CASE 1

# Ulcerative Stomatitis

Nina Zidar and Katarina Dimnik

## Clinical Presentation

A 44-year-old male with a 2-year history of dermatomyositis, treated with corticosteroids, developed painful ulcers on the tongue and hard palate, measuring up to 1 cm in the largest diameter. Incisional biopsy was performed. Following the biopsy diagnosis, he was treated with ganciclovir, and the ulcers slowly healed within the next 3 weeks and have not recurred.

## Histopathology

Biopsy shows oral mucosa with ulcers, covered by fibrinous exudate with necrotic debris, with a few inflammatory cells (Figure 1). In the adjacent epithelium and in the exudate, there are enlarged epithelial squamous cells (Figure 2A), some of which are multinucleated and contain nuclear inclusions, suggesting herpes simplex virus (HSV) infection, which was confirmed by immunohistochemistry (Figure 2B). In the subepithelial stroma, some endothelial cells in small blood vessels are enlarged, with large basophilic nuclei (Figure 3A), suspicious for infection with cytomegalovirus (CMV), which was also confirmed by immunohistochemistry (Figure 3B).

## Diagnosis

Ulcerative stomatitis, caused by coinfection with HSV 1 and CMV.

## Pearls

- Oral ulcers are frequent in immunocompetent and immunocompromised patients [1,2].
- They can be caused by various agents including tumors, precancerosis, infections (with fungi, bacteria, viruses), trauma, mechanical irritation, and drugs.
- A biopsy is needed to make the correct diagnosis.
- Herpes viruses are the most common viral infection of the oral mucosa.
- In an immunocompetent host, primary infection and reactivation are either asymptomatic or result in a self-limited disease.

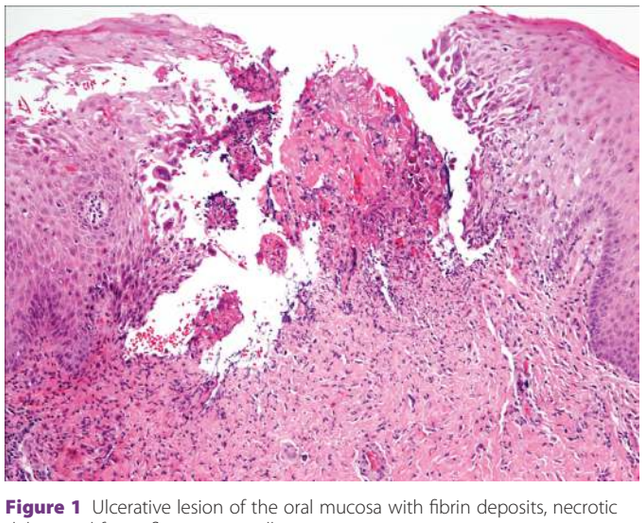

**Figure 1** Ulcerative lesion of the oral mucosa with fibrin deposits, necrotic debris, and few inflammatory cells.

(A)

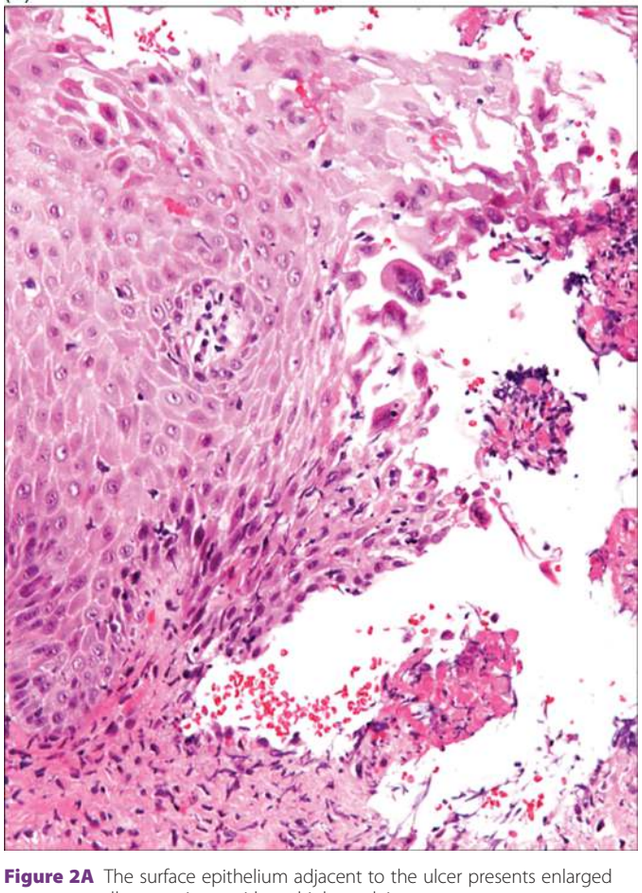

**Figure 2A** The surface epithelium adjacent to the ulcer presents enlarged squamous cells, sometimes with multiple nuclei.

(B)

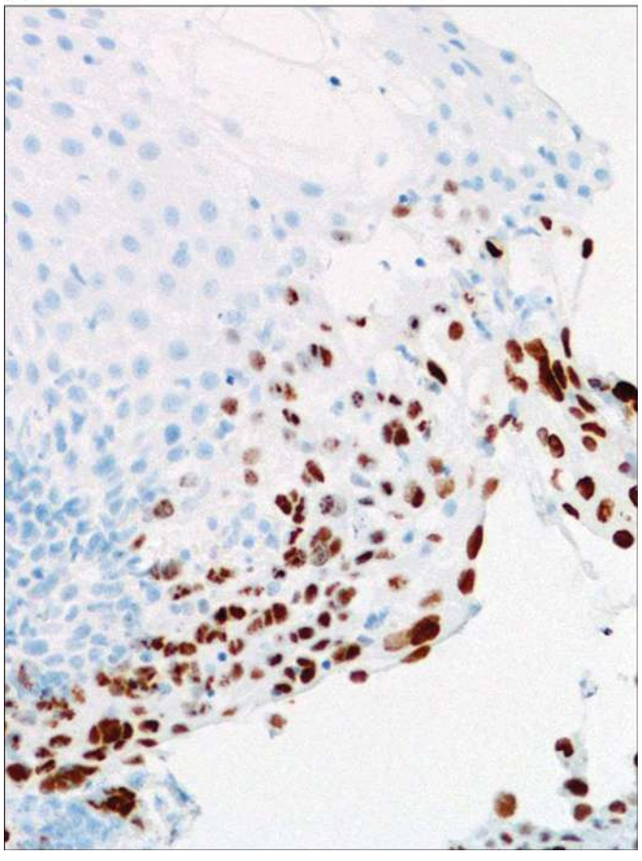

**Figure 2B** Nuclear positivity for HSV.

(A)

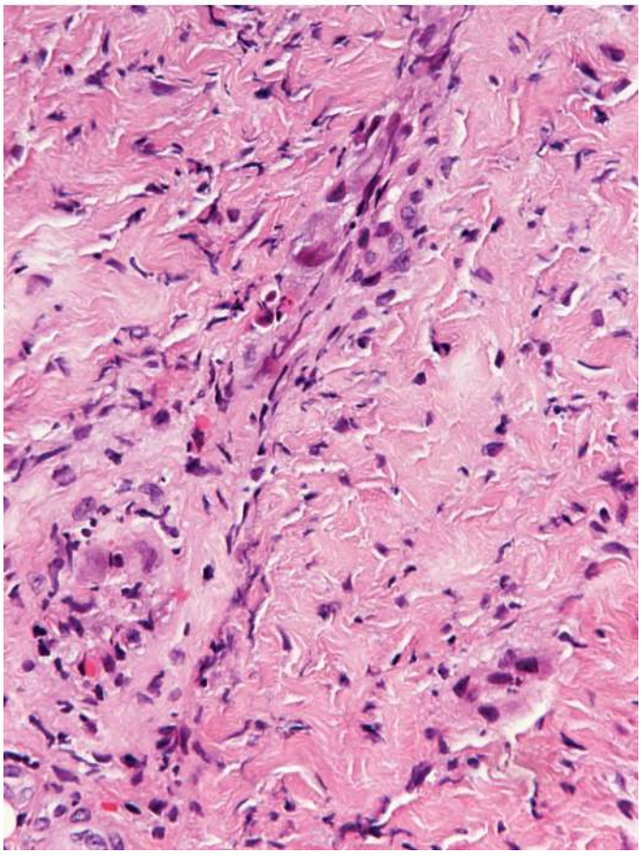

**Figure 3A** Some of the endothelial cells of subepithelial vessels are enlarged, suggesting infection with cytomegalovirus.

- In an immunosuppressed host, primary infection and reactivation, particularly with CMV, may result in a severe disease, with a high mortality rate.
- Diagnosis can usually be made on the basis of characteristic morphologic features.
- Sometimes CMV inclusions are small, without the halo, also referred to as atypical inclusions, and in these cases, immunohistochemistry and/or polymerase chain reaction (PCR) is needed to confirm the diagnosis [3].
- Coinfection with HSV and CMV is well documented in HIV-positive patients but can also occur in other immunosuppressed patients [4,5].

## Pitfalls

- HSV infection in the oral mucosa is usually easily recognized on the basis of characteristic morphologic features, while CMV infection can be missed, particularly when the characteristic viral inclusions are not present.
- It is clinically important to recognize CMV infection, as it suggests the possibility of a systemic CMV disease, which is associated with high morbidity and mortality.

(B)

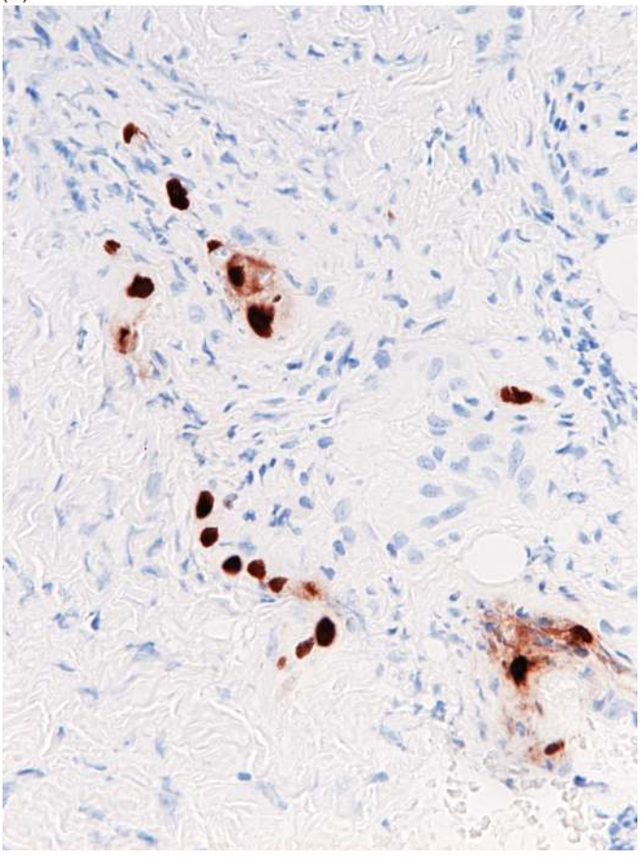

**Figure 3B** Nuclear positivity for CMV.

## References

1. Reichart PA. Oral ulcerations in HIV infection. *Oral Dis*. 1997;3 Suppl 1: S180–S182.
2. Schubert MM, Epstein JB, Lloid ME, Cooney E. Oral infections due to cytomegalovirus in immunocompromised patients. *J Oral Pathol Med*. 1993;22:268–273.
3. Zidar N, Ferkolj I, Tepeš K, Štabuc B, Kojc N, Uršič T, et al. Diagnosing cytomegalovirus in patients with inflammatory bowel disease – by immunohistochemistry or polymerase chain reaction? *Virchows Arch*. 2015;466:533–539.
4. Flaitz CM, Nichols CM, Hicks MJ. Herpesviridae-associated persistent mucocutaneous ulcers in acquired immunodeficiency syndrome. *Oral Surg Oral Med Oral Pathol*. 1996;81:443–441.
5. Lima RB, Santos PS, Malafronte P, Muller H, Caiaffa-Filho HH, Sens YA. Oral manifestation of cytomegalovirus associated with herpes simplex virus in renal transplant recipient. *Transplant Proc*. 2008;40:1378–1381.

# CASE 2 Mucosal Leishmaniasis

Llucia Alos and Paola Castillo

## Clinical Presentation

A 56-year-old woman with a clinical history of rheumatoid arthritis for 15 years was on treatment with methotrexate, corticosteroids, and TNF-α antagonists at the moment of the current disease. The patient was admitted with a two-month history of a progressive infiltrative mucosal tumor affecting the upper lip, hard palate, and nasal septum (Figure 1A, B). Oral antibiotics and antifungals were administered without clinical improvement. Because of the progression of the lesions, two biopsies from the lip were carried out. The clinical diagnosis of lymphoma was initially suspected.

## Histopathology

Histopathology revealed a diffuse polymorphic cellular infiltrate composed of small mononuclear inflammatory cells, mostly lymphocytes and histiocytes (Figure 2A, B). Ulceration and areas of necrosis were observed (Figure 2C). High-power magnification showed numerous small, round, basophilic intracellular amastigotes with kinetoplasts, indicative of leishmaniasis (Figure 2D). The polymerase chain reaction (PCR) for *Leishmania*-specific DNA sequencing was positive for *Leishmania infantum*.

## Diagnosis

Mucosal leishmaniasis (ML) with pseudolymphomatous inflammatory reaction.

## Pearls

- Leishmaniasis is a prevalent disease in 88 countries across four continents and it is endemic in Mediterranean countries.
- Estimates suggest that 1.6 million new cases are reported annually; however, the real burden of ML is largely unknown [1].
- Leishmaniasis is a vector-borne disease that is transmitted by sandflies and caused by obligate intracellular protozoa of the genus *Leishmania*.
- Human infection is caused by about 21 species that infect mammals.
- The different species are morphologically indistinguishable, but they can be differentiated by isoenzyme analysis, molecular methods, or monoclonal antibodies [2].
- ML is a destructive disease that predominantly affects the larynx, oral cavity, and nose [3].
- The histological features of ML may vary from a nonspecific polymorphic infiltrate to a granulomatous inflammatory reaction, with or without necrosis [4–6].
- The diagnosis of the disease is based on the demonstration of *Leishmania* amastigotes in the mucosal lesions through a Giemsa stain [4,6,7] or immunohistochemistry [8].

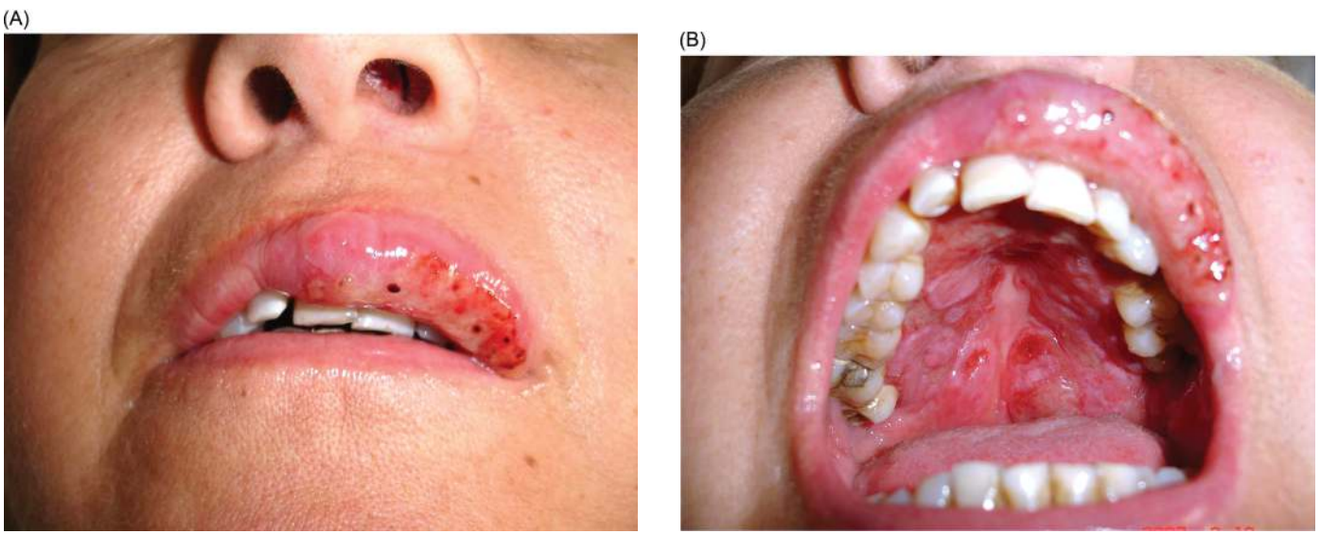


**Figure 1** A 56-year-old woman with a two-month history of a progressive infiltrative mucosal tumor. **(A)** The tumor ulcers affect the upper lip. **(B)** The tumor also affects the hard palate.

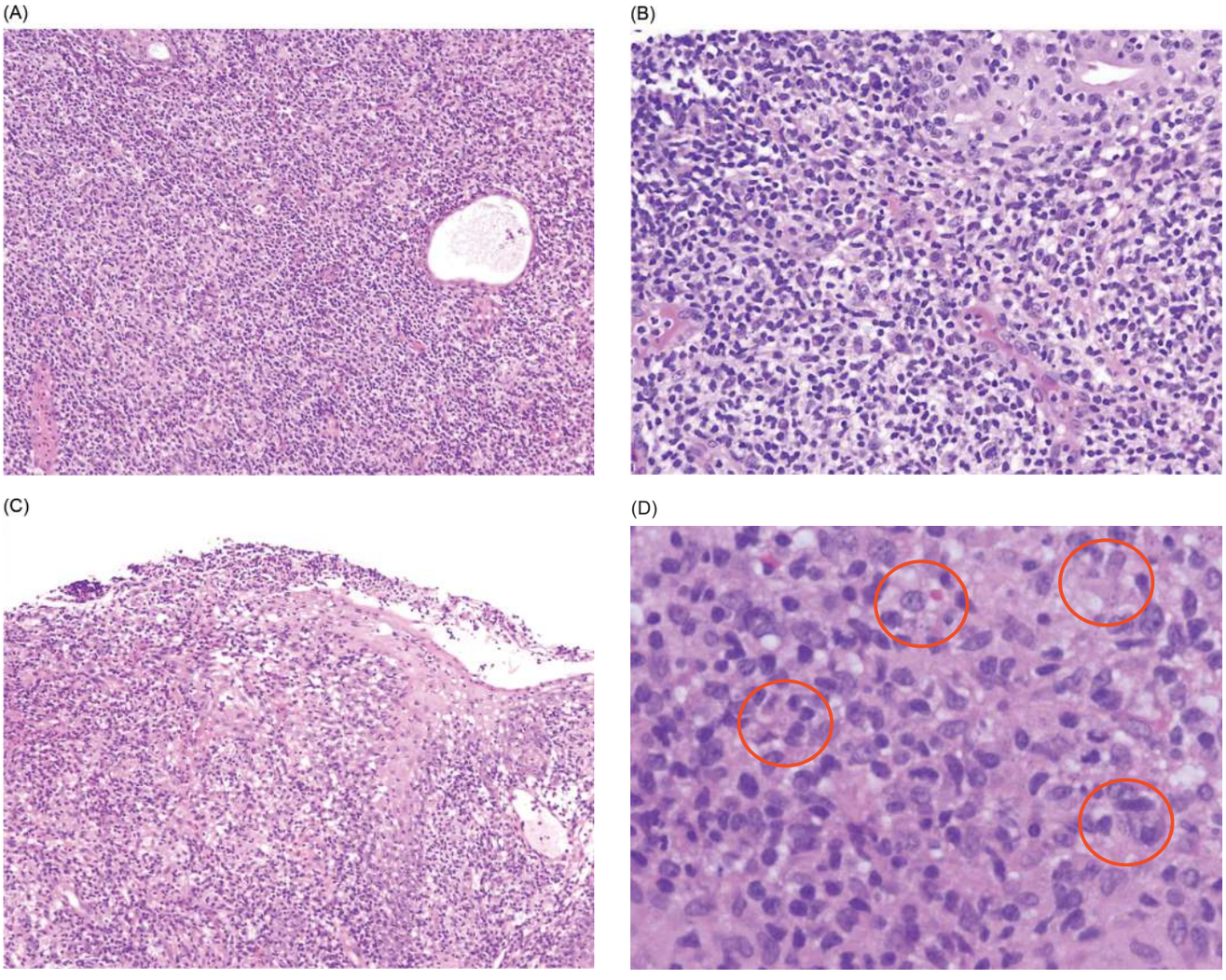


**Figure 2** Histopathology. **(A and B)** Diffuse polymorphic cellular infiltrate composed of small mononuclear inflammatory cells, mostly lymphocytes and histiocytes (hematoxylin and eosin, 100× and 200×, respectively). **(C)** Ulceration of the epithelium (hematoxylin and eosin, 100×). **(D)** Numerous small, round, basophilic intracellular amastigotes (red circles) indicative of leishmaniasis (hematoxylin and eosin, 400×).

- However, sometimes, there are too few parasites in the lesions to be visualized by microscopy, and more sensitive tests to evaluate ML such as the identification of *Leishmania* DNA by PCR are required [9,10].
- In up to 30% of the cases, ML appears after a treated cutaneous leishmaniasis. Of note, after diagnosis, this patient revealed a past history of cutaneous leishmaniasis (Figure 3).

## Pitfalls

- Depending on the clinical setting (e.g., immunosuppression), it is mandatory to rule out lymphoproliferative disorders, especially those associated with immunosuppression, which usually are Epstein—Barr virus driven, such as natural killer/T-cell lymphomas, nasal type, and lymphomatoid granulomatosis, both showing positive in situ hybridization for EBV in atypical cells.
- NK/T-cell lymphoma, nasal type, usually affects nasal cavities with extension to adjoining tissues and oral cavity and exhibits atypical CD56+ cytotoxic T cells.
- In contrast, lymphomatoid granulomatosis shows an atypical B-cell proliferation associated with exuberant T-cell reaction.
- Although rarely reported in the nasal cavity, peripheral T-cell lymphomas should be also ruled out since the histological features may include admixed inflammatory cells and even clusters of epithelioid histiocytes [11].

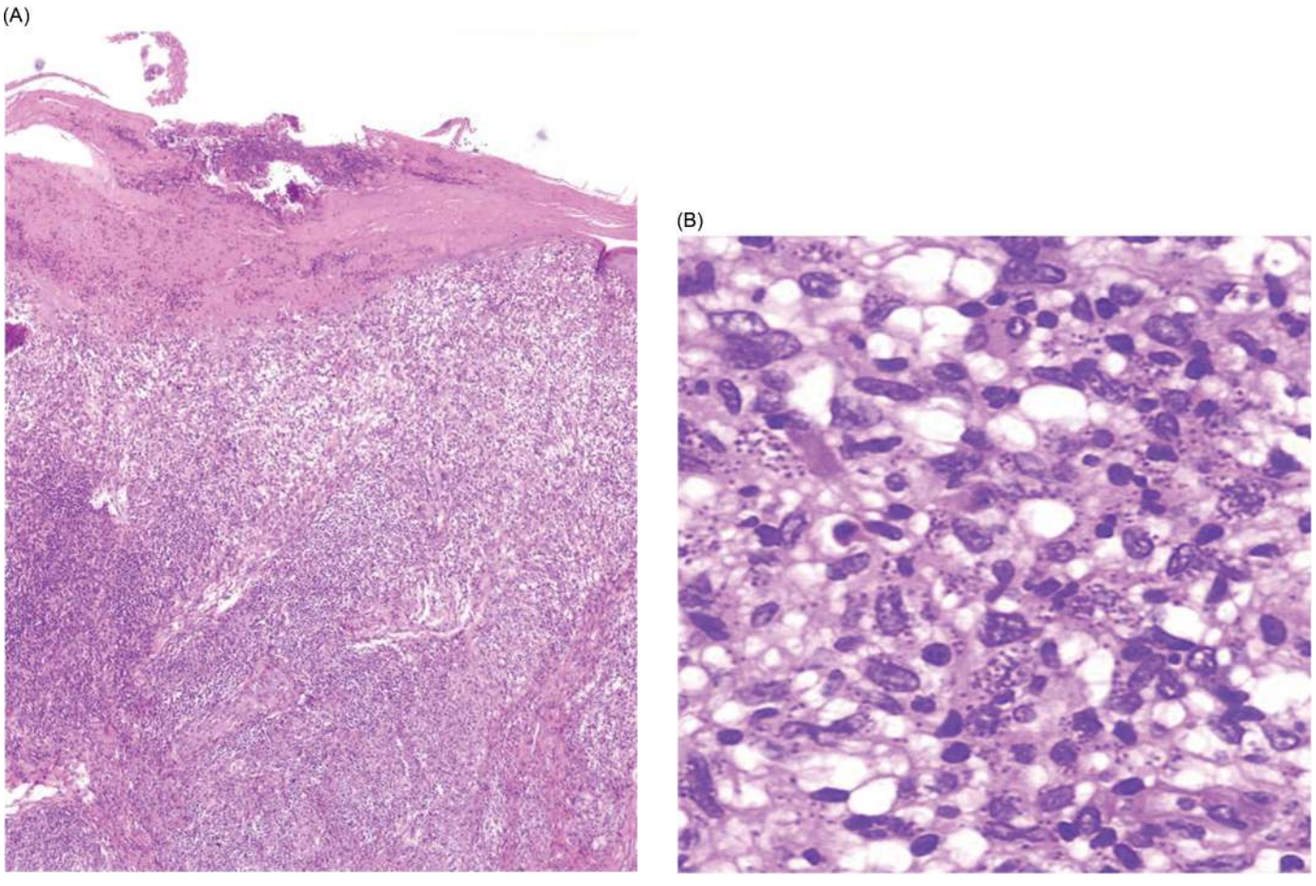


**Figure 3** Cutaneous leishmaniasis. **(A)** Leg skin biopsy showing a cellular infiltrate and ulceration (hematoxylin and eosin, 100×). **(B)** In this biopsy, intracellular amastigotes of leishmaniasis are easily observed (hematoxylin and eosin, 400×).

- Other differential diagnoses are inflammatory conditions, such as granulomatosis with polyangiitis (Wegener), which usually show an inflammatory component, with lymphoid cells and histiocytes; however, necrotizing vasculitis of medium-sized vessels is a characteristic feature not seen in ML.
- Some specific infectious processes that can also cause necrotizing sinonasal lesions include, among others, mycobacterial infection, syphilis, and rhinoscleroma [12,13]. All of them were excluded with special stains and microbiological analyses.
- Another etiological agent to take into account is *Histoplasma capsulatum*, a small intracellular fungus.

## References

1. World Health Organization. *Working to overcome the global impact of neglected tropical disease: first WHO report on neglected disease*. Geneva, Switzerland: World Health Organization; 2010.
2. Procop GW, Pritt BS, eds. *Pathology of infectious diseases*. Foundations in diagnostic pathology. Philadelphia, PA: Elsevier, Saunders; 2015. 707pp.
3. Aliaga L, Cobo F, Mediavilla JD, Bravo J, Osuna A, Amador JM, et al. Localized mucosal leishmaniasis due to Leishmania (Leishmania) infantum: clinical and microbiologic findings in 31 patients. *Medicine (Baltimore)*. 2003 May;82(3):147–158.
4. Daneshbod Y, Oryan A, Davarmanesh M, Shirian S, Negahban S, Aledavood A, et al. Clinical, histopathologic, and cytologic diagnosis of mucosal leishmaniasis and literature review. *Arch Pathol Lab Med*. 2011 Apr;135(4):478–482.
5. Cobo F, Rodríguez-Granger J, Gómez-Camarasa C, Sampedro A, Aliaga–Martínez L, Navarro JM, et al. Localized mucosal leishmaniasis caused by Leishmania infantum mimicking cancer in the rhinolaryngeal region. *Int J Infect Dis*. 2016 Sept;50:54–56.
6. Kevric I, Cappel MA, Keeling JH. New world and old world leishmania infections. *Dermatol Clin*. 2015 Jul;33 (3):579–593.
7. Herwaldt BL. Leishmaniasis. *The Lancet*. 1999 Oct;354(9185):1191–1199.
8. Kenner JR, Aronson NE, Bratthauer GL, Turnicky RP, Jackson JE, Tang DB, et al. Immunohistochemistry to identify Leishmania parasites in fixed tissues. *J Cutan Pathol*. 1999 Mar;26 (3):130–136.

9. Oliveira JGS, Novais FO, de Oliveira CI, da Cruz Junior AC, Campos LF, da Rocha AV, et al. Polymerase chain reaction (PCR) is highly sensitive for diagnosis of mucosal leishmaniasis. *Acta Trop*. 2005 Apr;94(1):55–59.
10. Scope A, Trau H, Anders G, Barzilai A, Confino Y, Schwartz E. Experience with New World cutaneous leishmaniasis in travelers. *J Am Acad Dermatol*. 2003 Oct;49(4):672–678.
11. Crane GM, Duffield AS. Hematolymphoid lesions of the sinonasal tract. *Semin Diagn Pathol*. 2016 Mar;33(2):71–80.
12. Montone KT. Differential diagnosis of necrotizing sinonasal lesions. *Arch Pathol Lab Med*. 2015 Dec;139 (12):1508–1514.
13. Handler MZ, Patel PA, Kapila R, Al-Qubati Y, Schwartz RA. Cutaneous and mucocutaneous leishmaniasis. *J Am Acad Dermatol*. 2015 Dec;73 (6):911–926.

# CASE 3 Oral Lichen Planus

Llucia Alos and Paola Castillo

## Clinical Presentation

An 84-year-old woman presented reticulate, lace-like and white keratotic bilateral lesions in the oral mucosa. No bullous or ulcerated lesions were observed (Figure 1). The diagnosis of oral lichen planus (OLP) was suspected and one lesion was biopsied.

## Histopathology

The lesion was composed of a dense, band-like, and lymphocytic inflammatory infiltrate in the superficial stroma, which obscured the junction of the epithelium and lamina propria (Figure 2). Liquefactive degeneration of the basal layer with subepithelial clefts and necrotic degenerated keratinocytes (Civatte bodies) were seen (Figures 3 and 4). Dysplasia was not observed.

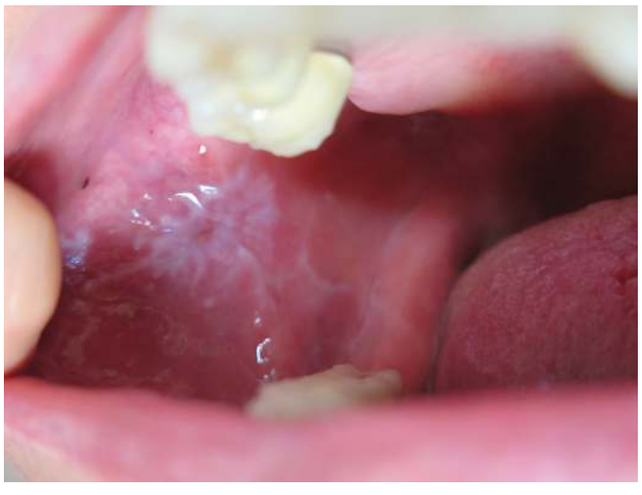

**Figure 1** Oral lichen planus, clinical image. The lesion exhibits a reticulate and white keratotic appearance.

## Diagnosis

Oral lichen planus.

## Pearls

- OLP usually involves the buccal mucosa (up to 90%), gingiva, dorsum of the tongue, labial mucosa, and lower vermilion lip. Less common sites include the palate, upper lip, and floor of the mouth [1,2].
- Women are more commonly affected than men. Onset of disease occurs around the fifth or sixth decade of life [1,2].
- Etiology of OLP is unknown. However, infectious, autoimmune, and genetic causes have been proposed. The association with hepatitis C-infection and human leukocyte antigen (HLA)-DR and HLA-DQ has been observed by some authors [2,3].
- OLP is a subacute to chronic disease with rare remission [2]. A malignant transformation of OLP has been reported from 0.8% to 3% of cases [2,4].

## Pitfalls

- Oral lichenoid drug reactions and oral lichenoid contact reactions may be histologically indistinguishable

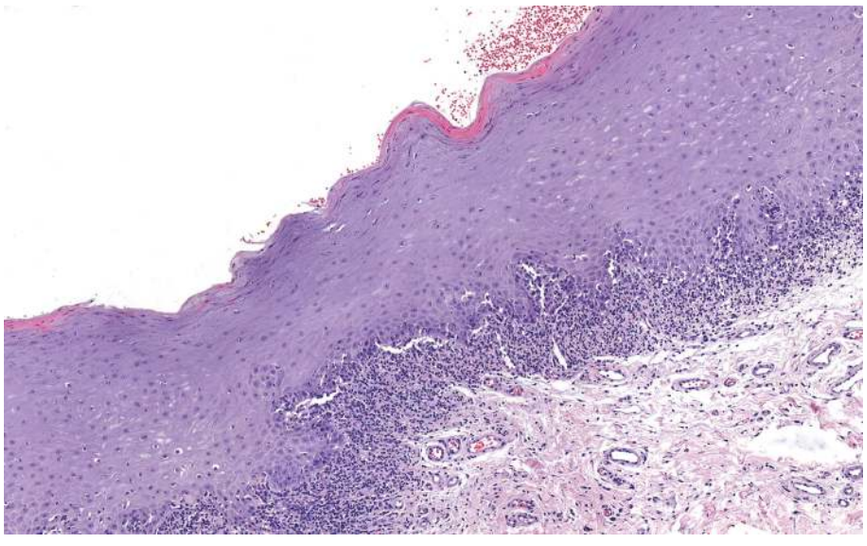

**Figure 2** Oral lichen planus, histology. The lesion is composed of a dense, band-like, lymphocytic, and superficial inflammatory infiltrate (hematoxylin and eosin, 40×).

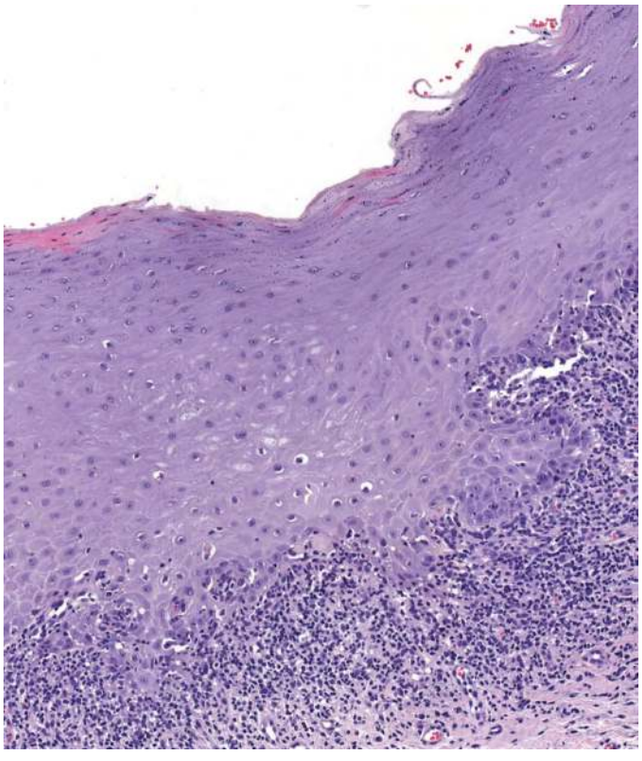

**Figure 3** Oral lichen planus, histology. The inflammatory infiltrate obscures the junction of the epithelium with irregular epithelial hyperplasia. Dysplasia is not observed (hematoxylin and eosin, 200×).

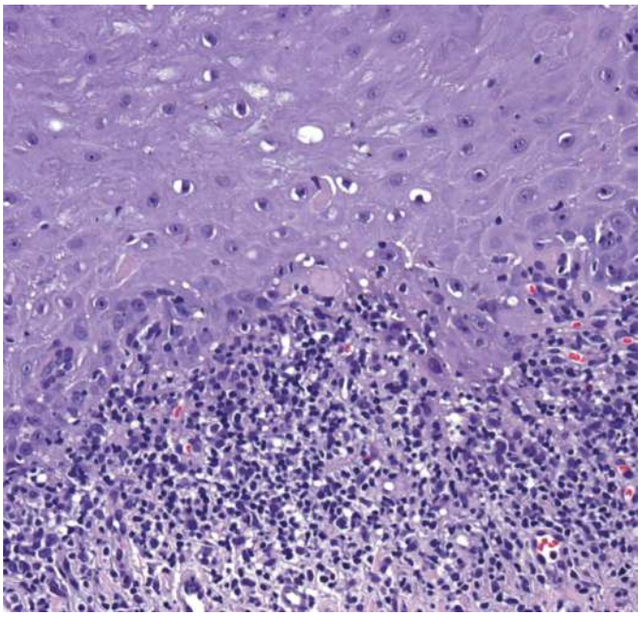

**Figure 4** Oral lichen planus, histology. Hydropic degeneration and necrotic keratinocytes (Civatte bodies) are observed in the epithelium (hematoxylin and eosin, 400×).

from OLP. However, both entities generally resolve once the causative agent has been eliminated [5].

- The differential diagnosis of OLP includes the lichenoid dysplasia, a variant of oral epithelial dysplasia [6].
- To perform the diagnosis of OLP, a clinicopathological correlation is mandatory [7].

## References

1. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J Am Acad Dermatol*. 2002; 46:207–214.
2. Carbone M, Arduino P, Carrozzo M, Gandolfo S, Argiolas MR, Bertolusso G, et al. Course of oral lichen planus: a retrospective study of 808 northern Italian patients. *Oral Dis*. 2009;15: 235–243.
3. Nagao Y, Nishida N, Toyo-Oka L, Kawaguchi A, Amoroso A, Carrozzo M, et al. Genome-wide association study identifies risk variants for lichen planus in patients with hepatitis C virus infection. *Clin Gastroenterol Hepatol*. 2017;15:937–944.
4. Bermejo-Fenoll A, Sanchez-Siles M, López-Jornet P, Camacho-Alonso F, Salazar-Sanchez N. Premalignant nature of oral lichen planus: a retrospective study of 550 oral lichen planus patients from South-Eastern Spain. *Oral Oncol*. 2009;45: e54–e56.
5. Schlosser BJ. Lichen planus and lichenoid reactions of the oral mucosa: oral lichen planus and lichenoid reactions. *Dermatol Ther*. 2010;23:251–267.
6. Mittal K, Jha M, Patil RS, Kapoor S. Lichenoid dysplasia – a case report with a review of differential diagnosis. *J Clin Diagn Res*. 2017;11(5):ZD01–ZD02.
7. van der Meij EH, Reibel J, Slootweg PJ, van der Wal JE, de Jong WF, van der Waal I. Interobserver and intraobserver variability in the histologic assessment of oral lichen planus. *J Oral Pathol Med*. 1999;28:274–277.

# CASE 4 Proliferative Verrucous Hyperplasia

Alessandro Franchi

## Clinical Presentation

A 69-year-old nonsmoking female presented with multiple white plaques with irregular, rough surface on the gingiva of the mandible and palate.

## Histopathology

The incisional biopsy of the larger lesion showed verruciform hyperplasia of the surface epithelium, marked hyperortho- and parakeratosis, and presence of mild atypia, with few suprabasal mitotic figures (Figures 1–3). A chronic lymphohistiocytic infiltrate of the interface was also noted.

## Diagnosis

Proliferative verrucous hyperplasia.

## Pearls

- Proliferative verrucous leukoplakia is a distinctive and aggressive form of oral precancerous lesion, which is associated with high recurrence and malignant transformation rates [1,2].
- It is mostly seen in older women (>60 years) and it is not associated with the usual risk factors for oral cancer, including tobacco and alcohol use [1].
- No association with HPV or other viruses has been detected as well.
- Proliferative verrucous leukoplakia is a multifocal disease which more frequently involves the gingiva, the alveolar mucosa, the palate, while the tongue and the floor of the mouth are less frequently involved [1,2].
- The risk of malignant transformation is high (around 70%) and progression occurs to either verrucous squamous cell carcinoma or conventional squamous cell carcinoma [3,4].

## Pitfalls

- In the early stages, proliferative verrucous leukoplakia lacks dysplasia, resulting in an underestimation of the risk of progression.
- The frequent presence of interface band-like inflammation may induce the misdiagnosis of lichen planus, which however does not present signs of atypia.

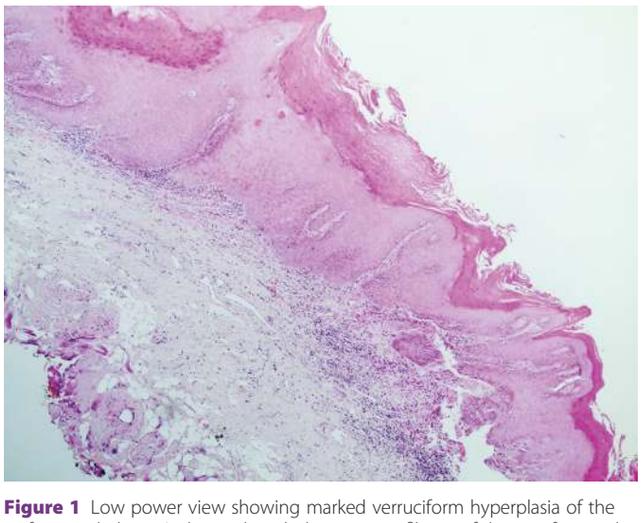

**Figure 1** Low power view showing marked verruciform hyperplasia of the surface epithelium. A chronic lymphohistiocytic infiltrate of the interface is also present.

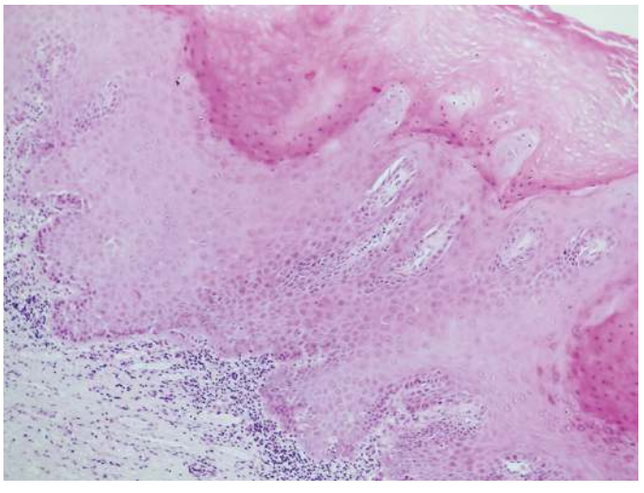

**Figure 2** There is marked hyperortho- and parakeratosis and presence of mild atypia.

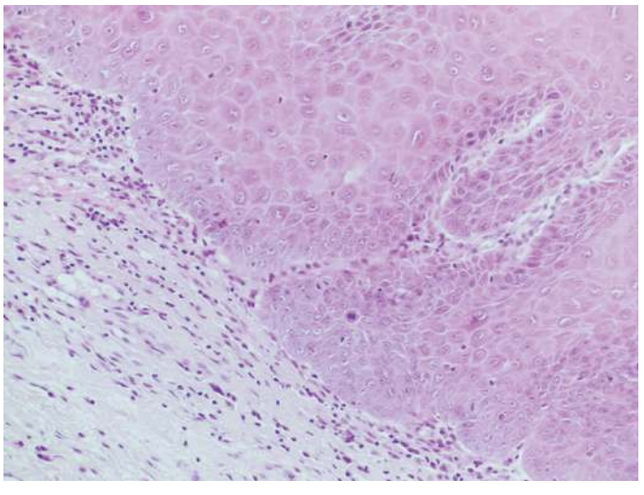

**Figure 3** A supra-basal mitotic figure is present in this field.