

# Management of erosive oral lichen planus associated with chronic hepatitis C

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## Abstract

Oral Lichen Planus (OLP) and chronic hepatitis C association have been widely discussed. Here, we presented a case of extensive, erosive OLP in a hepatitis C virus-positive patient for whom clinical management was challenging. Full remission was obtained after topical corticosteroid application and several sessions of oral cavity sanitation.

## MANUSCRIPT

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### Patient's consent

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### Abbreviations list

**HVC:** Hepatitis C virus

**OLP:** Oral lichen planus

**LP:** Lichen planus

**EHMs:** Extrahepatic manifestations

**I $\Phi$ N- $\alpha$ :** Interferon-alpha

**DAA:** Direct-acting antiviral

### ABSTRACT

Oral Lichen Planus (OLP) and chronic hepatitis C association have been widely discussed. Here, we presented a case of extensive, erosive OLP in a hepatitis C virus-positive patient for whom clinical management was challenging. Full remission was obtained after topical corticosteroid application and several sessions of oral cavity sanitation.

### Key Clinical Message

Dentists play a major role in diagnosing and managing Oral Lichen Planus. They may also contribute to hepatitis C infection screening. Thus the importance of regular follow-ups to prevent disease relapses, exacerbations, or malignant transformations.

## Keywords

Oral lichen planus, Hepatitis C virus, viral infection, oral diseases

## Introduction

The first histologically confirmed case of Oral Lichen Planus (OLP) in a patient with chronic hepatitis C was reported in 1991 (1). A meta-analysis integrating around forty studies showed that the hepatitis c virus (HCV) -OLP association was significant (2). In addition, the erosive form of OLP has been reported to be preferentially associated with HCV infection (1). However, more recent studies have shown significant variations in the OLP-HCV association according to patients' age and geographic origin (3). In particular, the presence of the broad-antigen serotype HLA-DR6 allele would be partly responsible for variations in the HCV-OLP association depending on the geographical area (4).

Hepatitis C virus is an enveloped RNA virus with an essentially hepatic tropism(5). This virus, capable of causing chronic infection in humans, is responsible for the hepatitis C epidemic, a severe consequence of which concerns the occurrence of hepatic carcinoma. The recent development of very effective antiviral molecules makes it possible today to have very effective treatments to fight against hepatitis C. However, some of these antiviral therapies such as interferon-alpha (IFN- $\alpha$ ) and ribavirin therapy were incriminated in the OLP onset (6).

This paper aims to highlight the importance of dentists' role in screening HCV infection associated with OLP, and the value of dental care and follow-ups in relieving the patient and preventing malignant transformation.

## Case report

A 70-year-old female patient consulted the oral medicine and oral surgery department of the academic dental clinic of Monastir, Monastir, Tunisia, with a chief complaint of 5 months on defusing oral lesions causing pain, burning mouth sensation, and discomfort, especially with chewing and speaking.

The medical history was significant to hypothyroidism, high blood pressure, Cardiac arrhythmia, and type II diabetes mellitus. Her medication included Levothyrox® 125 $\mu$ g per day, Actopril®, and insulin injections.

Extraoral examination showed itchy purplish patches over the arms and legs, and diffuse crusty ulcerative lesions over her lower lip (Figure 1A). These lesions were painful, bleeding with a tendency to infiltrate the adjacent skin.

The intraoral examination revealed poor oral hygiene, a deteriorated metallo-resinous bridge extending from the right mandibular canine to the second left premolar, and multiple amalgam fillings.

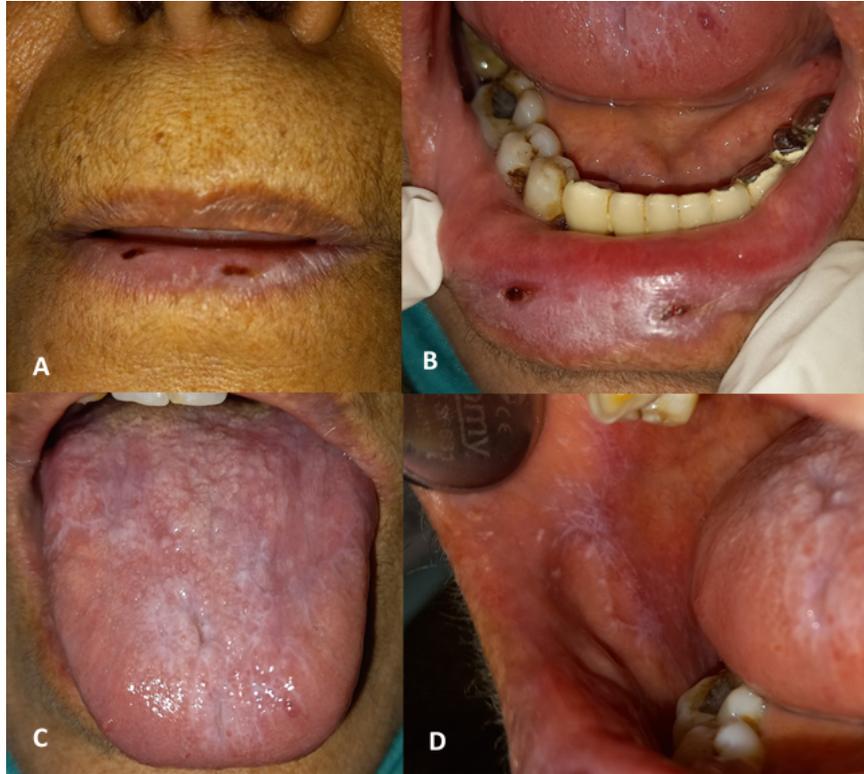
Diffuse erosive areas extending from the premolars region up to the retromolar area of the buccal mucosa were detected (Figures 1B and 1C). These erosions were surrounded by white radiating striae from the periphery of the lesions symmetrically on both sides. Similar lesions with an erythematous background were noted over the upper and lower, anterior and posterior vestibular regions, dorsal and ventral surfaces of the tongue, and the interior surface of the lower lip (Figures 1D and 1E), and posterior maxillary edentulous ridge (Figure 1F). Gingiva showed marginal erythema with superficial erosion on the attached gingiva. The lesions were extremely painful and sensitive to touch.



Although a secondary infection with candidiasis was suspected, the initial diagnosis was highly suggestive of erosive oral lichen planus.

Oral swabs were obtained from the above-mentioned locations for microbiological examinations which showed numerous pale yellowish dome-shaped colonies of *C. albicans* when cultured in Chromagar® medium.

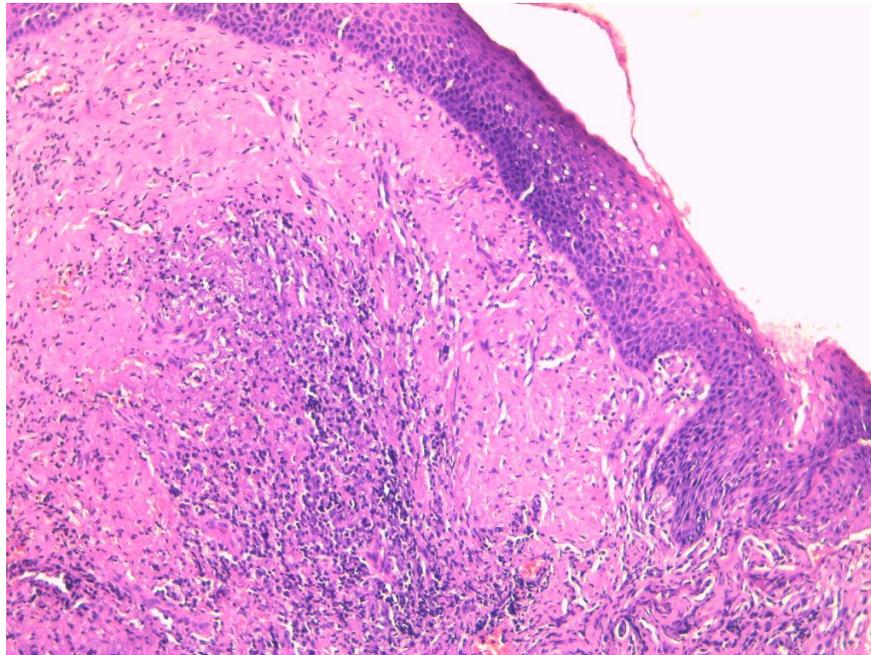
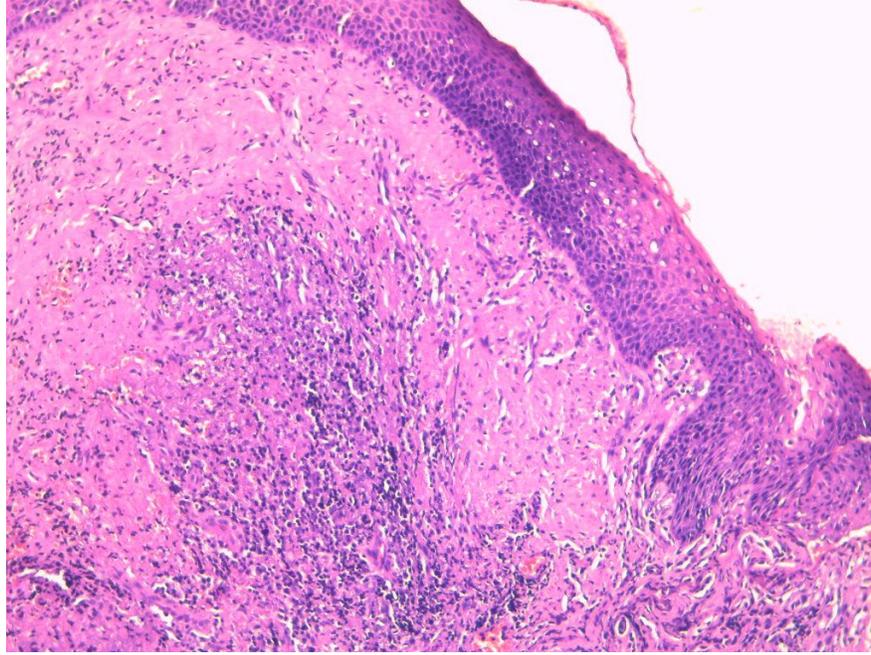
An initial prescription of antiseptic mouth wash (chlorhexidine, 0.12%) along with a topical antifungal agent (Fungizone®) 3 times a day for 2 weeks was made to treat the fungal infection. She was subjected to a complete hemogram, hepatitis B and C serology blood test, and Thyroid blood tests. After 2-week's follow-up, the patient reported a slight improvement in symptoms (Figures 2A, 2B, 2C, and 2D).



Sanitation of the oral cavity was initiated with periodontal scaling, root planning, and the removal of the bridge. Regarding the blood test results, all the hemogram parameters were found to be within the normal range. Thyroid blood tests revealed a hypothyroidism FT4: 23,88 pmol/L (10-22) and TSH < 0,05  $\mu$ L/ml (0.27-4,2), and an HCV serology using ELFA (Enzyme-Linked Fluorescent Assay) was positive.

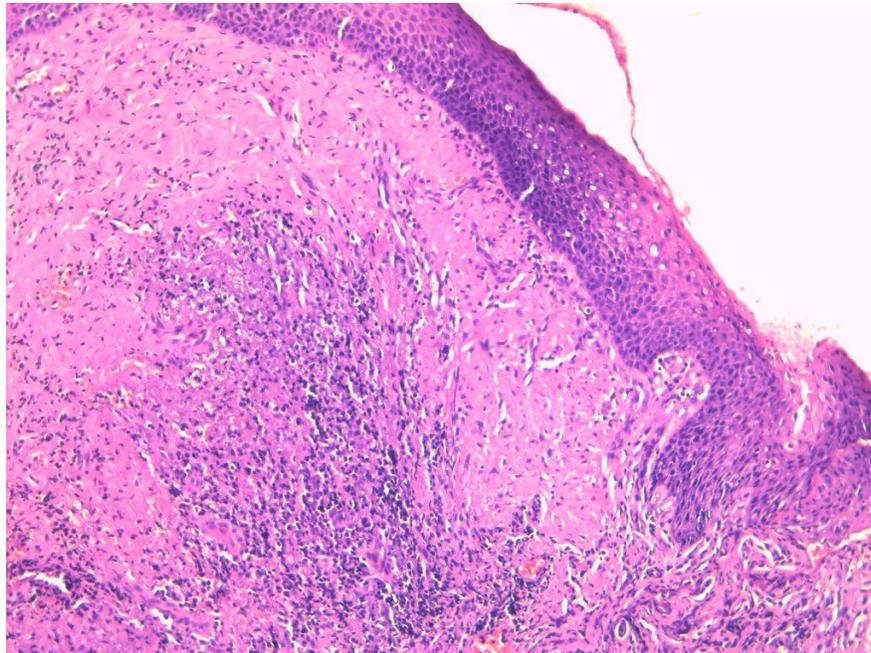
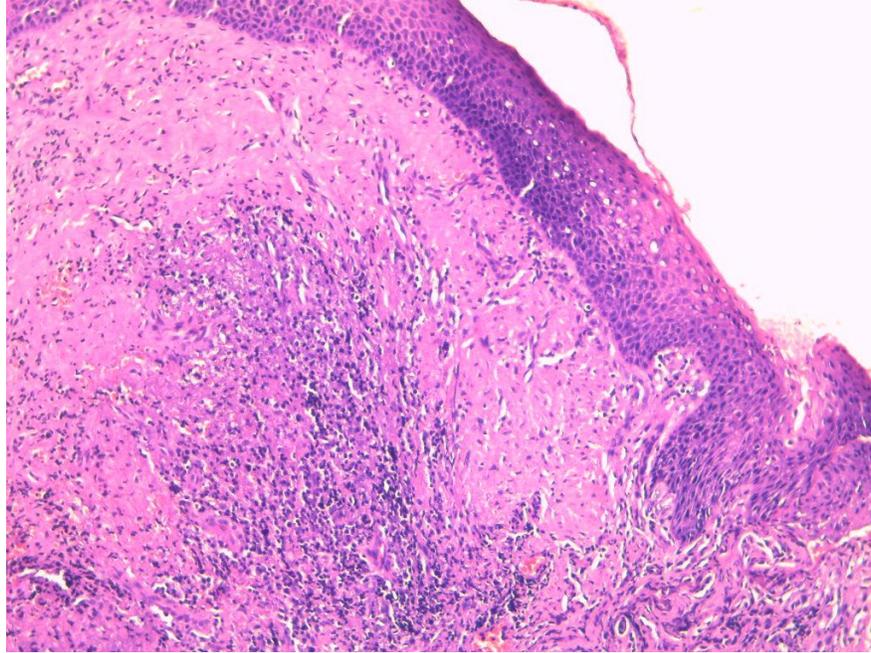
An incisional biopsy of the lesion was performed under local anesthesia (Medicaine 2% with adrenaline 1/100.000®<sup>R</sup>, Medis, Tunisia) from the left buccal mucosa. The specimen was divided into two parts, the first was kept in 10% formalin and submitted to the anatomopathological examination and the second was immediately placed in saline solution and immediately transported for direct immunofluorescence analysis.

The anatomopathological results revealed a band-like infiltrate made up of lymphocytes and plasma cells associated with liquefaction degeneration of the basal cell layer confirming the diagnosis of erosive OLP (Figure 3).



Topical corticosteroids (Solupred® 20 mg) were prescribed as a mouth rinse 3 times a day. The patient was subjected to regular follow-ups (Figures 4A, 4B, 4C, 4D, 4E, 4F) and dose tapering after 6 months when the erosive lesions and symptoms completely regressed (Figures 5A, 5B, 5C, 5D, 5E).

The patient is followed up with the collaboration of the gastroenterology and hepatology department.



## Discussion

Oral lichen planus (OLP) is a chronic inflammatory disease of unknown etiology that can occur as either a single condition of the oral mucosa or in association with lesions in genital mucosae, skin, or nails (7).

This disease is believed to affect around 0.2 to 2.3 percent of the overall population and accounts for nearly 0.6 percent of all conditions discovered by dentists regularly (7). OLP is widely distributed and affects all racial and ethnic groups, but it is most frequent in middle-aged female adults (8).

The clinical manifestations of OLP are largely polymorphic. Keratotic lesions, such as papules, reticular, or plaque-like lesions, are frequently associated with atrophic, erosive, ulcerative, or bullous forms (9). The erosive form is characterized by a variety of symptoms ranging from moderate discomfort to severe functional disturbances that affect the quality of life. Lesions are usually found bilaterally on the posterior buccal mucosa. The dorsal tongue, labial mucosa, and gingiva might also be impacted. Gingival mucosa involvement is referred as desquamative gingivitis (7).

The numerous factors that can trigger a cell-mediated reaction that results in OLP are discussed elsewhere. (7) Among the exogenous factors, several infectious agents, including viruses, have been associated with OLP.

Among the eight recognized human herpesviruses four (*Herpes simplex 1*, *Cytomegalovirus*, *Epstein-Barr virus*, *Herpesvirus 6* ) have been implicated in OLP as well as the *human papillomavirus* , the *human immunodeficiency virus*, and *hepatitis viruses B* and mainly *C* (10).

HCV infection is a common illness, with an estimated 71 million people worldwide chronically afflicted (11). Extrahepatic manifestations (EHMs) afflict about 74 percent of persons with HCV. (12).

Xerostomia, sialadenitis, Sjögren's disease, OLP, oral verrucous and squamous cell carcinomas (13), bleeding disorders, cheilitis, gingivitis, smooth and atrophic tongue, autoimmune bullous diseases such as Pemphigus Vulgaris and bullous pemphigoid (14, 15) are among the recorded EHMs in the oral cavity (15). As hepatitis C is most often asymptomatic, EHMs may be the first symptom of infection.

A recent systematic review and meta-analysis concluded that the overall prevalence of HCV in OLP patients was 22.3% (16). This prevalence varies according to geographical variations. A possible explanation is that the high co-occurrence of HCV and OLP in some geographic regions may be linked to an endemic distribution of HCV in those world regions(17).

Globally, the prevalence of HCV shows regional variations with an average of 3%, which is very likely to be underestimated. According to the latest World Health Organization global hepatitis Report in 2017 (18), the prevalence is the highest in the Eastern Mediterranean region (2.3%), followed by the European region (1.5%), whereas the South-East Asia region has the lowest prevalence (0.5%). Inside these regions, the difference in prevalence can be important (19).

In North Africa, the prevalence of HCV in the general population is estimated between 1.2 and 1.9 percent (20). Although, a recent systematic review showed that the prevalence in Tunisia between 1991 and 2019 did not exceed 1% in the general population, making it a low-endemic country (21).

Even though the association between OLP and chronic HCV infection seems to be well developed, the pathogenesis raises questions. Several hypotheses are currently being useful in explaining this association:

- The Hepatitis C virus initiates an auto-immune process, and the association of LP with other auto-immune diseases such as diabetes, vitiligo, or myasthenia gravis lends support to this theory (22).
- HCV directly affects cellular replication and causes immunological changes that lead to the occurrence of LP (23).
- In chronic HCV immunological alterations and circulating autoantibodies can emerge: anti-cardiolipin antibodies, anti-nuclear autoantibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies, rheumatoid factor, and anti-thyropoxidase antibodies. The lymphotropism of HCV explains the serological auto-immune expressions (24).

Several differences were observed when comparing OLP patients who have liver diseases and those who have a normal liver function. Thus, patients with chronic liver diseases exhibit extensive forms of OLP, with frequent periods of exacerbation of symptoms refractory to treatment, which is commensurate with the severity of the liver disease (25).

The acute erosive form of OLP is mostly related to chronic HCV infection in a phase that is biologically revealed by elevated serum levels of transaminases and increased viral replication.

Although in a recent study published by Arduino et al. (26) the automatic screening for HCV in OLP patients must be discussed since the general prevalence of HBV in the younger population is remarkably decreased.

However, in our case, it was important to investigate the viral implication of HCV since the patient was an old female living in a rural community, where there is a shortage of investigational, preventive, and educational campaigns on infectious diseases, also to manage the OLP with the collaboration of infectious disease specialists to balance the underlying and appropriate therapy.

Another issue is the necessity to test all patients diagnosed with OLP for the presence of HCV infection, as this liver disease often progresses asymptotically for a long period and goes undetected (1).

In determining the therapeutic approach of OLP, several factors must be considered; cost-effectiveness, patient's medical and dental history, drug interactions, treatment adherence, and psychological conditions. Early therapy based on a clear diagnosis is crucial (27).

Topical corticosteroids are recommended as first-line therapy for OLP (28). These drugs control inflammation and immunological response (29). If topical treatments are ineffective, systemic corticosteroids may be more useful.

Other Immunomodulatory drugs such as calcineurin inhibitors or retinoids or systemic immunosuppressives may be beneficial when topical and systemic corticosteroids are ineffective (28).

Biologic agents ( such as alefacept, efalizumab, basilixima, polysaccharide nucleic acid fraction of bacillus Calmette–Guerin (BCG-PSN)... ) have recently been used (28). However, due to the high cost, their application in OLP is limited to severe and refractory cases (28).

In OLP patients with localized plaques or non-healing erosions, surgical excision can be indicated (30). Cryosurgery has been used to treat erosive and drug-resistant OLP, however lesions may turn into scars (31).

Several research explored desquamative gingivitis in OLP patients, where gingival lesions are chronic and severe. This is caused by plaque accumulation which is higher in OLP patients, due to a decreased frequency of tooth brushing, leading to an increased risk of long-term periodontal disorders(32). Periodontal therapy including biofilm reduction, scaling, and root planning in association with a decay treatment and strict oral hygiene must be carried out with topical corticosteroids prescription for a better result (33).

In severe and refractory cases of erosive OLP, ultraviolet A (PUVA) therapy and photodynamic therapy have been employed (34).

The effect of laser therapy on erosive forms of OLP was reported in different studies (Diode laser (35), biostimulation with a pulsed diode laser (36), carbon dioxide laser evaporation (37), and low dose excimer laser with ultraviolet B rays (38)). Although promising results were reported, the effectiveness of this treatment approach is yet to be proven (34).

For HCV management, interferon-alpha (IFN- $\alpha$ ) monotherapy or combined therapy of IFN- $\alpha$  and ribavirin are typical treatments for chronic HCV. Several studies investigated the effect of IFN- $\alpha$  therapy on HCV patients with OLP, finding that IFN- $\alpha$  either improved, triggered, or exacerbated OLP lesions (6, 34, 39).

This suggests that HCV was not the primary cause of OLP and that other host-related factors, according to the authors, may have a role in the pathogenesis of HCV-related OLP (40).

Direct-acting antiviral (DAA) therapy is currently recommended as a treatment for chronic HCV, based on the degree of liver fibrosis, HCV genotype, resistance variants, previous treatment failure, and comorbidities. The advantages of DAA over IFN- $\alpha$  and ribavirin therapy are an increased response rate and reduced length of therapy (34, 39).

The effectiveness of DAA on OLP lesions was studied, and there are reports of improvement (41), In contrast, cases of OLP worsening and development of new cutaneous and genital LP were observed (42).

The studies of Nagao Y. and Tsuji M. (43) highlighted the importance of dentists in detecting HCV infection in patients with oral mucosal disorders who have not yet been treated. In the present case, we should emphasize that HCV infection could be discovered with OLP as a result of a dentist's demand for a complete investigation of hepatic disease. Dentists can also play an important role in the improvement of patients' life quality by providing adequate dental care. Periodic follow-ups are mandatory to prevent malignant transformation. It has been shown that oral cancer can be developed on OLP, particularly if associated with Hepatitis C infection (44).

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**Conflict of Interest.** The authors declare that there is no conflict of interest.

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