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CASE REPORT

Oral Ulcers Induced by Cytomegalovirus Infection: Report on Two Cases

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ABSTRACT

Human cytomegalovirus (CMV) is a virus that can compromise the lungs and the liver and cause infection in the gastrointestinal tract. In addition, this virus can cause infectious mononucleosis syndrome, infection in the CNS, and retinitis. Moreover, it has been associated with the development of oral hairy leukoplakia and ulcers. **Objective:** To report two cases of patients with HIV with oral manifestations associated with CMV infection. **Case Report:** In the first case, the patient sought medical attention, with complaints of weakness, fever, cough, and weight loss. In the second case, the patient complained of weakness and blurred vision for about a week. Both patients were infected with HIV and made irregular use of antiretroviral therapy. Several ulcers were observed in the mouth that caused much discomfort. The diagnosis of CMV infection was defined by the following tests: enzyme immunoassay fluorescence-CMV IgG and PCR for CMV in real time. Ganciclovir has been used in the treatment of patients, and oral ulcerations received symptomatic treatment. **Conclusion:** The dentist must be aware that CMV may also be responsible for the development of ulcers in the oral cavity, especially in immunocompromised patients.

Keywords*:* Cytomegalovirus infections; oral ulcer; HIV infections; acquired immunodeficiency syndrome

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INTRODUCTION

The human cytomegalovirus (CMV) is a virus belonging to the family *Herpesviridae* and subfamily *Betaherpesvirinae*.[1-3] It is also known as human herpesvirus type 5. CMV is a common virus that can cause primary and secondary infections. Surprisingly, its only natural reservoir is the human body.[4-5] Viral transmission occurs by direct contact with secretions containing the virus, such as semen, cervical secretions, urine, saliva, breast milk, blood products, or transplantation of organs and tissues.[6] Primary CMV infection usually occurs in childhood. Like all herpesviruses, the virus has the ability to be latent and reactivate. Periodic reactivations occur in situations of stress, immunosuppression, autoimmune diseases, and the use of chemotherapy.[7]

CMV infection usually goes undetected in immunocompetent individuals. However, in immunocompromised patients, CMV is associated with significant morbidity and mortality.[1,8] In the viremic phase, CMV can affect many organ systems and cause interstitial pneumonia, hepatitis, abdominal pain, and diarrhea.[6,9] In addition, other clinical manifestations are associated with CMV infection, including pancytopenia, infectious mononucleosis syndrome, infection in the CNS, and retinitis.[6,9,10-18] However, oral manifestations of CMV infection are considered rare.[19]

Although oral lesions resulting from CMV infection have been documented in several immunosuppressive conditions, oral involvement CMV has increased since the beginning of the AIDS epidemic. The diagnosis of CMV infection is made from a combination of clinical findings, as well as by laboratory tests. Histopathological examination may show cellular changes that suggest infection.[20] The literature has shown that there are effective treatments for CMV

infections in immunocompromised individuals. Thus, biopsies are recommended for chronic ulcers that do not respond to conservative treatment.[21] Although the majority of CMV infections resolve spontaneously, treatment is often required in immunocompromised patients. The aim of this paper is to report two cases of CMV infection in immunocompromised patients by acquired immunodeficiency syndrome with oral manifestation.

CASE REPORTS

Case 1

A 33-year-old white female sought medical care at the Oswaldo Cruz hospital (Curitiba/PR Brazil). She was complaining of fever, weakness, cough, and weight loss for two months. During anamnesis, the patient reported that she was a smoker (15 cigarettes/day for 15 years), an alcoholic (three doses of alcoholic drink/day), and a crack cocaine user for 10 years. The patient was HIV-positive since 2009 and gets irregular treatment for the disease. The intraoral clinical examination revealed the presence of periodontal disease, coated tongue, mucosal dryness, residual roots, missing teeth, and the presence of an ulcerated lesion covered with crust on the upper lip (Figure 1). In addition, several yellowish ulcers were seen in the soft palate (Figure 2), tongue, mouth floor, and vestibule (Figure 3). Oral ulcers were flat and had irregular margins. The patient reported too much pain associated with the lesions. The patient complained of difficulty eating, and consequently had lost body weight.

The following laboratory tests were requested: complete blood count, erythrocyte sedimentation rate, hepatic enzymes, creatinine, urea, serology (HCV, HBV, CMV, syphilis, toxoplasmosis), sputum examination, and chest X-ray. The results of these tests revealed an anemia (hemoglobin = 6.30g/dL), thrombocytopenia (platelets = 137 k/uL) and elevated erythrocyte sedimentation rate (ESR = 85mm), real-time PCR for CMV (= 1,059copies/mL), and fluorescence immunoassay test for CMV (reagent).

Chest X-ray revealed pneumonia with interstitial radiopacity suggestive of tuberculosis. This infection was later confirmed by sputum examination. She started pulmonary tuberculosis treatment by daily use of Rifampicin (150mg) + Isoniazid (75mg) + Pyrazinamide (400mg) + Ethambutol (275mg). Oral lesions were initially treated as an HSV infection. Thus, the patient received acyclovir 250mg PO, Acyclovir topical cream, and benzydamine hydrochloride mouthwash every 8 hours for 3 days. Upon confirmation of CMV infection (positive in real-time PCR and enzyme immunoassay fluorescence CMV), the definitive treatment was established. The patient used Ganciclovir 5mg/kg every 12 hours intravenously (IV) for 7 days. The ulcers began to show signs of remission

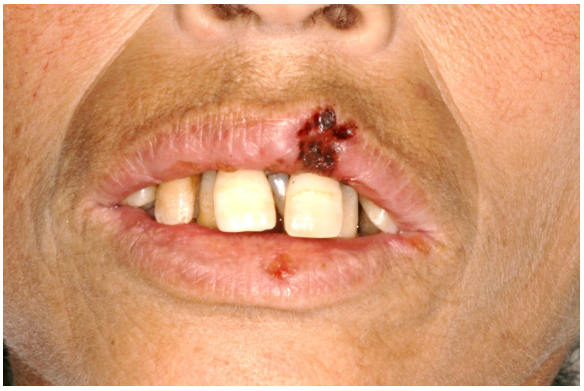

Figure 1. Ulcerated lesion covered with crust on top and bottom lip

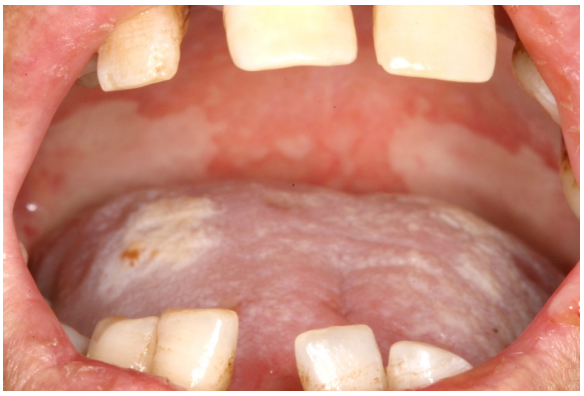

Figure 2. Extensive ulcerated lesions on the soft palate induced by CMV, and coated tongue

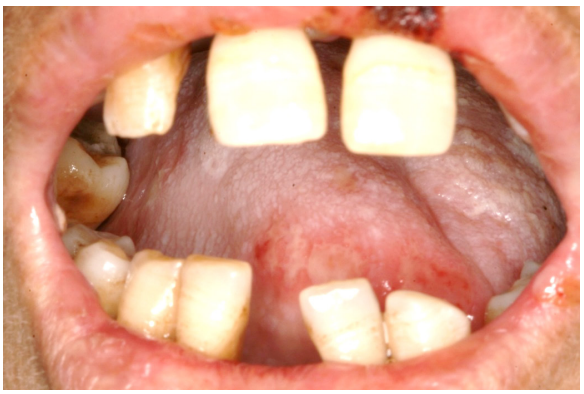

Figure 3. Ulcerated lesions induced by CMV in the dorsum of the tongue

3 days after the initiation of treatment. From the eighth day of admission, the patient went into withdrawal symptoms in relation to alcoholism and crack. She refused to continue treatment and asked to leave the hospital. It was thus not possible to follow the patient's treatment.

Case 2

A 38-year-old dark-skinned man sought medical care at the Oswaldo Cruz hospital (Curitiba/PR), complaining

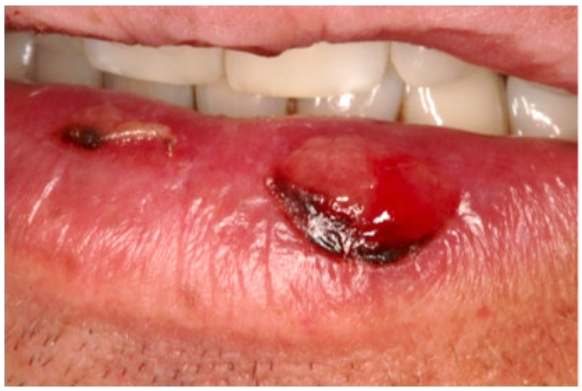

Figure 4. Ulcerated lesion induced by CMV in the lower lip vermilion

of weakness and blurred vision a week ago. During anamnesis, the patient reported that he was a smoker (three cigarettes/day for 20 years) and an alcoholic (four cups of fermentable type/week) and did not use illicit drugs. The patient was diagnosed with HIV 11 years ago and irregularly took antiretroviral drugs. In addition, the patient had bronchial asthma. Oral examination revealed the presence of a coated tongue, physiological melanin pigmentation in the dorsum of the tongue, and erythematous candidiasis in the hard and soft palate. Also, there were ulcerated lesions with yellow background located in the lower lip (Figures 4). The ulcerated lesions were flat and had regular margins. Additionally, the ulcers were extremely painful.

The following laboratory tests were requested: complete blood count, erythrocyte sedimentation rate, liver enzymes, creatinine, urea, serology (HSV, CMV, syphilis, toxoplasmosis), sputum tests, $CD4^+$ lymphocyte count, and computed tomography. The results of these tests revealed anemia (erythrocytes = 3.92mg/dL), leukopenia (leucocytes = 2.30), elevated erythrocyte sedimentation rate (ESR = 140mm), low CD4 count (CD4 = 30), real-time PCR for CMV (= 1,013 copies/mL), and fluorescence immunoassay test for CMV (reagent).

The patient was diagnosed with retinitis and mouth ulcers induced by CMV. Thus, he was treated by use of Ganciclovir 5 mg/kg intravenously every 12 hours for 14 days. Antiretroviral therapy was reintroduced, and anemia was treated with ferrous sulfate (8mg/8 hours) for 7 days. At the end of treatment, the patient had no more lesions in the mouth and no loss of visual acuity complaints. The patient was monitored monthly for six months and showed no clinical signs of CMV infection.

DISCUSSION

Ulceration occurs by disruptions in the oral epithelium, which usually exposes the nerve endings in the underlying lamina propria. They result in pain or discomfort, especially when the patient tries to eat spicy foods or citrus drinks. The degree of discomfort varies greatly from person to person. Some individuals suffer and complain of pain even with small ulcers. It is always important to the dentist to recognize the exact origin of a mouth ulcer to exclude serious diseases such as oral cancer or other serious diseases.[22]

This article has described two cases of patients with HIV/AIDS who had ulcerations in the mouth resulting from CMV infection. A study developed by Olczak-Kowalczyk et al.[23] revealed that 43% of patients with compromised immune systems due to liver and kidney transplantation might develop oral ulcerations associated with CMV.

CMV can infect the retina, gastrointestinal tract, liver, lungs, and nervous system.[6,9,10-18] The most common manifestation is retinitis, which is responsible for many cases of symptoms of CMV infection. In the mouth, this virus can cause oral hairy leukoplakia, especially in patients with compromised immune systems. However, several studies in the literature show the possibility of the involvement of this virus with periapical lesions, periodontal, and ulcerations.[23-26]

Oral ulcerative lesions are common in HIV/AIDS patients. Therefore, it is important to investigate the cause(s) of lesions. In general, both HSV and CMV can induce oral ulcerated lesions in immunocompromised patients. Clinically, the lesions caused by these viruses are very similar and may generate diagnostic doubts. However, yellowish, shallow, extensive ulcerations with irregular borders are common features of the ulcerated lesions associated with CMV. On the other hand, HSV-induced ulcers are small and rounded, and have a more obvious reddish halo.[20-21] However, CMV-induced oral ulcerations may be coinfected with other viruses, such as HSV and EBV.[20,27] On the lips, both ulcerations become covered by hemorrhagic crusts that embarrass their differentiation.

The diagnosis of CMV infection can be obtained by histological preparations by the presence of intranuclear inclusions known as "owl's eye." These structures may be stained with hematoxylin-eosin, papanicolaou, and giemsa. These inclusions can be found in tissue fragments of renal tubules, biliary ducts, lungs and liver parenchyma, intestines, and salivary glands, and less often in the brain tissue in urinary sediment, gastric lavage, and other materials.[28]

Basically, three laboratory techniques can be used for the detection of CMV infection: a) virus isolation in cultured human fibroblasts, b) detection of viral DNA by polymerase chain reaction (PCR), and c) serological tests (anti-CMV IgM and IgG anti-CMV). PCR allows identification of genes transcribed by the virus during replication in their host cells, thereby allowing identification of active infection.[29] In

both cases reported in this article, the diagnosis of ulcerated lesions in the mouth was attributed to CMV. Confirmation of infection was confirmed by PCR and enzyme immunoassay fluorescence reagent for CMV. Furthermore, we observed complete remission of oral lesions in patients after receiving treatment with ganciclovir.

The involvement of CMV is not uncommon in patients who were transplanted and/or are immunosuppressed. In some cases, they exhibit a low and temporary fever. In others, the infection may become aggressive. It is characterized by significant hepatitis, leukopenia, pneumonitis, and HIV wasting syndrome.[20] These clinical findings were observed in the patients described in this article. The first patient had a history of persistent fever and pneumonitis, and was presenting the wasting syndrome. Moreover, the second patient complained of retinitis and showed leukopenia. Opportunistic infections by CMV often happen in patients with HIV/AIDS. Chorioretinitis CMV affects almost one third of patients with AIDS. It tends to progress rapidly and often result in blindness.[20]

Immunocompromised patients who present CMV infection are usually treated symptomatically with antipyretic drugs and NSAIDs.[21] However, the most effective treatment for CMV infections has been ganciclovir. This drug should be maintained to prevent relapse in cases of immune dysfunction. Mouth ulcers may have co-infection with CMV and HSV. Intravenous ganciclovir is effective for the treatment of cases of co-infection. If there is resistance to ganciclovir, other drugs may be used, such as foscarnet, cidofovir, and valganciclovir. CMV and HSV coinfections were not found in the cases reported here, since HSV serology was negative.

CONCLUSION

Two cases of CMV infection in immunocompromised patients by acquired immunodeficiency syndrome with oral manifestation have been reported. The dentist must be able to make the correct diagnosis of ulcerations in the mouth to promote the correct treatment of these entities. In addition, they must be aware that CMV may also be responsible for the induction of oral ulcers, especially in patients with immunosuppression.

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