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Review

Cell-mediated mucositis of the oral cavity: narrative review on etiology, clinico-pathological aspects and malignant transformation

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Summary

Cell-mediated mucositis is the expression of a type IV hypersensitivity, in which cytotoxic CD8+ T lymphocytes attack the keratinocytes of the basal layer responsible for activating the immune response. There is sufficient evidence for an increased risk of oral cancer in patients with a diagnosis cell mediated mucositis. This review aims to examine the etiology, clinical-histological features, management and malignant transformation of a group of cell-mediated mucositis, including oral lichen planus, oral lichenoid lesions, Graft versus host disease, oral lesion of lupus erythematous.

The authors conducted a literature review, selecting relevant studies based on their novelty, applicability, and impact. The text highlights the varying rates of malignant transformation associated with different oral conditions. For oral lichen planus, the risk of transformation ranges from 0.44% to 2.28%, while for oral lichenoid lesions (OLLs), the rate is slightly higher, between 1.20% and 3.80%. Conditions like graft-versus-host disease are linked to a malignant transformation rate of 3.47%, and oral lesions associated with lupus erythematosus carry a similar risk at 3.3%, often involving squamous cell carcinoma of the lips. In cases of oral epithelial dysplasia, the risk increases significantly with severity, reaching 24.1% for severe dysplasia. The condition with the highest malignant potential is proliferative verrucous leukoplakia, with a transformation rate estimated at 49.5%. These findings underscore the importance of accurate diagnosis, vigilant monitoring, and the development of new therapeutic strategies. Recent advancements in treatments, such as nivolumab and imiquimod, show promise in early trials. These approaches aim to move beyond passive observation, shifting towards personalized medical interventions to reduce the risk of malignant transformation in high-risk patients.

Key words: cell-mediated mucositis of the interface, lichenoid immune response, oral potentially malignant disorders, malignant transformation rate

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Introduction

Oral mucositis is a heterogeneous group of disorders divided into two leading families according to the underlying etiopathology mechanism driven by adaptive immunity: antibody-mediated mucositis and cell-mediated mucositis [1] (CMM). This review will focus on all the subtypes of CMM.

CMM is the expression of a type IV hypersensitivity, in which cytotoxic CD8+ T lymphocytes attack the keratinocytes of the germinal layer responsible for activating the immune response. In addition to keratinocytes, the basement membrane appears to be the subject of immune-mediated aggression. It remains to be established whether this precedes or follows the migration of T lymphocytes[2,3].

This immunological aggression occurs in the presence of an antigen, recognized as non-self, which leads keratinocytes to become the target of the immune response. To date, it is not known what the anti-antigenic targets may be. Still, it is possible that various conditions, including the intake of drugs, contact with exogenous substances, mechanical trauma, bacterial or viral infections induce their expression[2].

From a histological point of view, the presence of a dense lymphocytic infiltrate arranged in a band close to the basement membrane and mainly made up of T cells near the epithelial-stromal interface indicates cell-mediated mucositis of the interface (ICMM) [4].

Interface dermatitis, introduced more than 50 years ago in dermatology, describes a typical histological pattern present in numerous inflammatory skin disorders. At its introduction, this pattern was also known as a lichenoid tissue reaction. Specific pathological features, including damage to the basal layer of the epidermis and a band-like infiltration of lymphocytes at the dermal-epidermal junction, characterize this histological hallmark [5].

This histological pattern is commonly observed in oral mucosal pathology diagnostics, but its interpretation is more complex due to the various pathogenetic pathways that can trigger such an immune response. Different pathologies with distinct pathogenetic mechanisms may exhibit a similar histological phenotype involving aspects of ICMM. ICMM is frequently described as a lichenoid manifestation, with oral lichen planus (OLP) being a prominent example of a condition marked by cell-mediated mucositis at the interface.

In 2007, a consensus sought to categorize lichenoid lesions in the oral cavity into several types: OLP, oral lichenoid drug reactions (OLDRs) caused by systemic drug exposure, oral lichenoid contact lesions (OLCLs) resulting from local hypersensitivity reactions, often to dental materials, and oral lichenoid lesions (OLLs) associated with graft-versus-host disease (GvHD) [6]. Regrettably, in daily practice, the differential diagnosis between OLL and OLP is quite difficult [7].

In addition, during the last decade other entities that may exhibit both clinical and histological lichen-like appearance emerged, as chronic ulcerative stomatitis (CUS). CUS typically presents as non-healing, erosive, or ulcerative lesions in the oral cavity, often affecting the tongue, buccal mucosa, and gingiva. It can mimic conditions like oral lichen planus or pemphigus vulgaris. Lesions are usually symmetrical and may cause pain and difficulty eating. Histopathology often shows non-specific features, including a mix of plasma cells and T-lymphocytes and degeneration of the basal cell layer. Direct immunofluorescence (DIF) is critical for diagnosis, revealing characteristic SES-ANA autoantibodies. Diagnosis requires collaboration among specialists, using clinical features, histopathology, and immunological tests [8]. Since CUS is not reported to undergo malignant transformation, no clinical surveillance for early detection of malignancies is suggested.

Additionally, a lichenoid immune response is frequently seen in several oral potentially malignant disorders (OPMDs) such as proliferative verrucous leukoplakia (PVL) and oral epithelial dysplasia (OED) [9].

Even if all these clinical entities share ICMM as histopathological hallmark, their risk of malignant transformation may differ significantly. Consequently, diagnosis plays a pivotal role in correct clinical management. In this review, we aim to update the current knowledge about oral disorders characterized by histological evidence of ICMM, together with the histopathological details that assist in reaching a correct diagnosis. We present the differential diagnoses, focusing on the cell-mediated immune response and the relationship with malignant transformation.

Oral lichen planus

OLP is the prototype of the cell-mediated mucositis affecting the oral cavity. OLP is a relatively common disease with a global prevalence around 1% but with marked geographical differences among countries (highest reported prevalence in Europe, 1.43 %) [10].

Clinical presentation

OLP more frequently affects middle-aged or adult female patients [11]. OLP frequently remains restricted to the oral cavity, but involvement of other mucosal sites, and in particular genital mucosa, is seen in approximately 20% of cases.

By contrast, as mucosal counterpart of cutaneous lichen planus, 70% of patients with cutaneous lichen planus show oral involvement [12].

Typical OLP lesions are reticular white patches (Wickham striae) distributed bilaterally on the cheek mucosa and lateral borders of the tongue (Fig. 1 A-B, Tab. I). White lesions can sometimes appear more plaque-like with areas of variable extension.

During the acute phases of the disease, erosive/ulcerative areas surrounded by reticular-like lesions may

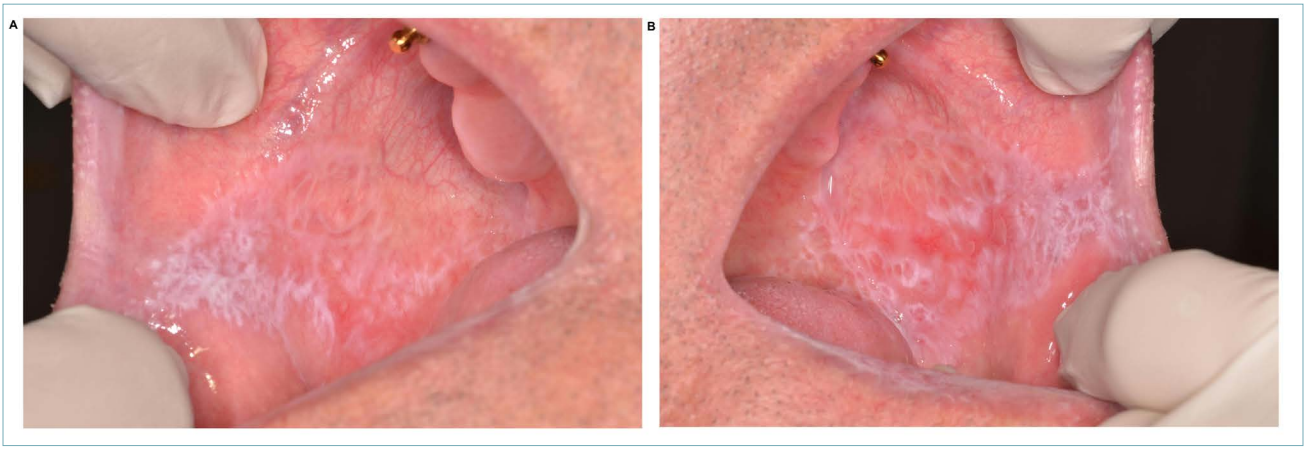

Figure 1. Clinical images of oral lichen planus. (A) Lichen oral planus: widespread white reticular striae (Whickham striae). (B) Bilateral and symmetric, asymptomatic.

develop appearing as erythematous lesions.
Symptoms are highly variable, ranging from asymptomatic to mild, moderate to severe forms that can compromise food intake and quality of life [13].
Both the extension of the lesions and the symptoms typically undergo periods of quiescence and exacerbations that often coincide with factors like stress, anxiety, or exposure to a chronic irritant [14].
While a cytotoxic aggression mediated by CD8+ T lymphocytes towards the basement membrane is universally recognized as the main event in OLP, the complete pathogenesis is not fully understood. A specific etiologic factor driving OLP is still unknown. Several lines of evidence suggests that basal keratinocytes present a non-self-antigen, triggering a T cell-mediated autoimmune response. However, studies that attempted to characterize the cell surface T cell receptor (TCR) expressed by T cells in order to identify the specific antigens that instigate OLP found heterogenous results suggesting that a number of antigens rather than one distinct antigen may be responsible for the disease[15]. Similarly, studies investigating the putative role of exogenous viral or microbial antigens (i.e. HCV, HPV, periodontal pathogenic bacteria) found ambiguous associations and showed regional differences thus failing to identify a single antigenic determinant [16,17,18]. Recently, also SARS-CoV-2 infection and vaccination have been advocated as a putative risk factor for triggering and exacerbation of OLP [19,20] but evidence is still limited and require further experimental validation [21].
All these results suggested that a great variety of factors may cause the unmasking or alteration of endogenously expressed self-antigens that stimulate a dysregulated T cell response in patients predisposed to OLP[22].

Histopathological features

Recent consensus studies agree on the following histological criteria [23],[23],[24] to reach a diagnosis of OLP:
i) Presence of a well-defined band-like zone of mature lymphocytic infiltration limited to the superficial part of the submucosa.
ii) Clear cell changes in the basal keratinocytes (vacuolar changes of the basal keratinocytes intimately associated with a band-like array of inflammatory cells together with exocytosis, which is a clear manifestation of the aggression of the lymphocytic infiltrate towards the epithelial components).
iii) Presence of apoptotic bodies: following lymphocyte aggression, keratinocytes can also undergo apoptosis and appear as rounded, intensely eosinophilic, homogeneous, PAS-positive globules called colloid or Civatte bodies. These necrotic, prematurely keratinized basal cells are found at the epithelial-stromal interface.
iv) In atrophic OLP, epithelial thinning and sometimes ulceration occur due to the failure of epithelial regeneration, which results from basal cell destruction. This can be associated with a mixed inflammatory infiltrate. In some cases, continuous aggression towards the basal layer leads to pigmentary incontinence. Melanin is released into the superficial portions of the lamina propria, where it is phagocytosed by macrophages, forming melanophages[5] (Tab. I).
The epithelial changes include acanthosis with a "saw-tooth" profile of the interpapillary ridges as a response to the cytotoxic aggression mediated by CD8+

Table I. Clinical and histological features of oral lesions associated with ICMM, their related malignant transformation rate, and the recommended interval for clinical surveillance.

Disease	Clinical	Histopathology	Malignant Transformation rate	Clinical Surveillance
OLP	Widespread white reticular striae (Whickham striae) frequently bilateral. Erosions, ulcerative or bullous lesions occasionally present.	Well-defined band-like zone of cellular infiltration mainly composed of mature T lymphocytes. No plasma cells. Signs of 'liquefaction degeneration' in the basal cell layer. Hyperkeratosis. "Saw-tooth" profile of the interpapillary. Absence of dysplasia.	0.44-2.28 % [28,35].	Recommended intervals range from 4 to 12 months.
OLLs (include OLCLs, OLDRs, Idiopathic OLL)	Lesions clinically similar if not identical to OLP lesions. Distribution not bilateral. OLCLs frequently in close contact with dental restorations (i.e amalgam).	Histology superimposable to OLP. Mixed inflammatory infiltrate with plasma cells and neutrophils, often located deeply in the submucosa.	1.20- 3.80 % [49,50].	Patients should be monitored at least annually, for atrophic erosive OLL lesions shorter intervals (4-6 months) [52,53].
CUS	Lesions clinically similar if not identical to OLP but refractory to steroid therapy.	Histology superimposable to OLP. SES-ANA deposit on the basal and lower third of cell layers at DIF.	Malignant transformation not reported.	Not reported.
GvHD	Lesions clinically similar if not identical to OLP lesions in patients with a history of bone marrow transplantation.	Histology superimposable to OLP.	3.47% [66,67].	At least once a year with a biopsy of any suspicious lesions.
DLE/SLE oral lesions	Lesions clinically similar if not identical to OLP lesions. Widespread gingival erythema and erosions surrounded by white striae.	Histology superimposable to OLP. Sometimes deeper and perivascular inflammatory infiltrate. Quantity and distribution pattern of CD123+ plasmacytoid dendritic cells (PDCs).	3.3% (mainly lip squamous cell carcinoma) [76,77].	Close follow up in collaborations with dermatologists
OED with ICMM	Mixed red and white lesions like OLP lesions.	Architectural and cytological changes within the context of ICMM.	10.3% Mild-moderate 24.1% severe (including carcinoma *in situ).* ICMM doesn't seem to influence MT [80,81].	Surgical exeresis in presence of moderate-severe dysplasia and close follow up (3-4 months)
PVL with ICMM	Progressive, persistent, and irreversible development of multiple leucoplakias that frequently become warty. Initial lesions may be clinically similar if not identical to OLP lesions.	Hyperkeratosis evolving into more complex epithelial changes. Typically, there is a sharp, abrupt transition from the adjacent unaffected normal epithelium. Frequent wart-like appearance due to verrucous architecture. Early lesions may show ICMM superimposable to OLP lesions. Dysplastic changes may appear during follow-up.	49.5 % [49]. PVLs that evolve preceded by OLP-like lesions in some studies seem to have a lower risk of malignancy [97].	Intervals for follow up are not standardized. 6 months for white nondysplastic lesions as compared to surgical excision [92]. 3 months for cases with genetic abnormalities (LOH) or aberrant expression of immunohistochemical biomarkers (P53, Ki-67, Podoplanin) [93, 94].

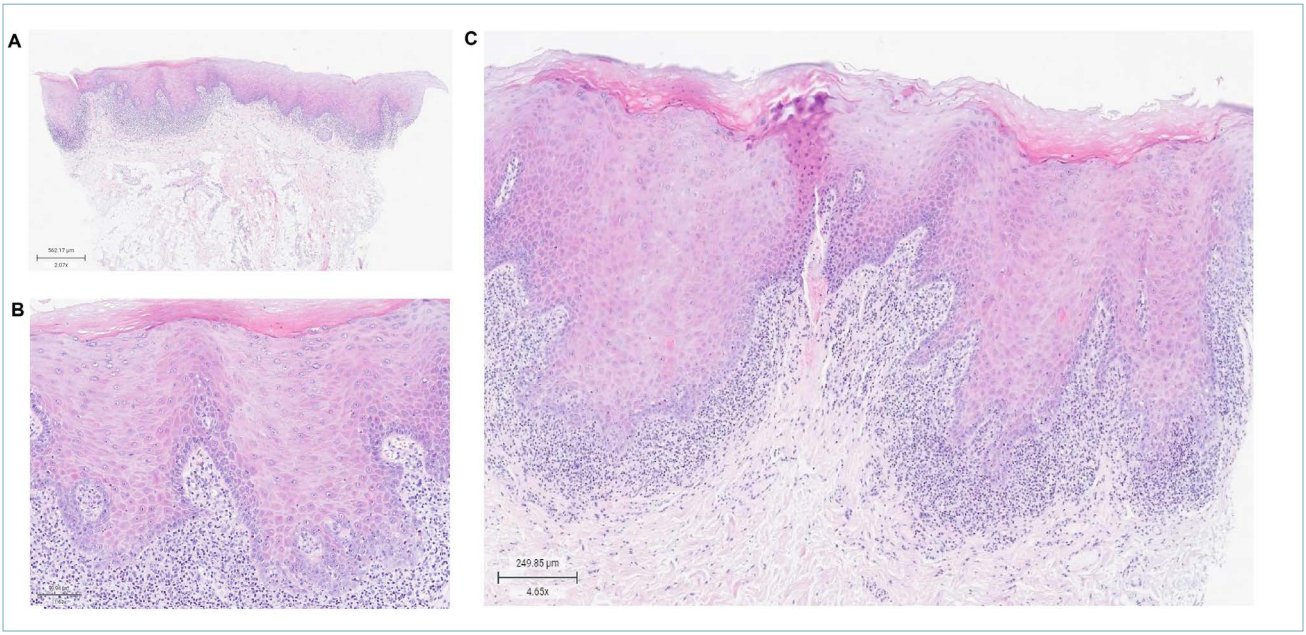

Figure 2. Histological images of oral lichen planus. (A) Lichen planus shows hyperplastic epithelium with a band-like lymphocytic infiltrate is seen adjacent to the basement membrane. (B) Acanthosis and sawtooth rete ridges of the epithelium with hyper orthokeratosis and lymphocyte exocytosis. (C) Degenerated basal cells with some apoptotic cells and incontinent melanin, within the infiltrate.

T lymphocytes. In addition, hyperorthokeratosis or hyperparakeratosis can be present (Fig. 2 A-B-C).
Recently agreed criteria [22,24,25] underlined the importance of considering dysplasia as an exclusion criteria for the diagnosis of OLP.
These statements are based on the fact that about one-third of dysplasia cases are associated with a lichenoid inflammatory infiltration, most probably related to genetic alterations evoking a ICMM reaction [26,27]. On the other hand, some authors believe that dysplasia in OLP may be one possible step in the roadmap of carcinogenesis[28].
In the past, the presence of dysplasia and ICMM used to be considered a distinct pathological entity (formerly known as "lichenoid dysplasia")[29], but recent evidence seems to contradict this belief [30]. This term should thus be abandoned and the term oral dysplasia associated with ICMM should be preferred.

Diagnosis and management

While the clinical aspects of OLP together with its typical distribution in oral cavity can be highly suggestive for diagnosis, histopathological examination for diagnostic confirmation is always advisable.
Indeed, given the wide range of oral lesions that may mimic OLP, oral biopsy remains the gold standard to achieve a definitive diagnosis and to exclude dysplastic alterations. The treatment of OLP should focus on the reduction of symptoms and on periodic follow-up to reach an early diagnosis in case of malignant transformation in oral squamous cell carcinoma (OSCC). By contrast, symptomatic and painful forms should be treated with the use of local or systemic medications. Topical corticosteroids remain the first-line treatment for mild to moderate OLP. These medications are typically prescribed for brief periods or as part of a long-term maintenance therapy regimen. Common topical formulations include triamcinolone acetonide, fluocinonide, and clobetasol propionate, available in various strengths. For severe or resistant lesions, prednisone, mycophenolate mofetil, methotrexate, azathioprine, cyclophosphamide, thalidomide and dapsone may be employed. In addition, low-level laser therapy and photodynamic therapy have been explored for OLP, providing a non-invasive and safe alternative to conventional treatments[31]. A recent study by Mansouri et al. highlighted the clinical efficacy of tofacitinib, a Janus kinase inhibitor, in alleviating symptoms and significantly improving patient satisfaction without any serious adverse effects[32]. Finally, emerging strategies based on specific receptor modulators (i.e. S1P1), the use of mesenchymal stem cells (MSCs), micro-RNA (miRNA) and small interfering RNA (siRNA) are being explored for the management of inflammatory diseases and supporting

tissue regeneration in areas that traditional therapies cannot address. These emerging strategies show great potential but require thorough in vitro and in vivo studies, followed by phased clinical trials, before they can be widely adopted in clinical practice.

Malignant Transformation

The first description of OSCC arising from OLP dates back to 1910 by Hallopeau et al. [33].

Since cutaneous LP is not commonly associated with neoplastic transformation, the possibility that OLP could turn into OSCC was initially met with skepticism, generating controversies [34].

Nevertheless, in the last 20 years, the increasing number of publications based on reliable criteria, pointing to a true risk of malignant transformation in OLP led the WHO to include OLP among the potentially malignant disorders [23].

However, quantifying the risk remains challenging since it is highly influenced by the diagnostic criteria adopted for calculation.

Gonzales-Moles in 2020 tried to estimate the proportion of OSCC arising from OLP, with the highest quality of evidence available [28], and found a malignant transformation rate of 2.28% (95% CI 1.49-3.20) based on a population of 3206 subjects.

More recently, a systematic review and meta-analysis based on a population of 12,838 subject and applying strict diagnostic and inclusion criteria, found a malignant transformation rate of 0.44%, lower than 1.20 % previously published [35] (Tab. I).

When OLP undergoes malignant transformation, multiple neoplastic lesions can occur.

Mignogna et al. found that, out of 45 transformed cases, 55% of patients developed at least two neoplastic events, and 2 cases (8%) even 12 and 16 neoplastic events, respectively [36]. This is in line with the theory of field cancerization [37].

Several authors have stressed on the importance of a regular surveillance of OLP patients to promptly intercept changes that may reflect the development of a dysplasia/neoplasia. Loss of homogeneity in keratotic lesions, speckled-like clinical appearance and non-healing erosive ulcerative lesions are all signals that should be meticulously investigated to differentiate between inflammatory benign changes and true dysplastic/neoplastic lesions.

OLP is a dynamic disorder characterized by red and white lesions that may change over time during follow-up. Therefore, suspected inflammatory lesions within the disease spectrum, particularly if symptomatic, should initially be treated empirically with steroids. If they do not regress, a histological examination is warranted. Nevertheless, histological evaluation remains the gold standard for diagnosing dysplasia or neoplasia during follow-up. Even if regular follow-up is effective for the early diagnosis of OLP related OSCC (recommended intervals range from 4 to 12 months) a small subgroup of patients does not benefit from such surveillance and are characterized by a rapid development of advanced-stage oral carcinomas, with consequent poor prognosis [38] (Tab. I). For this reason, future research should be focused on the identification of a biomarker that may help in stratification of OLP patients at risk of developing OSCC.

Oral lichenoid lesions

OLLs encompass a variety of conditions that exhibit clinical or histological features similar to OLP[39]. However, they are not entirely typical of OLP. Despite the absence of universally accepted clinicopathological criteria, OLLs can generally be categorized into:

1. Lesions resulting from reactions to external substances include:
   - Oral lichenoid contact reactions are often triggered by dental materials, such as amalgam.
   - Lichenoid drug reactions.
   - Oral lichenoid contact reactions associated with several substances (such as cinnamon) have been reported, but their real existence is still uncertain, as based on limited evidence [26,40].
2. Idiopathic lichenoid lesions.
3. Oral graft-versus-host disease (oGVHD).

These categories reflect the diverse etiologies and presentation of OLLs, which can complicate diagnosis and treatment.

Lesions resulting from reactions to external substances

Clinical presentation

These lesions can manifest similarly to OLP, making it difficult to distinguish between the two. When OLLs are related to hypersensitivity to dental materials like amalgam, the lesions typically appear adjacent to the implicated restoration. These lesions often show improvement or resolve completely once the causative material, such as the amalgam filling, is removed or replaced[6,41] (Fig. 3 A-B).

These lesions can appear white due to a thickened keratin layer or red due to atrophic, inflamed mucosa, and may also present as a combination of both. A pronounced lichenoid reaction can result in mucosal ulceration. Unlike OLP, which typically presents bilaterally and symmetrically, OLLs are often found in anatomical proximity to the source of irritation, such as a

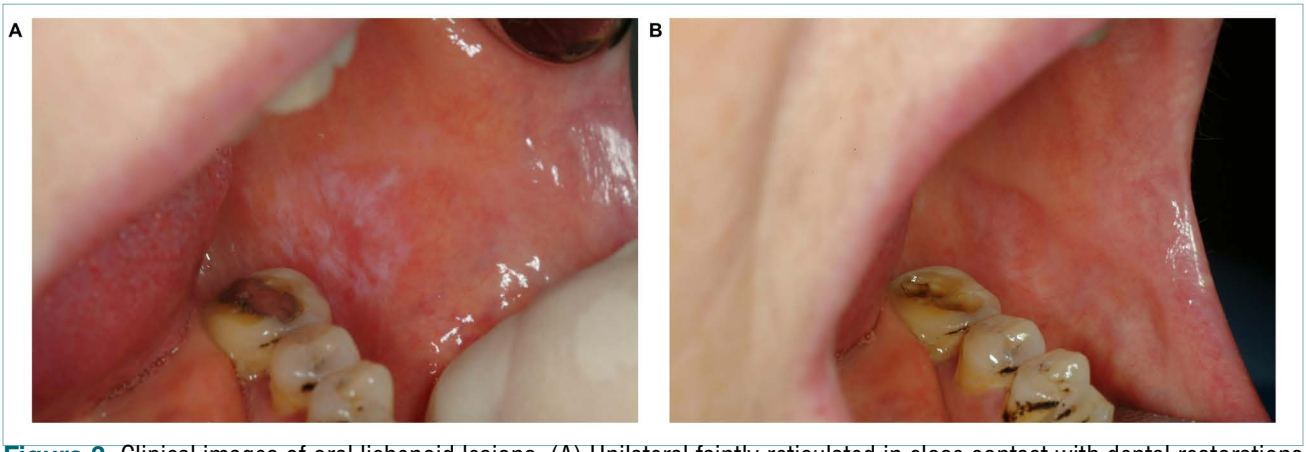

Figure 3. Clinical images of oral lichenoid lesions. (A) Unilateral faintly reticulated in close contact with dental restorations (i.e amalgam). (B) Complete resolution of the clinical condition once the causative material, such as the amalgam filling, is removed or replaced.

dental material or restoration [39] (Tab. I).

A recent review indicates that the average age of patients experiencing medication-induced OLLs is 58.5 years. The most implicated drugs were checkpoint inhibitors, specifically anti-PD-1/PD-L1 antibodies. After stopping the medication, the median duration for lesion resolution was approximately 15.7 weeks. However, discontinuing the offending drug requires careful evaluation of the risks and benefits. In some instances, such as cancer treatment, it may not always be feasible to withdraw the medication[42].

Histopathological features

OLLs exhibit overlapping histological features with OLP, which makes differentiation challenging. No specific histological markers can conclusively differentiate between the two conditions. However, the presence of plasma cells and perivascular inflammation in deeper tissues suggests a lichenoid reaction. (Fig. 4 A-B-C, Tab. I). Lesions associated with contact sensitivity to amalgam might develop small lymphoid follicles just beneath the mucosal surface. Drug-induced reactions tend to show a more intense lymphoplasmacytic response with pronounced perivascular inflammation [43]. The recognition of dysplastic epithelium in OLLs, and particularly low-grade epithelial dysplasia, is crucial. These atypical features include loss of polarity, hyperchromasia, and variation in nuclear size and shape, requiring careful observation at the interface mucositis site [43].

Diagnosis and treatment

To diagnose OLLs, clinicians assess the appearance of the lesions, clinical history (including extra-oral symptoms), and results from specific tests. Histopathology often cannot clearly differentiate OLP from OLLs due to their similar features, although subtle differences, such as deep perivascular lymphocytic infiltrate, can be noted. The World Health Organization (WHO) recommends histopathological examination by an oral pathologist as the gold standard [23]. Lichenoid reactions to dental materials most frequently occur with amalgam, although reactions to acrylics, resins, and composites have also been reported. The effectiveness of patch testing for suspected OLLs related to dental materials has yielded mixed results. Issues have been raised regarding the test's validity due to differences in reactivity between the skin and oral mucosa. Patch testing should be considered alongside clinical presentation, particularly in patients with extensive amalgam restorations and widespread lichenoid lesions, before pursuing complex dental treatments. However, it is rarely necessary for lesions directly in contact with amalgam restorations. Access to patch testing in primary care is limited[44].

When a lichenoid reaction to dental materials is suspected, direct contact of the lesion with the restoration often suffices for diagnosis without patch testing. Over 90% of cases improve following amalgam replacement. A positive patch test, combined with the clinical association of the lesion with amalgam, predicts lesion regression [45]. Evidence suggests replacing amalgam with alternative materials regardless of patch test results, due to a higher malignant transformation potential in OLLs compared to OLP[46]. Lesion resolution typically takes at least three months post-replacement. Suspected lichenoid drug reactions should be referred to secondary care for confirmation and potential drug substitution, as drugs of the same class may cause similar reactions.

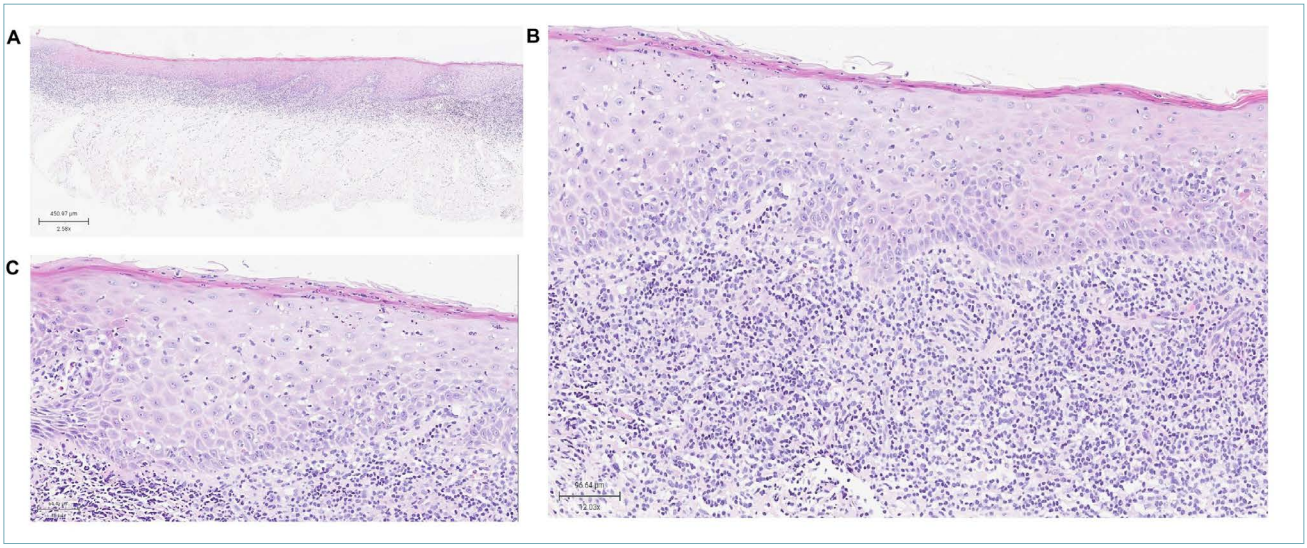

Figure 4. Histological images of oral lichenoid lesions. (A) At low magnification, the band-like distribution of the inflammatory infiltrate can be observed. (B) The infiltrate is composed of lymphocytes, plasma cells, and neutrophil granulocytes, with membrane degeneration and intraepithelial exocytosis of lymphocytes and neutrophils. (C). Histological detail of the neutrophil granulocyte component up to the stratum corneum.

When neither a putative etiologic factor nor a drug can be established as responsible for oral lesions onset, the term OLL should be adopted if histological or clinical features are only compatible with OLP[47].

Malignant transformation

In the past, some studies supported the hypothesis that only patients with OLL, and not OLP, are at a higher risk for oral cancer, leading to the recommendation that only these patients should be monitored bi-annually for early detection of potential malignancy [48].

Reasons for such higher malignant transformation may be found in the criteria adopted for diagnosis OLLs. As further explained in detail (see section OPMD with ICCM), it is often difficult to differentiate between OLLs and OPMD with ICMM, and especially, OPMDs exhibiting both ICMM and features of oral dysplasia. This may inevitably lead to the erroneous inclusion of non-OLL lesions and consequently altered calculations.

Recent findings from prolonged follow-up studies and the use of strict diagnostic criteria have provided new insights into OLL malignant transformation. Iocca et al. performed a systematic review and meta-analysis assessing the rates of malignant transformation in OPMDs rates found the rate to be 3.8% for OLL [49].

More recently, Gonzales-Moles, in another systematic review and meta-analysis, reported a pooled malignant transformation rate of 1.38% (95% CI = 0.16-3.38) for OLL and 1.20% (95% CI = 0.00-4.25) for lichenoid reactions. Interestingly, no significant differences were found between the OLL and lichenoid reaction groups [50] (Tab. I).

In lichenoid reactions and lichenoid contact lesions no clear consensus exists regarding the effect of etiologic factor removal on malignant transformation. For amalgam related lichenoid contact lesions, some authors highlighted that ICMM may persist after amalgam replacement, even in the absence of clinically detectable lesions [51]. Furthermore, cases of malignant transformation of amalgam related oral lichenoid contact lesions that clinically healed after amalgam replacement have been described [52].

Like OLP, it is recommended that patients with OLL undergo strict and regular surveillance as they share with OLP the same challenges deriving from dynamic periods of quiescence and flare up that may mimic malignant transformation.

Even if the majority of studies agree that OLP/OLL patients should be monitored at least annually, for atrophic erosive OLL lesions, given the higher risk of malignant transformation, shorter intervals (4-6 months) have been suggested [53,54] (Tab. I).

Graft versus host disease

GvHD is a multisystem immunologic reaction from grafting immunocompetent cells to an immunodeficient host and represents a common complication after allogeneic transplantation.

Clinical presentation

The oral manifestations of GvHD can be divided into three groups: the manifestations derived from the conditioning regimen and those of the acute and chronic forms of GvHD. Oral involvement in acute GvHD (aGvHD) is quite rare, and as a result, its characteristics are not well-established in the literature. Oral GvHD lesions typically appear 3 to 4 weeks post-transplantation. The most affected areas include the non-keratinized oral mucosa, the tongue (particularly the ventrolateral and dorsal surfaces), labial mucosa, and the hard and soft palate. Gingival involvement is less common. In severe instances, patients may also experience xerostomia and reduced salivary gland function. Chronic oral mucosa GvHD (cGvHD) presents clinical and histological features that are comparable to those of lichen planus with lichenoid lesions, resembling the Wickham's striae and with localized or diffuse erythema, often accompanied by edema or mucosal atrophy, which exposes the underlying vascular structures (Fig. 5A, Tab. I). However, in GvHD, chronic inflammatory cells originate from the donor rather than from the host. GvHD can also affect salivary glands in the head and neck area, leading to dry mouth (xerostomia), which can worsen mucosal inflammation. Chronic inflammation may cause scarring, fibrosis, and restricted mouth opening in severe cases.[55]

Multiple case studies [56,57,58] have documented oral cancer progression in cGvHD-related lesions of the oral cavity. In the last Workshop Report GvHD has been included among oral potentially malignant disorders [39].

Histopathological features

aGvHD in oral tissues is infrequently biopsied and shows nonspecific features. cGvHD shares many characteristics with lichen planus, such as hyperkeratosis and varying degrees of lymphocyte infiltration and basal cell apoptosis. Lymphocytes often form a band-like pattern or small clusters near the rete ridges (Tab. I). A notable feature is satellite cell necrosis, where lymphocytes surround apoptotic basal cells (Fig. 6 A-B). Additionally, GvHD affects minor salivary glands, with lymphocytes infiltrating ducts and acinar structures. Periductal fibrosis and significant acinar loss (10% or more) can support the diagnosis of cGvHD [59].

Diagnosis and treatment

The diagnosis of oGvHD involves clinical examination, histopathology and, sometimes, direct immunofluorescence. Treatment typically involves topical and systemic corticosteroids to reduce inflammation, calcineurin inhibitors, such as tacrolimus for resistant lesions, and systemic immunosuppressants, such as mycophenolate mofetil and rituximab. Symptomatic therapies, including artificial saliva, are used to manage xerostomia[59].

Malignant Transformation

Malignancies that occur after hematopoietic transplantation fall into three categories: hematologic malignancies, lymphoproliferative disorders, and secondary solid cancers. Solid cancers, including oral carcinoma (Fig. 5B) are the least common secondary malignancies but show an increasing incidence rate over time [60]. Specifically, progression to oral cancer from oral lichenoid lesions related to GvHD has been documented in several case studies [61,62,63,64,65]. An analysis published in the Annals of Oncology examined a database of 17,545 adult recipients of allogeneic stem

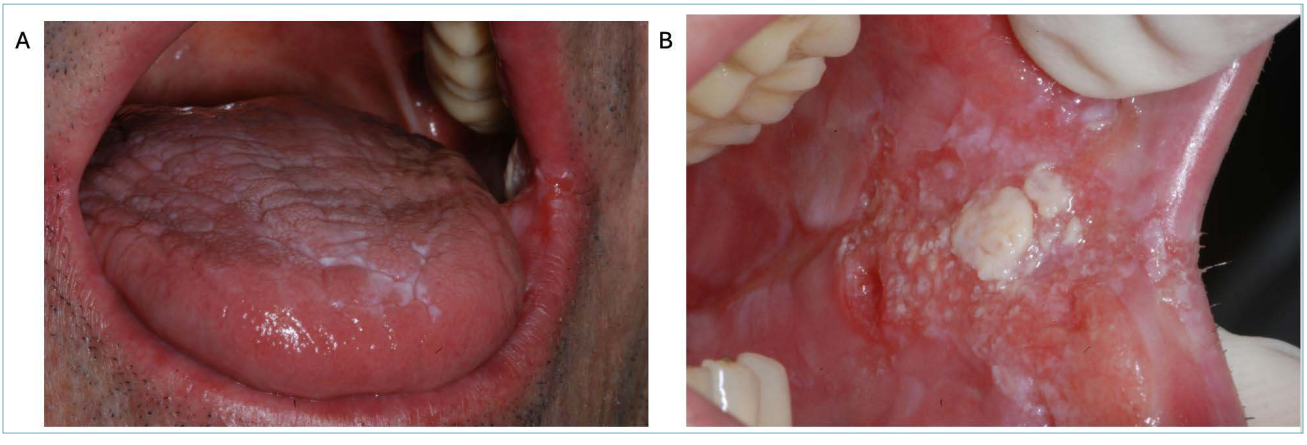

Figure 5. Clinical images of oral GvHD associated with a squamous cell carcinoma. (A) Edema, mucosal atrophy and reticulated lesions. (B) Squamous cell carcinoma in the cheek mucosa of the same patient.

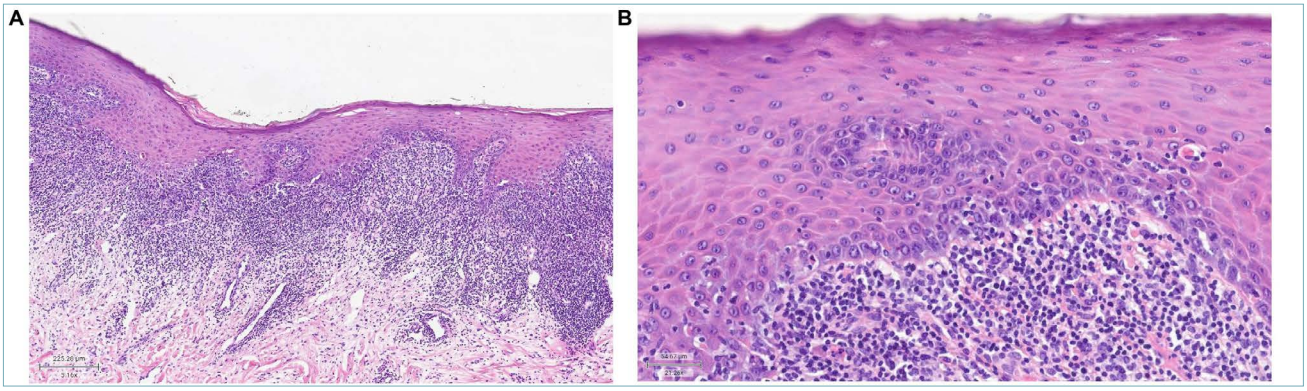

Figure 6. Histological images of oral GVHD. (A) In this low-magnification image, hyperplasia of the oral mucosa with a saw-tooth appearance and focal hyperparakeratosis can be observed. The subepithelial connective tissue shows an intense infiltrate with a lichenoid distribution, occasionally perivascular, composed of lymphocytes and plasma cells. (B) At higher magnification satellite cell necrosis, where lymphocytes surround apoptotic basal cells.

cell transplants in Japan from 1990 to 2007. The study found that chronic multisystem GvHD significantly increased the risk of developing solid tumors (RR = 1.8, P < 0.001), with an even higher risk specifically for oral cancer (RR = 2.9, P < 0.001) in patients more than one-year post-transplant [66] (Tab. I). Santarone et al. recently confirmed that an oral cGvHD duration of 15 months or more is an independent risk factor for the development of secondary oral cancer. They also demonstrated that patients with oral cGvHD developed OSCC at a significantly younger age (median age: 35 years) compared to the median age typically observed in classical OSCC cases (60 years) [67].

Reports and case series have shown that oral mucosal GvHD can manifest as hyperkeratotic plaques that may resolve, remain unchanged, or progress to secondary oral cancer. Retrospective studies have found various grades of dysplasia and in situ carcinoma within oral GvHD pathology specimens. Moreover, oral mucosal GvHD is associated with increased genomic alterations and multifocal OSCC transformation [68].

The pathogenetic mechanism based on T-lymphocytes that chronically attack the oral epithelium in cGvHD and long-term immunological damage to the mucosa by T-cells may predispose this tissue to malignant transformation [65]. Furthermore, immunosuppressive drugs used for long periods of time to prevent or treat cGvHD may play a role in malignant transformation, even if the interactions between chronic inflammation and therapy-induced immunosuppression in oral carcinogenesis have not been fully demonstrated [69].

Nevertheless, the recognized association between oral cGvHD and OSCC should alert physicians to follow-up these patients more closely (at least once a year) and to biopsy suspicious lesions (Tab. I).

Oral lesions of lupus erythematosus

Lupus erythematosus is a chronic autoimmune disease that can be principally divided into three forms: (1) systemic, (2) drug-induced, and (3) discoid. Oral lichenoid lesions occur in 15-20% of discoid lupus erythematous cases and in up to 40% of cases of systemic lupus [70]. Oral lesions of lupus erythematosus (OLE) have clinical presentations like those found in oral lichen planus (OLP). Immunofluorescent tests are not always useful in the differential diagnosis; in addition an overlap syndrome lupus erythematous/lichen planus has been described [71].

Clinical presentation

Oral manifestations of discoid erythematous lupus (DLE) and systemic erythematous lupus (SLE) are similar and appear as a central circular area of atrophic mucosa with superficial ulceration, surrounded by whitish striae, which are less defined than in oral lichen planus. The buccal mucosa, palate, and lips are most affected, with a unilateral distribution (Tab. I).

Histopathological features

The histopathological criteria for diagnosing oral involvement by lupus erythematosus were described by Edwars in 1971 [72] and Schiødt in 1984 [73]. Morphological features include hyperortho and/or parakeratosis (hyperparakeratosis), with keratotic plugging, liquefaction degeneration of the basal layer, focal or perivascular infiltrates of lymphocytes. PAS staining for the mucopolysaccharide has great value in diagnosing the oral lesions of chronic lupus erythematosus: the characteristic finding is an extremely intense reaction beneath the basal layer of the epithelium and around small blood vessels [74].

Diagnosis and treatment

Histopathology frequently is not specific, particularly in differentiating DLE from OLP; the presence of a deeper and perivascular inflammatory infiltrate could help when present. The 'lupus band test' (granular deposition of immunoglobulin and/or complement at the epithelial/connective tissue junction) is characteristic but not pathognomic.
Recently Chanprapaph suggested that the quantity and the distribution pattern of dendritic plasmacytoid cells (CD123 positive on immunohistochemistry) may have a diagnostic implication in differentiating OLE from OLP and other OLLs [75].

Malignant Transformation

Carcinomas developing within OLE lesions are rare intraorally, with most cases occurring on the lips, with a malignant transformation rate of 3.3% [76] also in longstanding lesions [77] (Tab. I). Recommendations for clinical surveillance in OLE are lacking but given the similarities with OLP the same approach is recommendable (at least once a year and 4-6 months for atrophic-erosive lesions).

Oral potentially malignant disorders (OPMDs) with cell-mediated mucositis of the interface (ICMM)

As anticipated, ICMM can be found as histologic feature in several oral lesions many of which are OPMDs. Given the absence of definitive diagnostic criteria, the presence of a lichenoid mucositis developed within the context of a OMPD can make it difficult to differentiate confidently one clinical entity from the others.
In addition, in cases of ambiguous histologic features, OPMDs with ICMM may initially be mistaken for OLP/OLLs as clinical appearance can be superimposable if not identical for true OLP/OLLs lesions. Frequently, these difficult to diagnose entities receive a definitive diagnosis late during follow-up. Hence, clinicians and pathologists are called for vigilant alert and evolving interpretation of single patient clinical history [78].

Oral Epithelial Dysplasia associated with ICMM

The term lichenoid dysplasia was introduced to describe cases in which the diagnosis was indeterminate [29]. However, the terminology was confounding.
Indeed, the coexistence of dysplasia and a lichenoid mucositis can be seen in other OPMDs such as proliferative verrucous leukoplakia (PVL) [79].
In addition, molecular investigations failed to find unique transcriptomic and immunophenotypic profile in OLP with a without dysplasia [30].
For this reason, the term "lichenoid dysplasia" has been abandoned and clinicians are encouraged to use terms like OLP/OLL with dysplasia or oral dysplasia associated with ICMM.
Histological features of oral epithelial dysplasia (OED), with respect to oral lichen planus, may include a more mixed inflammatory infiltrate with plasma cells, a less well demarcated infiltrate and a relatively intact basal cell layer. Nevertheless, these features are not distinctive enough to always allow an unambiguous differentiation (Fig. 7 A-B-C). The malignant transformation rate of dysplasia ranges from 10.3% for mild to moderate cases to 24.1% for severe dysplasia, including carcinoma in situ [80]. Notably, the presence of a lichenoid immune response does not appear to influence the risk of malignant transformation [81] (Tab. I).

Diagnosis and treatment

The degree of dysplasia in OPMD is a key factor for decision making between wait and see approach or surgery [82]. The presence of dysplasia (any grade) requires particular attention and should never be underestimated. A moderate or severe dysplasia may be adjacent to an occult carcinoma and a surgical approach is often preferred. In case of mild dysplasia clinical surveillance at intervals shorter than one year (3-4 months) should be adopted although universally accepted criteria are lacking.
Up of 29% of cases with oral dysplasia may also show lichenoid features [83].

Proliferative verrucous leukoplakia

PVL has been included in this narrative review because recent studies have been published describing cases initially diagnosed as OLP/OLL (presence of ICMM) that in their evolution acquired features of PVL [79]. PVL is recognized as a distinct form of multifocal oral leukoplakia. It is notable for its progressive clinical course and evolving clinical and histopathological features, and it carries the highest risk of developing into oral cavity cancer compared to other OPMDs [9,84].
Alternative terms used in the literature include proliferative multifocal leukoplakia [85] and proliferative leukoplakia [86].

Clinical presentation

Clinically, PVL typically starts as one or more leukoplakic lesions and may subsequently appear in multiple lo-

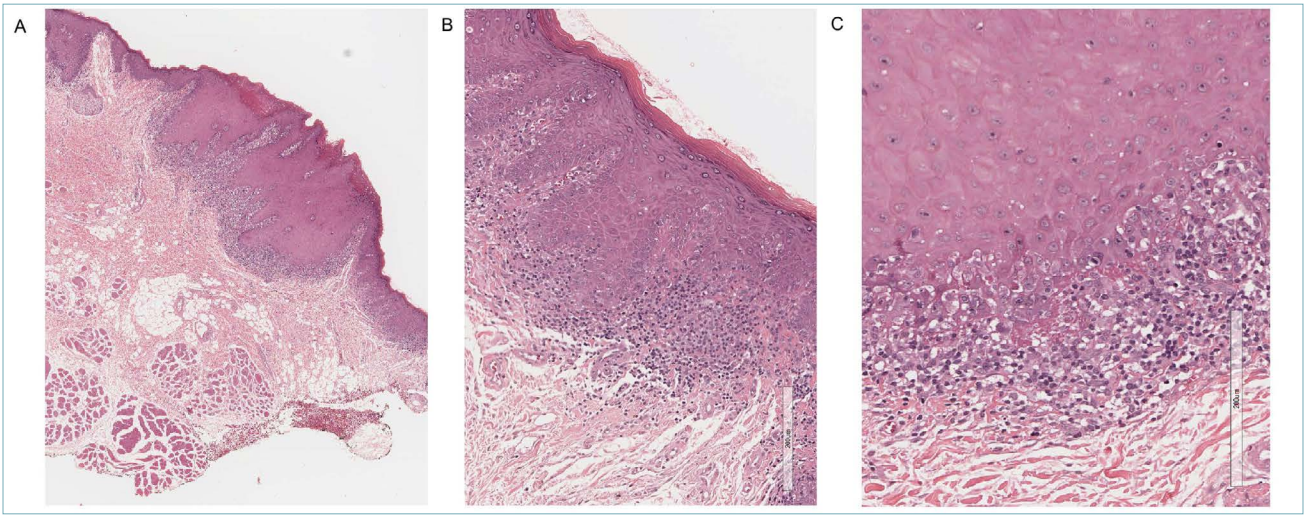

Figure 7. Histological images of oral epithelial dysplasia with lichenoid inflammation. (A) Band-like inflammatory infiltrate at the epithelial-stromal interface imparting a lichenoid appearance. (B) The epithelium is hyperplastic with hyperkeratosis and hypergranulosis, but with general preservation of a slightly expanded and hyperchromatic basal cell layer. (C) Degeneration of the basal layer with lymphocytic exocytosis.

cations. This spread can occur either through the gradual expansion of an individual focus or by the merging of several nearby foci over time [86] (Fig. 8 A-B, Tab. I.

Histopathological features

Early PVL lesions are unremarkable flat keratoses with premature keratinization, sharp lateral margins, increased keratin, and no cytological atypia. Corrugated hyperkeratotic lesions display a verrucopapillary or disproportionate flat hyperorthokeratosis/hyperparakeratosis with minimal or no dysplasia. It is common to observe skip areas where normal tissue alternates with abnormal tissue (Fig. 9 A-B-C). Typically, there is a sharp, abrupt transition from the adjacent unaffected normal epithelium (Tab. I). Proliferative bulky epithelial lesions exhibit atypical, hyperkeratotic epithelial architecture with or without dysplasia. Both exophytic and endophytic growth patterns may be present, and the

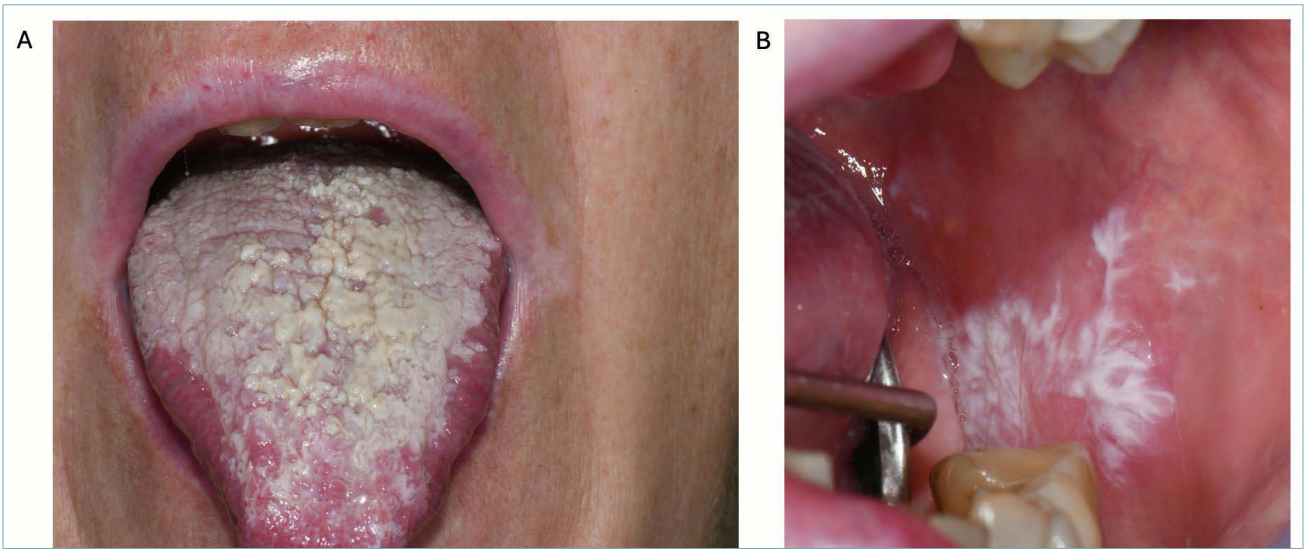

Figure 8. Clinical images of proliferative verrucous leukoplakia. (A) Dorsal tongue with widespread, unevenly thickened leukoplakia with pronounced fissures and poorly defined edges. (B) Proliferative verrucous leukoplakia often resembles oral lichen planus, presenting as smooth, fissured white or combined white-and-red patches, typically without ulceration.

epithelium shows bulbous rete pegs that sometimes merge. Over time, PVL can show dysplastic changes with nuclear abnormalities, increased mitotic activity, and loss of normal cellular structure. There is a significant risk of progression to squamous cell carcinoma or verrucous carcinoma [87]. Throughout all stages of PVL, lymphocytic infiltration at the epithelial-stromal interface can be mistaken for OLP. When present, intact basal cells layer and/or dysplasia rules out the OLP diagnosis.

Diagnosis and treatment

Hansen et al. [88] first introduced the term PVL, suggesting that diagnosis should be based on a combination of clinical and histological criteria. Subsequent criteria were refined by Cerero-Lapiedra et al. [89] and Carrard et al. [90], which included the involvement of more than two distinct oral sites and the presence of a verrucous lesion. Initially, PVL can present as flat white lesions without a verrucous component[86], and may occasionally mimic a lichenoid appearance[79], potentially leading to misdiagnosis as OLP and subsequent delay in recognizing malignancy. Although the term PVL may not perfectly encompass all cases of multifocal disease, it remains widely used, and a Working Group has recommended its continued use [91].

Treatment options for oral leukoplakia and PVL include surgical excision or clinical surveillance. Treatment often depends on the extension of the lesions and the histopathological assessment through incisional biopsy. In particular, the presence of moderate-severe dysplasia is highly suggestive for surgical removal since the presence of a neoplasia may be underestimated in the snapshot of a diagnostic biopsy. However, PVL often involves wide areas of the oral cavity, and it is often impossible to completely eradicate all areas involved by PVL lesions without extremely invasive surgeries. In addition, recent studies have highlighted that there is no significant difference in terms of relapse and malignant transformation between observation and any technique of surgical excision (scalpel vs laser ablation). Consequently, for lesions without dysplasia a wait and see approach is frequently preferred for PVLs [92].

Intervals for follow-up are not standardized. A recent randomized trial demonstrated the efficacy of clinical surveillance every 6 months for white nondysplastic lesions as compared to surgical excision, with equivalent transformation rates [93]. However, shorter intervals (i.e. 3 months) may be preferred in case of evidence of genetic abnormalities (LOH) or aberrant expression of immunohistochemical biomarkers (P53, Ki-67, podoplanin) [94, 95].

Recently, new data from research on chemoprevention have emerged. In particular, Hanna et al. conducted a phase II nonrandomized controlled trial (NCT03692325) to assess the efficacy of nivolumab in PVL demonstrating a partial response and overall tolerability of treatment in 36% and 88% of patients, respectively [96].

Other authors investigated the use of imiquimod [97] showing promising results, but further prospective randomized trials are needed for clinical validation. Nevertheless, similar studies represent the effort for a shift from clinical observation to personalized medical intervention in PVL patients at risk of OSCC.

Malignant Transformation

A significant number of patients diagnosed with PVL eventually develop oral cancer. According to a recent systematic review, the proportion is estimated to be 49.5% (CI 26.7-72.4%) [49], and what is particularly interesting is that PVLs that develop following OLP-like lesions appear to have a lower risk of malignancy [98] (Tab. I). Patients diagnosed with PVL may subsequently develop either conventional squamous cell carcinomas or verrucous carcinomas. A case series

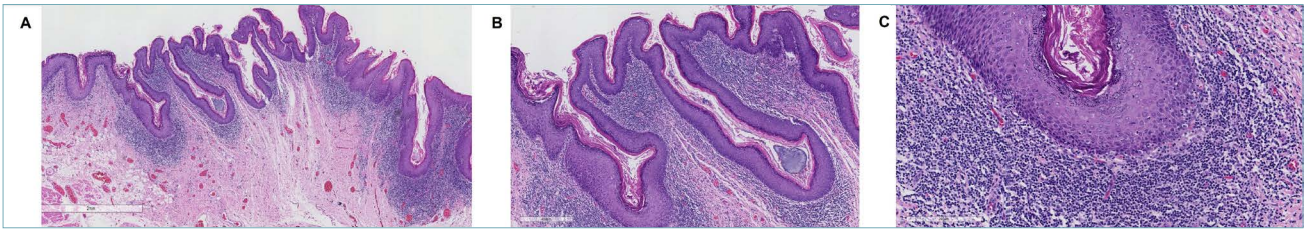

Figure 9. Histological images of proliferative verrucous leukoplakia: (A) A prominent hyperkeratotic proliferation accompanied by lichenoid inflammation. The lesion displays both exophytic and endophytic growth patterns, is covered by parakeratin, and features an irregular, undulating surface with surface crypts. (B) A dense lymphocytic infiltrate with a lichenoid pattern is present in the lamina propria, closely associated with the basal portions of the rete ridges. (C) No cytological atypia and occasional lymphocytic exocytosis.

documented multiple primary carcinomas, mostly affecting gingival sites [99,100].

In the last decades, several attempts have been made to identify biomarkers able to predict malignant transformation. P53, podoplanin, and chromosomal loci abnormalities/loss of heterozygosity are the most widely studied and the most promising. However, the presence of dysplasia remains so far, the strongest predictor of malignant transformation for oral leukoplakia. Unfortunately, neither oral dysplasia nor DNA ploidy seem to be a reliable predictor of malignant in patients with PVL highlighting the difficult management of this clinical entity [101].

Conclusions

All entities reviewed here share histological features of lichenoid mucositis. As clinical manifestations alone are not sufficient for discriminating among different lesions, mutual presence of ICMM is a major limitation for diagnosis. Indeed, as reviewed, differential diagnosis is often challenging, nomenclatures tend to evolve, and diagnostic criteria are under debate. ICMM likely occur in different clinical situations ranging from autoimmunity to immunosurveillance. Consequently, marked differences in malignant transformation are the expression of differences in etiopathology which are masked by the mutual histological appearance of cell mediated mucositis. For this reason, the management of oral cell mediated mucositis represent a true challenge. Collaboration among experienced clinicians and pathologists are thus of pivotal importance to achieve a proper diagnosis and a correct treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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Ethical consideration

Written informed consent was obtained from all patients for the publication of clinical and histological images

Authors contribution

G.Q., G.A., D.B.G., S.B., and M.P.F. conceived and designed the study and wrote the manuscript. G.Q. and M.P.F. contributed to the histological images. A.G., D.B.G., A.T., L.M., and R.R. provided the clinical images. All authors reviewed and approved the final version of the manuscript.

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