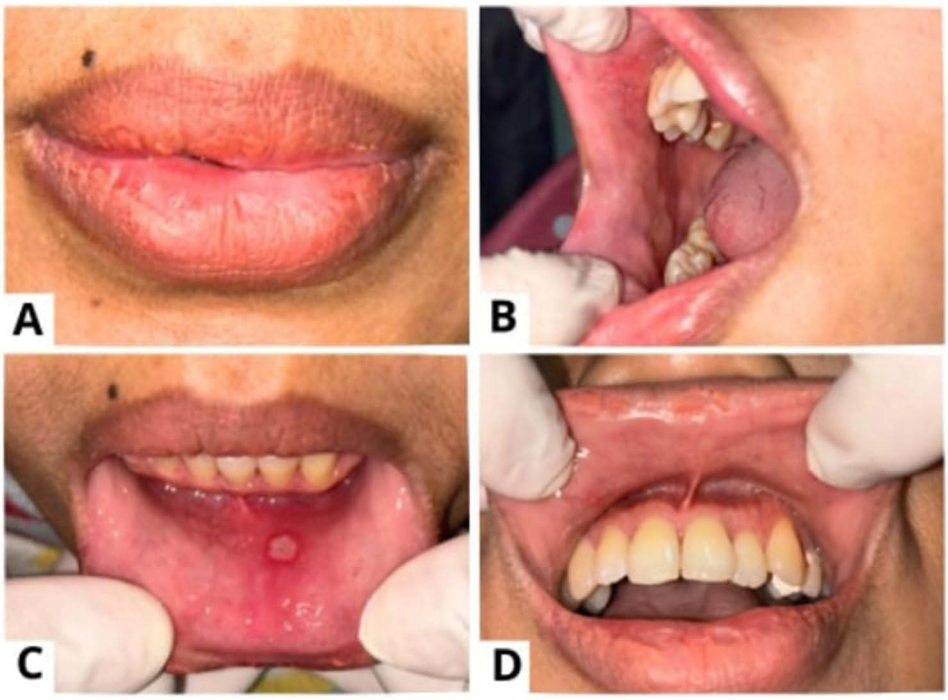

Figure 3 Healed ulcer with erythematous edges on the right lower lip (**A**), in the region of teeth 17 and 14 (**B**), new ulcer on the lower labial mucosa (**C**), healed ulcer in the region of tooth 23 (**D**).

The DASS-21 evaluation showed mild depression (12), normal stress (6), and normal anxiety (1). Intraoral examination showed improvement in the lower lip ulcer in the region of tooth 32, as seen in Figure 4. The acyclovir tablets were finished, and the patient was instructed to use a 0.2% chlorhexidine gluconate mouthwash and apply 0.2% hyaluronic acid gel to the ulcer twice daily. At the fifth visit (two weeks after the fourth visit), the lower lip ulcer had completely healed, and the patient reported feeling comfortable eating and talking. The DASS-21 evaluation remained consistent, showing mild depression (12), normal stress (6), and normal anxiety (1). Patients were advised to maintain good oral hygiene with a soft-bristled toothbrush and fluoride toothpaste twice daily, along with a healthy lifestyle such as a balanced diet, drinking 2 L of water daily, and regular physical activity. This visit marks the resolution of recurrent intraoral herpes (RIH) and preventive care to avoid future recurrences.

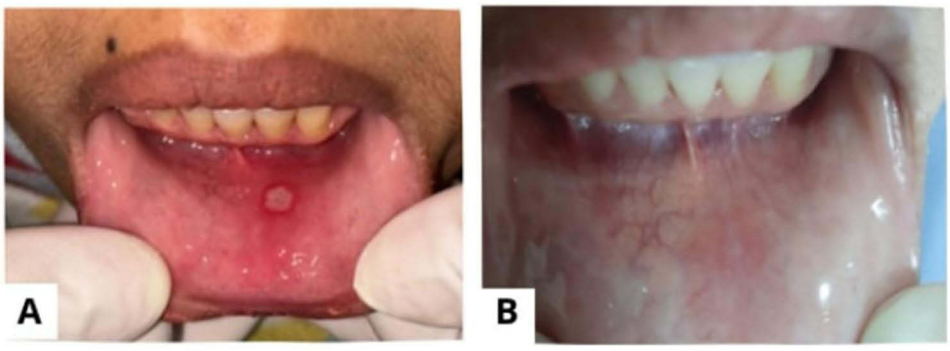

Figure 4 Ulcer repair on the lower labial mucosa from the fourth visit (**A**) to the fifth visit (**B**).

Discussion

This case discusses a 39-year-old woman who came with recurrent oral ulcers, preceded by fever that had lasted for the past few months, caused by several risk factors such as stress, nutrition, and hormones. The multifactorial triggers that played a role in triggering this case were stress, hormonal, and nutritional. In this case, family problems led to the patient being hospitalized under stressful conditions. Long-term stress causes fatigue, lack of sleep, and changes in sleep patterns.

Stress is defined as one of the triggers of somatic reactions outside the body's normal processes, which can alter body systems such as the central nervous system, endocrine system, and immune system. In addition, psychological stress can increase HSV titers. The DASS-21 scale initially revealed moderate depression and mild stress, indicating the need for stress management. This plays an important role in reducing the risk or frequency of reactivation and improving overall health.[7]

As part of the alpha herpesvirus group, HSV-1 exhibits neurovirulence to invade and replicate in the nervous system, establish latency in nerve ganglia cells, and reactivate from latency. Reactivation can be triggered by central or peripheral stimuli in the sensory nuclei.[7–9] Stress contributes to herpes reactivation through activation of the hypothalamic-pituitary-adrenal (HPA) axis, which causes the release of stress hormones such as cortisol and epinephrine. Cortisol is a glucocorticoid produced by the adrenal cortex that suppresses the immune response by reducing the production of proinflammatory cytokines, chemokines, and adhesion molecules. This immunosuppression affects cellular defense mechanisms, including natural killer (NK) cells, which are critical in controlling viral infections. This condition is favorable for the virus to replicate due to its opportunistic nature in immunosuppressed conditions.[7–9] Glucocorticoids may trigger reactivation not only by suppressing the immune system but also by providing a trigger for reactivation in neurons containing latent HSV, possibly by activating cAMP adrenergic receptors or by stimulating HSV-derived regulation.[7,8,10,11] At the fourth visit, there was significant improvement, with DASS-21 scores indicating mild depression, normal stress, and normal anxiety.

Based on the results of the Body Mass Index (BMI) examination, the patient showed results below normal, namely 18. This condition is related to the patient's habit of not routinely consuming nutritious food. This plays a role in weakening the patient's immune system.[12,13] Nutritional content, such as vitamins B12, C, and D, is very important for regulating the immune system, and supplementation of these vitamins is an integral part of the treatment plan. The consistent improvement of the patient's condition after dietary adjustment underlines the importance of addressing nutritional imbalances in managing chronic HSV reactivation. The hemogram (complete blood count) was performed, which showed normal values. Low Body Mass Index (BMI) is usually followed by low hematology values, but in this patient, the complete hematology values were within normal limits. In general, low BMI can be associated with poor nutritional status, which can have an impact on hematology parameters such as hemoglobin and hematocrit. However, this relationship is not always consistent and can be influenced by many other things, such as diet, food processing, diet composition, individual metabolism, physical activity, and general health conditions.[14–16] Laboratory parameters, such as electrolytes and hematologic parameters, may change with the degree of underweight. These changes may indicate increased health risks, which may be influenced by the way food is processed and the availability of nutrients. Individuals with a low BMI may have normal glucose tolerance and show no signs of diabetes, indicating that their metabolism may be adapted to efficiently utilize nutrients despite low caloric intake.[14,15,17,18]

This patient had ulcers on the oral mucosa only. HSV-1 typically causes lesions in the oral area, whereas HSV-2 is more common in the genital area. In this case, ulcers were not found in the genital area, so the working diagnosis is more likely to be HSV-1 infection. In contrast, HSV-2 infection is characterized by inflammatory lesions in the genital or anal area, which begin with systemic symptoms such as fever, muscle aches, itching, and headache, followed by papules, blisters, and ulcerations. Although primary infection is often more severe, many primary cases are asymptomatic. Reactivation of HSV-2 is relatively common, occurring at a rate of 20–60%, and this infection is also known to increase the risk of HIV transmission because it affects immune cells at the site of infection.[10,11]

Other laboratory test results showed an increase in anti-HSV IgG levels, confirming the diagnosis of Recurrent Intraoral Herpes (RIH) and herpes labialis. Anti-HSV IgM examination showed non-reactive results. IgG with reactive results and non-reactive IgM can occur for several reasons. One is that IgG can still be detected in the body after a previous infection, while IgM usually appears earlier in the immune response and will decrease over time. In this case, IgM was not detected despite an active infection because the patient had experienced this ulcer for two weeks, indicating

that the infection was chronic and recurrent. The diagnosis of recurrent intraoral herpes and herpes labialis is primarily clinical. Although anti-HSV IgG may provide supportive information, it has limited diagnostic value in recurrent infections. The presence of anti-HSV IgG indicates prior exposure but does not distinguish between past and current infection. Therefore, serologic findings were considered supportive but not definitive for the diagnosis.[19,20]

In addition, the history of patients with recurrent ulcers that appear during menstruation suggests the role of fluctuations in the hormones estrogen and progesterone in modulating the body's immune function. Studies have shown that high estrogen levels can directly promote HSV-1 reactivation from the latent phase, while progesterone inhibits the function of HSV-specific CD8+ T cells that play a role in maintaining viral latency.[21–24] Progesterone also triggers reactivation through a mechanism that is independent of immune cells. Estrogen also has an effect on HSV-1 reinfection, although it has no significant effect on CD8+ T cells; it can directly affect neurons that harbor latent virus, thereby contributing to virus reactivation. This combination of hormonal effects on immune function and neuronal activity highlights the importance of female sex hormones in HSV-1 reactivation.[25,26]

The relationship between oral hygiene and herpes simplex virus type 1 (HSV-1) infection is also important. Good oral hygiene plays a supportive role during active HSV-1 episodes. In addition, patients who maintain good oral hygiene can help reduce the discomfort experienced by patients during the active phase of the infection.[27] In this case, oral hygiene is a component of patient care that emphasizes the use of a soft-bristled toothbrush and fluoride toothpaste twice daily, as well as tongue cleaning to promote mucosal healing. The use of a soft-bristled toothbrush is useful to avoid irritation of the inflamed tissue. This helps to clean the teeth without causing additional pain to the ulcerated area.[28,29]

On intraoral examination, the patient had dry and exfoliative lips, so petroleum jelly therapy was given as a lip moisturizer. The use of petroleum jelly provides additional protection and maintains moisture, preventing secondary infection and accelerating healing. Petroleum jelly is one of the most commonly used topical ingredients to increase the production of antimicrobial peptides, repair the skin barrier, and maintain skin moisture. As an occlusive moisturizer that does not contain water, petroleum jelly can reduce water loss through the skin by 50–99%.[30]

Multiple ulcers on the oral mucosa of this patient were treated with chlorine dioxide (0.2%) mouthwash and acyclovir antiviral therapy. Chlorine dioxide (0.2%) mouthwash effectively provides antiseptic and anti-inflammatory benefits for ulcerated lesions.[13] Chlorine dioxide works by oxidizing the cellular components of microorganisms, causing damage to cell membranes and internal structures. Chlorine dioxide has antibacterial, antiviral, and antifungal properties, and it can penetrate biofilms well, making it effective in killing a variety of pathogens in the oral environment. In addition, chlorine dioxide exhibits selective properties toward non-eukaryotic microorganisms, meaning it can function at lower concentrations than eukaryotic cells.[31]

Topical acyclovir 5% cream applied three times daily to these patients was prescribed to target the viral activity locally at the site of the lip lesions. This is consistent with evidence showing that the use of acyclovir 5% cream in propylene glycol or modified water-based cream, applied five times daily for five days at the onset of prodromal symptoms, can significantly reduce the lesions.[32–34] Recurrent intraoral HSV infections are effectively treated with systemic acyclovir (400 mg, three times daily) or systemic valacyclovir (500–1000 mg, twice daily) for 3 to 5 days, with longer durations recommended for immunocompromised patients. The treatment provided to these patients is consistent with current recommendations. During the patient's management, switching from topical to systemic antiviral therapy is an important step in the treatment plan. Oral acyclovir (400 mg, five times daily) is prescribed to target persistent viral activity and prevent new lesions from forming.[7,10,35,36] The mechanism of action of acyclovir involves phosphorylation by HSV thymidine kinase, forming acyclovir monophosphate (ACV-MP), which is then converted to acyclovir triphosphate (ACV-TP). ACV-TP selectively inhibits HSV DNA polymerase, effectively stopping viral replication in infected cells. The mainstay of antiviral therapy, acyclovir, is effective in reducing the duration of lesions, minimizing the severity of symptoms, and preventing complications. The mechanism of action of acyclovir has high efficacy while limiting systemic toxicity because the active form (ACV-TP) is selectively produced in infected cells.[11,37–39]

Stress management and advice on a balanced diet and complementary pharmacological interventions promoted overall recovery. The active lesions had resolved by the fifth visit, but the patient's history of recurrences needs to be taken into consideration due to the chronic nature of HSV-1 reactivation. This underlines the importance of preventive measures, such as maintaining good oral hygiene, managing stress, and ensuring a balanced diet to reduce the risk of

recurrence. A positive patient response to stress management and better lifestyle choices plays a vital role in managing chronic conditions such as RIH.

This case report emphasizes the significance of a multifaceted strategy to managing recurrent HSV-1 infection, especially when there are some trigger factors, such as psychological stress, dietary deficiencies, and hormonal variations are present. Although each of these characteristics has been linked to HSV-1 reactivation in the literature, they are rarely addressed together in a single clinical situation.

The limitation of this case report is the lack of long-term follow-up after all of the ulcers healed, which prevents a full assessment of the sustained effectiveness of the treatment. Furthermore, no virological validation by PCR or viral culture was conducted, and the diagnosis was made only on clinical characteristics, recurrence pattern, and serological data. HSV serology, particularly IgG and IgM, should be interpreted with caution in recurrent infections, as IgM may not rise and IgG may stay positive for years after the initial infection. Furthermore, no additional tests were undertaken to rule out alternative diagnoses such as recurrent aphthous stomatitis, Behçet's disease, or Crohn's disease, all of which can cause chronic or recurring oral ulcers and may be accompanied by systemic symptoms.

Conclusion

The recurrence of HSV-1 infection in this patient is influenced by various triggering factors such as nutrition, stress, and hormones. Therefore, it requires comprehensive management that includes antiviral therapy, stress management, and lifestyle improvements. Proper management reduces the symptom frequency and improves lesion healing. This case report contributes to clinical practice for future studies, particularly the importance of considering multiple biopsychosocial factors (such as stress, diet, and hormonal changes) in the management of recurrent herpes simplex virus type 1 (HSV-1).

Consent Statements

The patient has approved and written informed consent for the treatment and publication of this case report, including the images. All patient identifiers have been removed to ensure anonymity and confidentiality. The institution has also approved the publication of this article. This case report was conducted in accordance with the ethical standards of the institution.

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Disclosure

The authors report no conflicts of interest in this work.

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