J Oral Med Oral Surg 2019;25:22
https://doi.org/10.1051/mbcb/2019006

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Short Case Report

A rare case of cytomegalovirus induced oral ulcer in an immunocompromised patient

Samuel Huang[1,2,*], Isabelle Delacroix[3], Diane Labrousse[2]

[1] Interne en Chirurgie Orale, Université Paris Diderot, Paris, France
[2] Service d'ORL-Stomatologie, Hôpital Intercommunal de Créteil, Créteil, France
[3] Service de Médecine Interne, Hôpital Intercommunal de Créteil, Créteil, France

(Received: 19 July 2018, accepted: 23 February 2019)

Keywords:
oral ulcers / cytomegalovirus / immuno-compromised patient

Abstract – Introduction: Oral manifestations of cytomegalovirus are rare. **Observation:** We report the case of an atypical and persistent oral location of cytomegalovirus, in the form of ulcers, in a patient suffering from granulomatosis with polyangiitis and treated by rituximab. **Discussion:** In front of a chronic ulcer, a differential diagnosis must be made to exclude different etiologies, by order of severity, frequency or according to the clinical situation of the patient. The main differential diagnosis that must be excluded is a squamous-cell carcinoma. **Conclusion:** Cytomegalovirus ulcers are not specific and its etiology cannot be affirmed clinically. A pathological examination is essential to allow the quick establishing of a treatment in an immuno-compromised patient to prevent further complications.

Observation

A 65-year-old patient treated for granulomatosis with polyangiitis (formerly known as Wegener's disease) since 2003 was referred to our institute due to intraoral ulceration.

He was initially treated with cyclophosphamide (Endoxan®) bolus (chemotherapy) followed by corticosteroid therapy and azathioprine (Imurel®) (immunosuppressive) until 2006.

Following relapse of the condition in September 2017, four successive infusions of rituximab (375 mg/m^2) spaced a week apart and general corticosteroid therapy with prednisone (55 mg/day for 3 months) were initiated.

Intraoral clinical examination of the patient revealed a painful vestibular gingival ulcer near teeth 33-34; the ulcer appeared few days after the first rituximab infusion and had a fibrinous base with well-defined contours (Fig. 1); no budding, swelling, or associated adenopathy was observed. Tooth 34 was mobile and had considerable amount of tartar on the front side.

The patient exhibited no extraoral clinical symptoms.

Ulcerated gingivitis with no signs of granulomatosis or tumor lesions was diagnosed based on the initial biopsy performed in September 2017 in the otorhinolaryngology department. Scaling and avulsion of tooth 34 were scheduled to eliminate local irritating factors. Moreover, the results of serological tests for syphilis, Human immunodeficiency virus (HIV), and hepatitis C and B were all negative.

Because the ulcer persisted, in November 2017, another biopsy was performed, this time in the oral surgery department. Immunohistochemical analysis revealed a cytomegalovirus (CMV)-induced ulcer with a granulation tissue formation.

Because biological assessment revealed normal results and other clinical manifestations of CMV were absent, no systemic treatment was implemented and only symptomatic analgesic treatment was prescribed.

In January 2018, new ulcers were detected on the patient's tongue. Biopsy of the medial lingual ulcer (Fig. 2) revealed that the new ulcers too were CMV-induced.

Serological tests performed *via* polymerase chain reaction (PCR) confirmed CMV in the blood and found herpes simplex virus type 1 DNA on the lingual ulcers. Because the first ulcer persisted and new lesions appeared and CMV was confirmed, treatment with ganciclovir (Cymevan®; 500 mg) was initiated for 2 weeks, which improved the ulcers.

Commentary

This case describes an atypical and persistent localization of CMV in the form of multiple oral ulcers.

Human CMV (HHV-5) belongs to the family *Herpesviridae*. Approximately 50–100% of adults have antibodies to CMV [1].

Primary infection usually occurs during childhood and is asymptomatic, except in immunocompromised patients or newborns.

* Correspondence: sch.samhuang@gmail.com

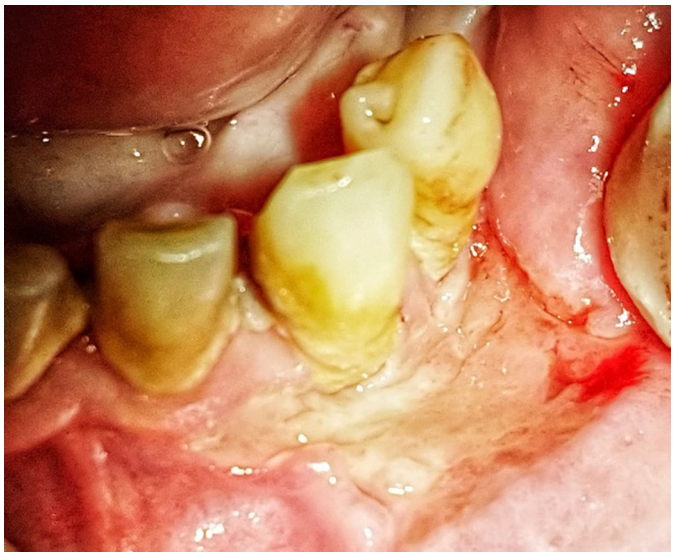

Fig. 1. Intraoral view of the gingival ulcer.

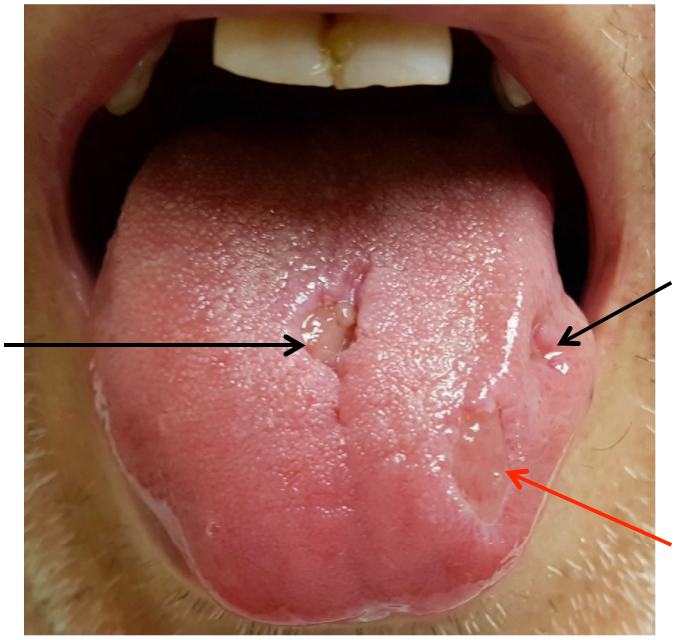

Fig. 2. Cytomegalovirus-induced lingual ulcers (black arrows) and erosion (red arrow).

In infected hosts, the cellular tropism of the virus is extensive, thereby contributing to the diversity of clinical symptoms. The virus is particularly present in monocytes and lymphocytes, both of which are the main focus sites for CMV reactivation [1]. Following the primary infection, the virus remains latent in the human body.

In highly immunocompromised patients, CMV reactivation may lead to infection with viremia and massive viral excretion. The condition may manifest as leukopenia, thrombocytopenia, myalgia, arthralgia, pneumonia, hepatitis, myocarditis/pericarditis, retinitis, and/or gastrointestinal and neurological disorders [2].

Oral manifestations of the virus are rare and are mostly observed in highly immunocompromised patients, such as those with HIV, after chemotherapy or after heart or bone marrow transplants [1].

The most common oral manifestations include persistent oral ulcers or major salivary gland diseases (*e.g.*, hyposialia). In rare cases, CMV can cause gingival hyperplasia, periodontal disease, and/or sinusitis. CMV is frequently associated with other members of the family *Herpesviridae* [1].

Oral ulcers can occur in any part of the oral cavity but are most commonly found in the hard or soft palate. They are persistent, mostly unique, painful, and shallow and present a yellowish pseudomembrane and irregular margins [1].

Histologically, endothelial cells are altered; moreover, infected cells have a large cytoplasm with nuclear inclusions [2].

Detection of viral DNA *via* PCR using blood or cerebrospinal fluid as the sample is the technique of choice for diagnosis. Immunohistochemistry or *in situ* hybridization can also be used for diagnosis from biopsies; however, the results can be ambiguous if only few cells are affected. Further, the link between ulcers and CMV cannot be confirmed without further testing using PCR.

Ganciclovir is the first line of treatment for highly immunocompromised (those with transplantation and/or AIDS) and symptomatic (those with induction therapy with 5 mg/kg of the drug twice a day for 14–21 days) patients [2]. For patients with CMV infections treated with immunosuppressive agents for chronic inflammatory disease, curative treatment can be suggested even in the absence of a threatening clinical condition because the disease course is unpredictable and potentially serious [3].

In the event of chronic ulcers, differential diagnoses should be eliminated. The main differential diagnosis that should be excluded is squamous cell carcinoma. The other differential diagnoses that should be eliminated (in the order of frequency and severity) are as follows: infectious disease-induced ulcers (*e.g.*, tuberculosis and syphilis), inflammatory diseases (*e.g.*, chronic inflammatory intestinal disease), autoimmune disorders, hematological disorders (*e.g.*, neutropenia), and deficiencies (*e.g.*, iron, vitamin B9, and vitamin B12 deficiencies). Ulcers related to Wegener's disease and those that have resulted secondary to the drug toxicity of rituximab are the main differential diagnoses to be considered in this case.

According to the literature, rituximab use is associated with CMV infections. Patients treated with rituximab for hematologic diseases exhibited increased risk of developing CMV-related complications [4]. Rituximab is a monoclonal antibody that leads to B lymphocyte depletion with immunoglobulin level decrease. The use of rituximab in the treatment of granulomatosis with polyangiitis may reactivate some latent viruses; however, no such case has yet been reported (pilot study with small sample) [5].

Because CMV-induced ulcers are usually not very specific and indicative of the etiology, anatomopathological examination, which allows for rapid implementation of the appropriate treatment in immunocompromised patients, becomes essential for preventing complications.

Conflicts of interest: The authors declare that they have no conflicts of interest in relation to this article.

References

1. Doumas S, Vladikas A, Papagianni M, Kolokotronis A. Human cytomegalovirus-associated oral and maxillo-facial disease. Clin Microbiol Infect 2007;13:557-559
2. Mainville GN, Marsh WL, Allen CM. Oral ulceration associated with concurrent herpes simplex virus, cytomegalovirus, and Epstein-Barr virus infection in an immunocompromised patient. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;119(6):306-314
3. Tnani N, Massoumi A, Lortholary O, Soussan P, Prinseau JA, Baglin A, *et al.* Prise en charge de l'infection à cytomégalovirus symptomatique chez les patients traités par immunosuppresseurs pour une maladie inflammatoire chronique. Rev Med Interne 2008;29:305-310
4. Lee MY, Chiou TJ, Hsiao LT, Yang MH, Lin PC, Poh SB, *et al.* Rituximab therapy increased post-transplant cytomegalovirus complications in Non-Hodgkin's lymphoma patients receiving autologous hematopoietic stem cell transplantation. Ann Hematol 2008;87:285-289
5. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: Report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006;173:815-816