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ARQUIVOS EM ODONTOLOGIA

Cytopathological diagnosis of herpes simplex virus infection causing oral aphthous ulcers in a patient with acute lymphocytic leukemia: case report

Danielle Nobre Lopes[1] | Letícia Côgo Marques[1] | Rafaela Elvira Rozza de Menezes[1] Karin Soares Gonçalves Cunha[1] | Maria Elisa Rangel Janini[2]

[1]School of Medicine, Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brazil
[2] School of Dentistry, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil

Aim: This paper aims to report an atypical oral HSV infection diagnosed by cytopathological examination in a patient with acute lymphocytic leukemia.

Case report: A nine-year-old white female was admitted with acute lymphocytic leukemia, presenting ulcers covered with pseudomembrane and spontaneous bleeding on the left soft palate, measuring approximately 2 cm, as well as other ulcers measuring 1 cm on the left lateral border of the tongue. Exfoliative cytopathology revealed neutrophils and cytopathic effects of HSV in the keratinocytes in a fibrin background. Based on the exfoliative examination, the diagnosis of HSV infection was obtained.

Conclusion: Oral HSV infection can be atypical in immunocompromised patients and can cause high morbidity and mortality. Healthcare professionals, especially those working in a hospital environment, should be aware of the possibility of HSV infection in atypical lesions in these patients and evaluate the need to include antiviral prophylactic therapy.

Uniterms: Simplexvirus. Cytology. Precursor Cell Lymphoblastic Leukemia-Lymphoma.

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INTRODUCTION

The herpes simplex virus (HSV) is a DNA virus and a member of the human herpesvirus (HHV) family, also known as *Herpesviridae*[1]. HSVs, like all HHVs, have the ability to establish latent infections and persist throughout life within the host[1]. There are two types of HSV: type 1 (HSV-1 or HHV-1) and type two (HSV-2 or HHV-2)[2]. These are structurally similar but differ antigenically[1]. The majority of oral lesions are caused by HSV-1. Although HSV-2 is more commonly associated with genital lesions, it can also cause oral lesions[2]. After the primary infection, HSV remains in latency in the trigeminal ganglion and can be reactivated, causing an asymptomatic release of the virus in saliva or lesions, which can be located in the site of the initial infection or near it[1].

Viral infections constitute a significant cause of morbidity and mortality in immunocompromised patients, of which HSV infection is the most common[3]. In these cases, HSV infection can be atypical, resembling aphthous ulcerations, traumatic ulcers, and mucositis. Therefore, the traditional clinical diagnostic criteria used for immunocompetent patients to differentiate the oral lesions caused by HSV from other alterations are not applicable[4]. This paper aims to report an atypical oral HSV infection diagnosed by cytopathological examination in a patient with acute lymphocytic leukemia.

CASE REPORT

The present study evaluated a nine-year-old white female with acute lymphocytic leukemia, who had been hospitalized due to extremely painful oral ulcers and a history of fever (38°C) for two days. The patient had been treated with chemotherapy for two months with 4.5 mg of ondansetron, 1.3 mg

Corresponding author:
Danielle Nobre Lopes
Rua Domingos Ferreira 192/204, Copacabana, Rio de Janeiro, Rio de Janeiro. CEP 22.050-012. Phone: + 55 21 2255 1059
E-mail: daninobrelopes@yahoo.com.br

of vincristine, 20 mg of daunoblastine, and 4.400 UI L-asparginase, when the lesions appeared.

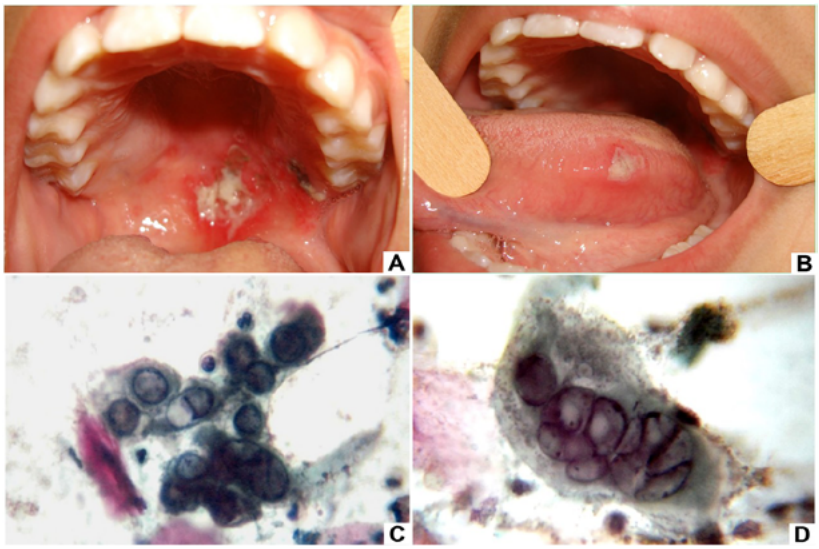
Upon intra-oral physical examination, we observed ulcers covered with pseudomembrane with spontaneous bleeding on the left soft palate, measuring approximately 2 cm, as well as other ulcers measuring 1 cm on the left lateral border of the tongue. The initial clinical diagnoses were non-specific ulcers and ulcers caused by the herpes simplex virus (HSV). While awaiting cytopathology results, a 0.12% chlorhexidine mouth rinse was prescribed twice a day to take advantage of its antiseptic and anti-inflammatory properties.

Exfoliative cytopathology revealed the presence of neutrophils and cytopathic effects of HSV in the keratinocytes, including cytomegaly, cariomegaly, Tzank cells, multinucleated giant cells with nuclear molding, ground-glass nuclei, and some cells with Cowdry A inclusions, in a fibrin background.

Following the diagnosis of HSV infection, which was made two days after the collection of the material for the cytopathological analysis, oral acyclovir was prescribed (400 mg, five times per day). Within seven days of the beginning of treatment, there was a complete improvement of the oral lesions.

However, six months later, while still undergoing chemotherapy, the patient returned to the hospital with painful oral ulcers and fever. The patient was hospitalized once more, and oral acyclovir (400 mg) was prescribed again, resulting in the healing of oral ulcers within seven days.

Figure. Clinical aspects of the patient. Aphthous ulcer in the center of the soft palate (**A**). Aphthous ulcer on the left lateral border of the tongue (**B**). Cytopathological aspects of the patient. Acantholytic cells with round and large nuclei (40 x) (**C**). Note the presence of a multinucleated giant cell with nuclear molding and ground-glass nuclei (40 x) (**D**).



DISCUSSION

Within the *Herpesviridae* family, HSV-1, HSV-2, EBV, and CMV are significant etiological agents of oral lesions. These serve as important indicators of immunosuppression, as they have the potential to reactivate when the immune system is compromised[1].

In immunocompetent patients, recurrent oral manifestations of HSV infection are limited to the keratinized mucosa, mainly the attached gingiva, hard palate, and vermilion border (mainly lower lips), appearing as vesicles that coalesce and rupture, forming shallow painful ulcers covered by fibrin, which last seven to ten days[5].

In immunocompromised patients, such as in the case reported here, there is a higher susceptibility to recurrent herpetic infections. These infections can be progressive and may also affect the respiratory tract, esophagus, and gastrointestinal tract. The lesions in these individuals often exhibit atypical characteristics, including increased size, greater pain, and extended duration (sometimes lasting for months), and may or may not be accompanied by episodes of fever. They can appear in any region of the oral mucosa, including areas not attached to the periosteum, such as soft palate mucosa and the tongue, particularly the dorsum and borders[4]. This unusual behavior is

a consequence of increased viral replication in epithelial cells, which results from the depletion of cellular immunity.

In the present case, the diagnosis of HSV infection was made shortly after the appearance of oral ulcers, and the patient promptly initiated antiviral therapy. This timely intervention helped prevent the infection from progressing to a life-threatening stage.

In a study conducted by Greenberg et al.[6], which involved leukemia patients hospitalized for chemotherapy, it was observed that 50% of recurrent oral lesions were caused by HSV-1. According to Sepúlveda et al.[4], lesions caused by HSV in leukemia, patients, although they may be associated with the presence of the neoplasia, are usually secondary to the oncologic therapy. This was also observed in the reported case, where the patient developed oral lesions during the induction phase of chemotherapy.

The diagnosis of oral lesions caused by HSV is usually based on the clinical aspects, except in cases with atypical features, as in the case of immunocompromised patients. In these cases, some complementary diagnostic tools can be used, such as cytological examination, histopathology examination, viral culture, in situ hybridization, polymerase chain reaction (PCR), direct immunofluorescence, immunocytochemistry, and immunohistochemistry[7–9].

Herpetic lesions in immunocompromised patients can often be mistaken for other conditions, such as drug allergies, mucositis, neutropenic ulcers, and viral infections, including herpangina and cytomegalovirus. Given the morbidity of the lesions, a prompt and accurate diagnosis is crucial for early treatment. In our study, cytological examination played a pivotal role in diagnosing HSV, revealing the presence of cytomegaly, cariomegaly, Tzank cells, multinucleated giant cells with nuclear molding, ground-glass nuclei, and some cells with Cowdry A inclusions[5]. Therefore, cytological examination is a valuable diagnostic tool due to its simplicity, speed, ease of execution, and cost-effectiveness[5].

Antiviral therapy for mucocutaneous lesions caused by HSV in immunocompromised patients can be administrated orally or intravenously (IV). Acyclovir is the preferred choice, but other drugs like famciclovir, valaciclovir, and penciclovir are also options. The recommended dosage of acyclovir to treat immunocompromised patients is 200 to 400 mg orally, taken five times a day for 7 to 10 days, or 5 mg/kg IV every 8 hours for 7 to 10 days[10]. After seven days of acyclovir treatment (400 mg orally, five times per day), our patient showed complete remission of oral lesions.

Prophylaxis with acyclovir, whether administered orally or intravenously, is of significant clinical importance, particularly in patients undergoing chemotherapy or organ transplantation[11]. Nevertheless, the timing of intervention and the duration of therapy depend on each case. It is important to note that immunocompromised patients using these antivirals for extended periods can develop drug resistance, which may diminish the effectiveness of the treatment[11]. Resistance to acyclovir occurs due to mutations in the viral gene responsible for encoding the enzyme thymidine kinase (TK), which is essential for phosphorylation and the subsequent activation and inhibition of viral DNA synthesis in infected cells.[12]

Foscarnet (phosphonoformic acid) and cidofovir are often used as treatments for herpetic lesions in patients with antiviral resistance. They function by acting on viral DNA to inhibit its replication[11,12]. Nevertheless, in clinical practice, these drugs are frequently associated with a high risk of toxicity, particularly nephrotoxicity[13]. Therefore, the other antiviral drugs, such as acyclovir, remain the preferred and more favorable alternative for treating these lesions[14].

CONCLUSION

Oral HSV infection can be atypical in immunocompromised patients and can cause high morbidity and mortality. Healthcare professionals, especially those working in a hospital environment, should be aware of the possibility of HSV infection in atypical lesions in these patients and evaluate the need to include antiviral prophylactic therapy.

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DECLARATION OF CONFLICTING INTERESTS

The authors have no conflicts of interest to disclose.

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AUTHOR CONTRIBUTIONS

DNL participated in the conceptualization, methodology and writing of this report.

LCM, participated in writing and reviewing the text in addition to creating boards with

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supervising the manuscript, review, editing of text and images.

ORCID

Danielle Nobre Lopes https://orcid.org/0000-0001-8389-5150
Leticia Cogo Marques https://orcid.org/0000-0002-5701-6842
Rafaela Elvira Rozza de Menezes https://orcid.org/0000-0001-7985-0507
Karin Soares Gonçalves Cunha https://orcid.org/0000-0002-5647-282X
Maria Elisa Rangel Janini https://orcid.org/0000-0002-0153-1079

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Diagnóstico citopatológico de infecção pelo vírus herpes simples causando úlceras aftosas orais em paciente com leucemia linfocítica aguda: relato de caso

Objetivo: Este trabalho tem como objetivo relatar uma infecção oral atípica por HSV diagnosticada por exame citopatológico em um paciente com leucemia linfocítica aguda.

Relato de caso: Paciente do sexo feminino, nove anos, branca, portadora de leucemia linfocítica aguda, apresentando úlceras recobertas por pseudomembrana e sangramento espontâneo em palato mole esquerdo medindo aproximadamente 2 cm, além de outras úlceras medindo 1 cm na borda lateral esquerda da língua. A citopatologia esfoliativa revelou neutrófilos e efeitos citopáticos do HSV nos ceratinócitos em um fundo de fibrina. Com base no exame esfoliativo, foi obtido o diagnóstico de infecção por HSV.

Conclusão: A infecção oral por HSV pode ser atípica em pacientes imunocomprometidos e pode causar alta morbidade e mortalidade. Os profissionais de saúde, principalmente os que atuam em ambiente hospitalar, devem estar atentos à possibilidade de infecção pelo HSV em lesões atípicas nesses pacientes e avaliar a necessidade de inclusão de terapia antiviral profilática.

Descritores: Simplexvirus. Citologia. Leucemia-Linfoma Linfoblástico de Células Precursoras.