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Review Article

Chronic Inflammation as a Diagnostic Modifier in Oral Potentially Malignant Disorders: A Clinical Perspective

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Abstract

Objective. To discuss how chronic inflammatory conditions may complicate the clinical and histopathological interpretation of oral potentially malignant disorders (OPMDs) in daily oral medicine and oral surgery practice.

Clinical Perspective. This article presents an expert clinical perspective supported by selected literature and representative clinical scenarios illustrating diagnostic challenges encountered when OPMDs coexist with chronic mechanical irritation, oral dysbiosis, and Candida-associated inflammation. This perspective aims to highlight unresolved

clinicopathological gray zones that may influence biopsy interpretation and clinical decision-making.

Discussion. Chronic inflammatory stimuli may alter lesion phenotype by accentuating erythema, ulceration, hyperkeratosis, and reactive epithelial changes, potentially complicating the distinction between reactive atypia and true oral epithelial dysplasia (OED). In selected cases, these inflammatory modifiers may contribute to diagnostic uncertainty, particularly in clinically ambiguous or low-grade lesions. In addition, local inflammatory conditions may influence communication between clinicians and pathologists regarding biopsy timing, site selection, and clinicopathological correlation. Representative clinical examples are discussed to illustrate how inflammatory factors may confound interpretation of OPMDs in routine practice.

Conclusions. Awareness of local inflammatory modifiers may help contextualize the interpretation of selected OPMDs during clinical and surgical assessment. This clinical perspective underscores the importance of careful clinicopathological correlation and encourages further prospective research exploring the interaction between chronic inflammation and epithelial alterations in OPMDs.

Statement of Clinical Significance

Chronic inflammation may modify the clinical and histopathological features of oral potentially malignant disorders, complicating distinction between reactive atypia and oral epithelial dysplasia. Recognizing and, when appropriate, controlling local inflammatory factors may improve biopsy planning, clinicopathological correlation, and diagnostic accuracy.

Keywords

Oral potentially malignant disorders; chronic inflammation; oral epithelial dysplasia; chronic mechanical irritation; Candida

Introduction

Oral Potentially Malignant Disorders (OPMDs) comprise a heterogeneous group of mucosal conditions associated with an increased risk of malignant transformation to oral squamous cell carcinoma (OSCC)[1]. Several reports have highlighted a degree of heterogeneity and ambiguity in the evaluation, classification, and reporting of OPMDs across different consensus statements[2]. In this context, local factors acting as sources of chronic inflammation of the oral mucosa have been infrequently and inconsistently addressed, despite their potential to overlap with both the clinical and histopathological features of OPMDs. Despite advances in molecular biology and histopathology, predicting the biological behavior of OPMDs remains a major clinical challenge. At present, the assessment of oral epithelial dysplasia (OED) continues to be the cornerstone for risk stratification and clinical decision-making[3]. However, dysplasia grading is subject to well-recognized limitations, including interobserver variability and susceptibility to modification by local inflammatory processes[4].

In routine clinical practice, OPMDs frequently coexist with chronic inflammatory conditions such as oral dysbiosis, fungal colonization, and chronic mechanical irritation (CMI)[5]. These factors may alter lesion phenotype, increase inflammatory infiltrates, and generate epithelial changes that complicate both clinical interpretation and histopathological evaluation. As a result, distinguishing reactive epithelial atypia from true dysplastic alterations may become particularly challenging, potentially affecting diagnostic accuracy and treatment planning[6].

While chronic inflammation has been increasingly implicated in the oral carcinogenic microenvironment, its precise role in OPMD progression remains incompletely understood. Importantly, inflammation-related changes may act less as direct drivers of carcinogenesis and more as diagnostic modifiers, capable of masking, mimicking, or amplifying epithelial alterations traditionally interpreted as OED. Failure to recognize this interaction may lead to overestimation of OED severity in some cases or to inappropriate clinical risk stratification, ultimately affecting diagnostic accuracy and management decisions. In this context, it is important to distinguish different levels at which chronic inflammatory conditions may interact with OPMDs or OED. First, inflammation may modify the clinical phenotype of a lesion, influencing features such as erythema, ulceration, surface texture, symptoms, and lesion demarcation. Second, inflammation-associated reactive epithelial changes may overlap with features of OED and complicate histopathological interpretation[7]. These clinical and histopathological effects constitute the primary focus of the present perspective. A separate question

concerns the potential biological effects of persistent inflammation on an already altered epithelium, including changes in proliferative activity, oxidative stress, or inflammatory signaling. Whether such biological effects ultimately influence the malignant transformation risk of OPMDs represents a further and substantially less established question. Accordingly, mechanistic observations discussed herein should be interpreted as hypothesis-generating and not as evidence that chronic inflammatory conditions independently promote malignant transformation

The aim of this clinical perspective is to highlight unresolved diagnostic pitfalls in the evaluation of OPMDs when chronic inflammatory stimuli are present. This article does not aim to establish causal relationships or propose evidence-based management protocols. Rather, it seeks to discuss clinically relevant diagnostic dilemmas frequently encountered in oral medicine and oral surgery practice when inflammatory conditions coexist with OPMDs.

Chronic mechanical irritation: from debated risk factor to diagnostic confounder

CMI represents a common and underestimated source of persistent oral inflammation. These factors are frequently encountered in anatomical sites where OPMDs preferentially arise, such as the lateral border of the tongue, the buccal mucosa, and the alveolar ridges[8]. A growing body of epidemiological and clinicopathological evidence supports an association between CMI and OSCC, suggesting that persistent mechanical irritation may represent a relevant local risk factor in oral carcinogenesis. However, oral carcinogenesis is a multifactorial and multistep process, and CMI should not be interpreted as an isolated or sufficient carcinogenic agent. Rather, its potential contribution should be considered within the broader interaction of established carcinogenic exposures, host susceptibility, pre-existing epithelial alterations, and local microenvironmental factors[9,10].

Beyond its role as a diagnostic confounder, a separate and less established question is whether CMI may induce biological alterations in the exposed oral epithelium. In a cytological study of clinically healthy individuals, oral mucosa chronically exposed to sharp dental surfaces showed an increased frequency of micronuclei compared with non-exposed mucosa, suggesting increased cytogenetic damage in this specific clinical setting[11]. Importantly, this study excluded individuals with OPMDs and did not evaluate malignant transformation. In addition, immunohistochemical and genetic studies of human non-healing chronic traumatic ulcers mainly located on the lateral tongue border have identified alterations in epithelial proliferation and differentiation markers as well as

genes methylation[12,13]. Other proposed mechanisms involving genomic instability or complex chromosomal alterations remain largely hypothetical and are derived from conceptual or mechanistic literature rather than direct evidence in human OPMDs. Therefore, these observations should be regarded as hypothesis-generating and should not be interpreted as evidence that CMI independently promotes malignant transformation[14,15]. In this context, CMI functions primarily as a *diagnostic confounder*, capable of modifying the clinical appearance of OPMDs and complicating histopathological interpretation.

The distinction between reactive atypia and true OED -within OPMDs- is especially problematic when biopsies are obtained in the presence of ongoing CMI[7] (Figure 1). For example, mechanical trauma or CMI has been recognized as a potential exacerbating factor in oral lichen planus (OLP), where repeated local injury may induce or aggravate lesions through the isomorphic Koebner phenomenon[16]. In the oral cavity, CMI sources, parafunctional habits, or occlusal trauma may act as persistent triggers, promoting epithelial damage, sustaining local inflammation, and favouring disease chronicity[17,18] (Figure 2). From a clinical perspective, adequate identification and control of traumatic factors are essential in patients with OLP, not only to reduce symptom severity and improve mucosal healing, but also to avoid misinterpretation of trauma-related epithelial changes as disease progression or OED, particularly in erosive or ulcerated lesions.

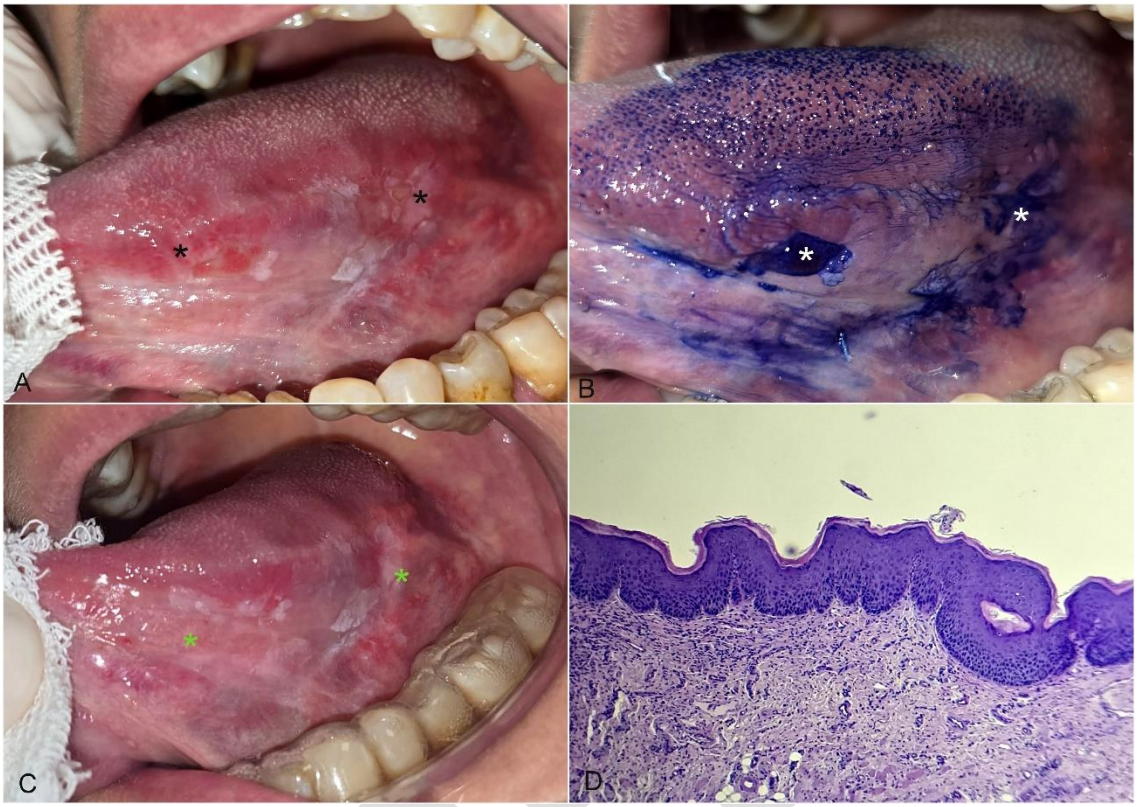

Figure 1. A- A 45-year-old female patient presented with discomfort and a burning sensation on the left lateral border of the tongue. She was a non-smoker and non-drinker. A heterogeneous lesion consistent with non-homogeneous leukoplakia was identified (in A, black asterisks denote the regions with the highest suspicion of malignancy). The lesion showed a strong association with sharp dental surfaces along its entire extension, which significantly contributed to symptom exacerbation. The patient also reported a tongue-biting habit and experiencing substantial psychosocial stress. In B, toluidine blue staining reveals two positive sites corresponding to the red areas clinically suspected of malignancy. C- Before performing the biopsy, the patient underwent topical antifungal therapy with nystatin 100,000 IU, and upper and lower thermoformed mucosal protective appliances were fabricated to minimize CMI from the sharp teeth. At the time of biopsy, a clinical improvement was observed, including reduction of burning symptoms, resolution of some of the erythematous components, and clearer delineation of the leukoplastic white areas. D- Histopathological examination (H&E, 10×) revealed stratified squamous epithelium with hyperkeratosis and evident dysplastic changes. This case raises an important question: What histopathological features would have been found if the biopsy had been performed under active chronic mechanical irritation (CMI) and inflammation? Would a more advanced degree of dysplasia have been detected—reactive in nature or truly neoplastic? In this context, toluidine blue staining is shown not as a definitive diagnostic tool for OED, but to illustrate how clinically suspicious inflamed

areas may also exhibit dye retention. The subsequent clinical improvement after control of local inflammatory factors reinforces the need to interpret adjunctive clinical findings within the overall inflammatory and clinicopathological context.

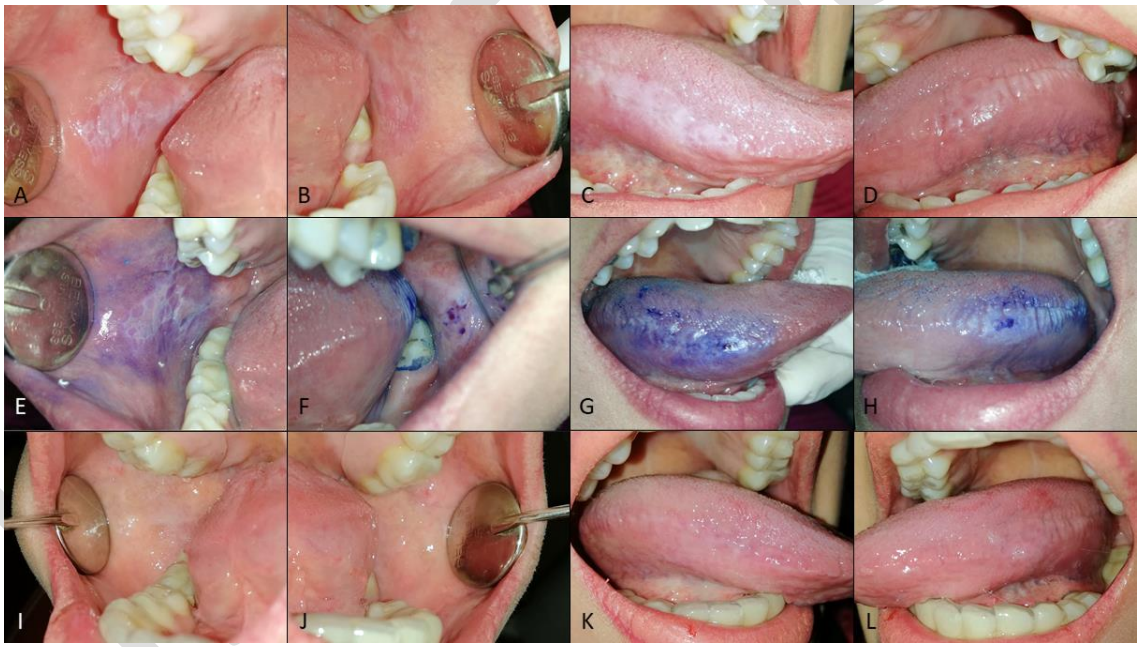

FIGURE 2 – A, B, C, D: Oral lichen planus with a classical bilateral and symmetrical clinical presentation involving the right and left buccal mucosa and the lateral border of the tongue.

E, F, G, H: Toluidine Blue vital staining. E shows a negative result. F, G, and H show positive areas with intense staining of the white lesions. These lesions were associated with chronic mechanical irritation (CMI) of dental and parafunctional origin.

I, J, K, L: After 15 days of using a protective device to reduce CMI, complete remission of the white reticular lesions was observed. In this case, CMI may be considered a

triggering factor (Koebner phenomenon) in the development of OLP lesions. The positive toluidine blue staining is illustrated to emphasize that dye retention may occur in clinically altered areas exposed to persistent mechanical irritation and inflammation and should therefore be interpreted cautiously and within the overall clinical context. The subsequent remission of the lesions after reduction of CMI supports the role of mechanical trauma as a local exacerbating factor, consistent with the Koebner phenomenon, and illustrates the dynamic influence of inflammatory modifiers on lesion phenotype.

Notably, although reactive epithelial changes are well recognized, their morphological overlap with low to moderate grade OED underscores a critical diagnostic gray zone. Several clinical observations suggest that removal of mechanical irritants may lead to changes in lesion phenotype, such as reduction of erythematous components or surface irregularities[19]. Such observations reinforce the concept that CMI may influence lesion expression and inflammatory burden, thereby affecting the accuracy of both clinical assessment and histopathological grading. A key unresolved question is how an epithelium already harboring dysplastic alterations—within the spectrum of an OPMD—responds when is exposed to sustained CMI (Figure 3). CMI may increase epithelial turnover, replication stress, and proliferative signaling, potentially amplifying morphological atypia and inflammatory crosstalk[12]. Importantly, whether such responses represent merely a reversible reactive component superimposed on OED, or whether they influence clonal dynamics and lesion behavior, remains unknown. Experimental animal studies have demonstrated that the application of a traumatic stimulus to the oral mucosa of animals previously initiated with carcinogens may result in the development of OSCC with a more aggressive and predominantly endophytic growth pattern, fulfilling the first two stages of multistep oral carcinogenesis, namely initiation and promotion[20]. When considered in the context of the human oral mucosa, these findings may provide a conceptual framework. Local traumatic factors superimposed on dysplastic epithelium within an OPMD could increase the complexity of clinical and histopathological interpretation. In addition, they may be associated with enhanced proliferative activity in already altered epithelial cell populations, potentially driven by trauma-induced epithelial proliferation. Demonstrating this interaction in humans is inherently challenging due to ethical constraints, underscoring the need for carefully designed translational approaches. Nevertheless, these mechanistic observations should not be interpreted as evidence that CMI independently increases the malignant transformation risk of OPMDs.

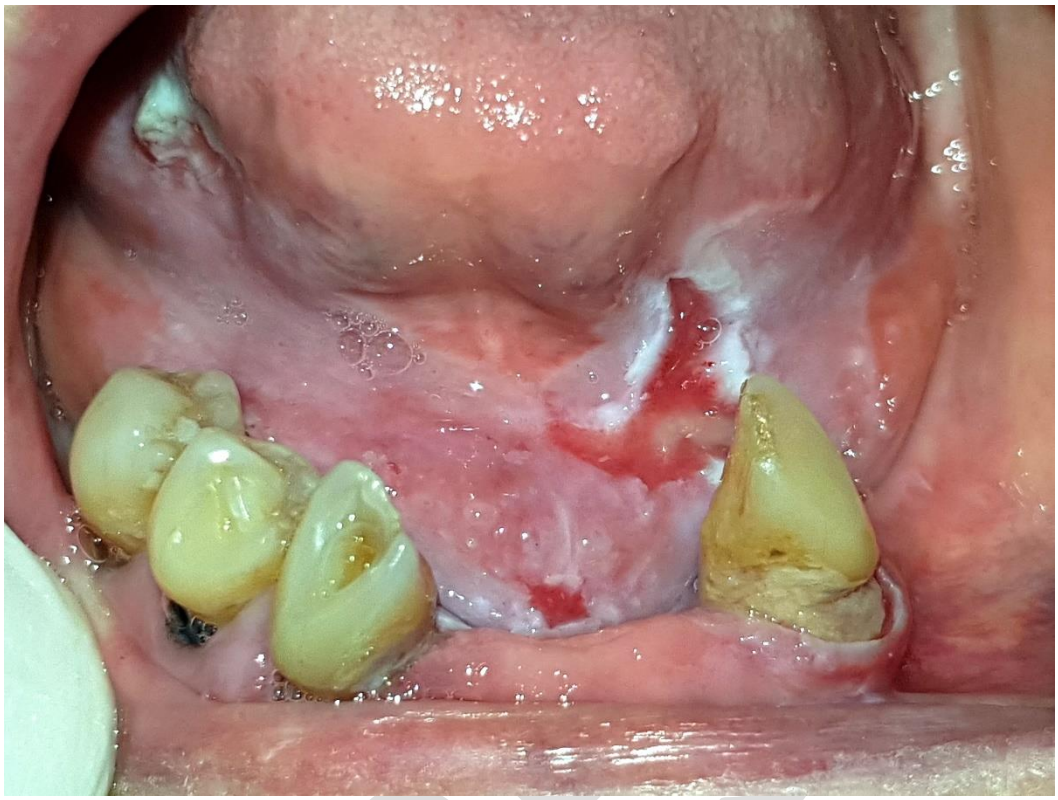

Figure 3. This figure illustrates the case of an 85-year-old female patient, non-smoker and non-drinker, presenting with a widespread white plaque involving the floor of the mouth and ventral surface of the tongue. The lesion had been previously diagnosed as proliferative verrucous leukoplakia (PVL). Clinical examination revealed that the rough and sharp surface of the left mandibular canine acted as a source of CMI, likely exacerbated by parafunctional tongue movements, resulting in repeated mucosal trauma on the floor of the mouth. Subsequently, a painful ulcer with an adjacent erythroplakic area developed in close proximity to the injuring tooth, closely reproducing the contour of the mandibular canine. Following elimination of the traumatic factor through extraction of the offending tooth, an incisional biopsy was performed at the ulcer margins, revealing severe epithelial dysplasia.

Interestingly, the literature highlights ongoing controversies in the evaluation, classification, and management of OPMDs across different consensus statements[2]. Notably, local factors acting as sources of chronic inflammation are seldom systematically considered. A more careful assessment of these local inflammatory and traumatic factors could not only generate new research hypotheses, but also contribute to the refinement of future guidelines for OPMD management and diagnosis for clinicians. In this context, the identification and control of local sources of trauma prior to clinical and histopathological assessment or biopsy may represent a relevant strategy to

improve diagnostic accuracy and OED grading in the landscape of OPMDs. Conversely, the diagnostic interaction may also operate in the opposite direction: persistent oral lesions may be erroneously attributed to mechanical trauma, potentially delaying the recognition of an underlying OSCC. Recent case reports illustrate this diagnostic pitfall, although such observations should not be interpreted as evidence of direct causality between CMI and OSCC[21].

From a clinical perspective, chronic inflammatory conditions may substantially modify the phenotype of an OPMD and, consequently, the clinician's initial perception of its biological risk. Superimposed inflammation may accentuate erythema, ulceration, surface irregularity, keratotic changes, and local symptoms such as pain or burning sensation, thereby producing a more heterogeneous or clinically alarming appearance. Conversely, reduction of the inflammatory component after elimination of CMI, improvement of plaque control, or treatment of concomitant fungal infection may result in changes in color, surface texture, symptom intensity, and lesion demarcation, without necessarily implying modification of the underlying OPMD or its intrinsic malignant potential. These dynamic clinical changes are particularly relevant because erythematous components, ulceration, non-homogeneity, and surface irregularity are commonly considered during clinical risk assessment and biopsy-site selection. Thus, inflammatory modifiers may influence not only histopathological interpretation but also the clinical classification of a lesion, the identification of the most representative biopsy site, and the perceived urgency of diagnostic intervention. Recognition of this potential overlap reinforces the importance of documenting and, when clinically appropriate, controlling evident inflammatory factors while avoiding any delay in biopsy of lesions showing features suspicious for malignancy.

Oral dysbiosis and inflammatory background changes in OPMDs

From a broader oral health perspective, the role of periodontal status deserves particular consideration in the diagnostic assessment of OPMDs. Periodontal inflammation represents one of the most prevalent and sustained sources of chronic inflammatory burden in the oral cavity and is closely linked to oral dysbiosis, epithelial barrier disruption, and persistent cytokine release. In this context, untreated periodontitis or poor plaque control may act as background modifiers of mucosal inflammation[5], potentially influencing the clinical appearance of OPMDs and the histopathological interpretation of epithelial alterations.

The oral microbiome plays a central role in maintaining mucosal homeostasis. Disruption of this equilibrium, commonly referred to as oral dysbiosis, involves qualitative and quantitative alterations in microbial communities that may promote a persistent inflammatory microenvironment[22]. Increasing evidence has documented differences in microbial composition between healthy oral mucosa, OPMDs, and OSCC. However, whether dysbiosis represents a causal factor in oral carcinogenesis or a secondary phenomenon remains unresolved[23,24].

Several bacterial taxa—including *Fusobacterium*, *Prevotella*, *Porphyromonas*, and *Corynebacterium*—have been reported with increased prevalence in OPMDs and OSCC. Proposed mechanisms include upregulation of pro-inflammatory cytokines, induction of oxidative stress, interference with epithelial barrier integrity, and modulation of cell proliferation and apoptosis pathways. Despite these associations, the available evidence is largely observational and heterogeneous, limiting causal inference[25]. From a diagnostic perspective, oral dysbiosis may be particularly relevant as a *modifier of lesion phenotype*. Chronic microbial-driven inflammation can intensify erythema, ulceration, or surface irregularities in OPMDs, potentially simulating higher-risk clinical presentations. In addition, inflammatory epithelial activation associated with dysbiosis may accentuate histopathological features that overlap with low-grade OED, thereby complicating histological interpretation.

Importantly, periodontal therapy, biofilm control, and antimicrobial interventions have been shown to reduce local inflammatory burden and restore mucosal homeostasis in adjacent oral tissues. In some clinical contexts, improvement in lesion appearance following such interventions has been reported, supporting the notion that the inflammatory load may significantly influence the clinical expression of OPMDs[26]. Although these measures should not be interpreted as treatments for OPMDs per se, they may contribute to optimizing diagnostic conditions by reducing confounding inflammatory signals. Failure to consider periodontal status and dysbiosis at the time of biopsy may therefore introduce additional variability into OED grading and clinical risk stratification. Collectively, these observations support the need for an integrated diagnostic approach in which periodontal evaluation and control of plaque-associated inflammation are incorporated as contextual elements in the clinicopathological assessment of OPMDs, rather than as direct determinants of malignant transformation.

Candida-associated inflammatory changes and diagnostic interpretation

Fungal colonization, particularly by *Candida albicans*, represents another major source of chronic inflammation in OPMDs, especially in non-homogeneous leukoplakias. Candida species are capable of adhering to keratinized epithelium, penetrating superficial epithelial layers, and inducing local inflammatory responses. In addition, fungal metabolism may generate carcinogenic by-products such as nitrosamines and reactive oxygen species, further amplifying epithelial stress[27–29].

Several studies have documented higher prevalence of Candida hyphae in leukoplakias exhibiting erythematous or speckled components[29,30]. Clinically, these lesions could demonstrate partial regression of erythema after antifungal therapy, supporting the concept that fungal-associated inflammation may exacerbate lesion phenotype. However, as with bacterial dysbiosis, the extent to which fungal colonization contributes to epithelial OED or malignant risk remains uncertain. From a diagnostic standpoint, fungal-associated inflammation may complicate both clinical and histopathological assessment. Erythematous areas secondary to candidiasis may mimic high-risk OPMDs, such as erythroleukoplakia, and potentially prompt more aggressive clinical interpretation. Histologically, epithelial alterations induced by fungal irritation may overlap with dysplastic features, further reinforcing diagnostic ambiguity[31,32]. From a diagnostic standpoint, fungal-associated inflammation may complicate both clinical and histopathological assessment. Erythematous changes associated with candidal infection or colonization may contribute to a more heterogeneous clinical appearance and may overlap with features observed in non-homogeneous leukoplakias. Histologically, inflammation-associated epithelial alterations may also overlap with some features considered in the assessment of OED, further complicating interpretation. Importantly, improvement or resolution of an erythematous component following antifungal therapy should only be interpreted as evidence that a potentially reversible inflammatory component contributed to the initial clinical phenotype; it does not provide information regarding the biological behavior or malignant potential of the underlying OPMD. This hypothesis underscores the importance of recognizing fungal colonization as a potentially reversible inflammatory component that may influence lesion appearance and diagnostic interpretation (Figure 4).

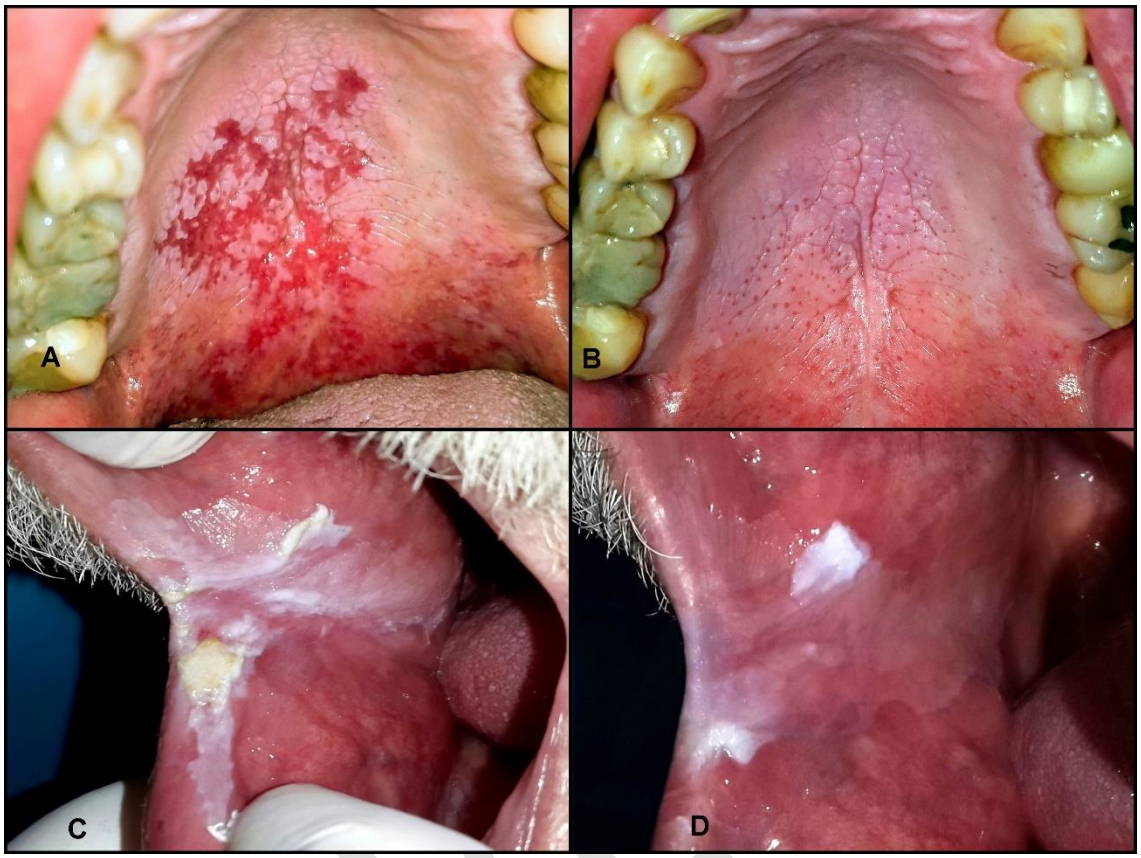

Figure 4. (A) Illustrative example of a palatal lesion with a provisional clinical diagnosis of erythroleukoplakia, characterized by intermixed white and prominent erythematous areas. The patient was a heavy smoker and consumed mate infusion at high temperatures. Local treatment with miconazole 20 mg t.i.d. was administered for 10 days to address potential concomitant Candida spp. colonization prior to biopsy. Following antifungal therapy, the erythematous component completely resolved despite continued smoking, and the lesion acquired a more homogeneous leukoplastic appearance (B). Histopathological analysis revealed hyperkeratosis with mild epithelial dysplasia (nicotinic stomatitis/palatitis).” (C) Lesion located in the retrocommissural area, presenting white warty areas in a heavy smoker and heavy drinker, compatible with non-homogeneous (speckled) leukoplakia. Local antifungal treatment (miconazole 20 mg) was prescribed for 21 days. (D) Follow-up visit showing a reduction of warty areas and improvement of erythematous zones. The biopsied specimen revealed hyperkeratosis with areas of mild epithelial dysplasia.

Although several biological mechanisms have been proposed through which Candida spp. could potentially contribute to oral carcinogenesis, the clinical evidence supporting an independent carcinogenic role remains limited and heterogeneous. Similarly, current evidence is insufficient to establish chronic hyperplastic candidiasis as an OPMD with intrinsic malignant potential[33]. By definition, lesions associated with Candida infection are considered potentially reversible once the infection is adequately eliminated. Accordingly, the WHO Collaborating Group, in the latest 2020 OPMD consensus, excludes chronic hyperplastic candidosis from the OPMD category and does not attribute to it an intrinsic malignant potential[1]. Nevertheless, a careful and systematic assessment of lesions clinically suspected of chronic candidosis is strongly recommended, in order to ensure that any observed epithelial alterations represent reactive or inflammatory changes rather than true OED. From a clinical standpoint, chronic hyperplastic candidosis lesions that fail to resolve following appropriate antifungal therapy warrant further investigation, including biopsy of any residual clinically abnormal mucosa, particularly in patients presenting with established clinical risk factors. Based on published recommendations, when clinically appropriate, biopsy or re-biopsy following antifungal treatment may be deferred for approximately six weeks (considering that the turnover time of the oral epithelium is approximately three weeks, and that additional time is required for the resolution of inflammation and re-establishment of normal epithelial architecture)[4].This interval should not be regarded as a rigid requirement, and the timing of histopathological assessment should ultimately be individualized according to the clinical evolution and level of suspicion. Importantly, antifungal treatment or observation should not delay biopsy when clinical features raise concern for OED or OSCC.

In this context, OPMDs - which are frequently overinfected or colonized by Candida spp- may be influenced by fungal presence not only as a confounding factor in histopathological interpretation, but also as a modifier of the epithelial microenvironment during the assessment of dysplastic changes. In such dysplastic lesions, superimposed fungal infection may contribute to a local inflammatory milieu capable of modifying the clinical phenotype and potentially complicating histopathological interpretation; whether it independently influences malignant transformation risk remains uncertain. Similar to oral dysbiosis and the proposed role of CMI, these sources of persistent inflammation merit further investigation and should be incorporated into future research frameworks and clinical guidelines when evaluating malignant transformation risk across different OPMDs (Figure 4).

Reactive epithelial atypia versus oral epithelial dysplasia: unresolved diagnostic boundaries

Reactive epithelial atypia represents a well-recognized histopathological phenomenon in the oral mucosa and may arise in response to persistent inflammatory, infectious, or traumatic stimuli[34]. In the setting of OPMDs, the coexistence of chronic inflammation may further blur the histological distinction between reactive changes and early dysplastic alterations. Increased inflammatory infiltrates, cytokine-mediated epithelial activation, and oxidative stress may exaggerate epithelial abnormalities, particularly in low-grade lesions. Interestingly, the histopathological features of OED may overlap with those of several inflammatory and reactive conditions, commonly referred to as reactive epithelial atypia. In these contexts, the epithelium typically exhibits hyperkeratosis with acanthosis, basal cell hyperplasia, and intracellular edema, usually in the absence of disordered epithelial stratification or marked basal cell pleomorphism, although mild basal cell hyperchromatism may be observed. In addition, a more densely collagenized lamina propria is often present as a reactive response to trauma, aiding in the distinction from true OED when clinicopathological correlation is carefully applied[4,34].

Despite these established histopathological criteria, diagnostic distinction—especially from mild OED—remains challenging, and misclassification may lead to either overtreatment of reactive lesions or undertreatment of true OED. While current diagnostic frameworks emphasize the importance of clinical context and site-specific susceptibility to CMI, no longitudinal studies have specifically evaluated whether epithelial atypia secondary to CMI, Candida colonization, or inflammation related to oral dysbiosis may subsequently evolve into true epithelial OED. In most reported cases, professional evaluation and timely clinical intervention likely intercept these reactive changes at an early stage. However, it remains unclear how such lesions might biologically behave in the absence of diagnosis or treatment, particularly in patients with persistent exposure to local inflammatory or traumatic stimuli. This unresolved issue highlights an important gap in current knowledge regarding the dynamic relationship between chronic inflammation, reactive epithelial changes, and dysplastic transformation within the oral mucosa. While clinical improvement after elimination of inflammatory stimuli has been reported, such observations may not represent a clinically relevant consideration as proof of OED regression or reduced malignant potential. Rather, they underscore the dynamic interaction between inflammation and epithelial morphology and highlight the limitations of static histopathological assessment in isolation.

Ancillary techniques, including immunohistochemical markers such as p53, Ki-67, and cell adhesion molecules, have been explored to aid in the differentiation between reactive atypia and true OED [6,7]. Previous evidence has demonstrated the expression of early carcinogenesis-related biomarkers in dysplastic or atypical epithelial changes arising in the context of chronic inflammation, suggesting that persistent inflammatory stimuli may promote pro-oncogenic molecular alterations[35]. In this setting, selected immunohistochemical markers may assist in more accurately distinguishing reactive epithelial changes from true dysplastic alterations. However, their routine clinical application remains limited by inconsistent performance, lack of standardized thresholds, and also some overlap between reactive and dysplastic patterns. Consequently, the distinction between reactive atypia and early OED continues to rely on integrated clinicopathological judgment rather than definitive objective criteria. These unresolved diagnostic boundaries reinforce the need for cautious interpretation of OED grading in the presence of active inflammation and for transparent communication between clinicians and pathologists regarding local irritative or infectious factors at the time of biopsy.

Limitations

This manuscript presents a conceptual and clinically oriented perspective rather than a systematic or scoping review. The literature discussed was selected to illustrate key diagnostic challenges rather than to provide exhaustive coverage of all available evidence. As such, the observations and interpretations offered herein may assist interpretation as hypothesis-generating rather than definitive. In addition, much of the current evidence addressing inflammation, dysbiosis, fungal colonization, and CMI in OPMDs is derived from observational studies with inherent methodological limitations, precluding causal inferences. The considerations presented herein are primarily based on expert clinical interpretation, selected literature, and illustrative clinical observations rather than prospective controlled evidence. Finally, the clinical considerations proposed do not replace established diagnostic protocols and should be applied with caution, particularly in lesions with features suggestive of early OSCC.

Clinical reflections and future directions

The recognition of chronic inflammation as a modifier in OPMDs has important clinical implications. In everyday practice, inflammatory factors are frequently present at the time of biopsy, yet they are rarely addressed systematically in diagnostic protocols. Failure to consider these modifiers may compromise diagnostic precision and contribute

to variability in OED grading. Importantly, inflammation control could be considered in selected cases and should not be a substitute for biopsy nor as a strategy to delay diagnosis in lesions with high clinical suspicion for OSCC or severe OED. Features such as induration, rapid growth, persistent ulceration, or a prominent or persistent erythroplakic component should prompt timely histopathological evaluation. Adjunctive techniques such as toluidine blue staining may assist clinical assessment and biopsy-site selection in selected cases; however, positive staining is not sufficiently specific to constitute an independent indication for biopsy and should always be interpreted in conjunction with the overall clinical findings[36]. However, in selected low-risk lesions without alarming features, preliminary management of local inflammatory factors may represent a pragmatic approach to optimize diagnostic conditions and reduce confounding influences.

Finally, recent evidence-based position papers, such as the protocol proposed by the Society of Oral Medicine of the Chinese Stomatological Association, highlight the importance of a comprehensive and multifactorial approach to the management and diagnosis of OPMD, particularly oral leukoplakia. Beyond lesion-directed therapies, these guidelines emphasize the systematic control of local modifying factors, including CMI, defective restorations or prostheses, oral hygiene status, and concomitant infections such as Candida spp., as integral components of patient management. This integrative model supports the concept that controlling sources of chronic inflammation may not only improve clinical outcomes, but also refine diagnostic accuracy and histopathological interpretation, reducing the risk of misclassification and overtreatment. Current evidence indicates that the management and monitoring of patients with oral leukoplakia should be undertaken by experienced clinicians, aiming both to control the lesion and to allow early detection of malignant transformation[37]. However, it must also be acknowledged that most existing recommendations are based on low or very low levels of evidence and may therefore require further refinement as new data emerge.

Future prospective studies could explore whether local inflammatory conditions influence clinicopathological interpretation in selected OPMDs. Longitudinal observational studies evaluating lesion phenotype before and after control of evident inflammatory factors may help clarify the clinical relevance of these observations.

Conclusions

Chronic inflammatory conditions frequently coexist with OPMDs and may complicate both clinical assessment and histopathological interpretation in daily practice.

Awareness of these inflammatory modifiers may assist clinicians, oral surgeons and pathologists in contextualizing selected clinicopathological findings, particularly in clinically ambiguous lesions. Rather than proposing evidence-based protocols, this clinical perspective aims to encourage critical reflection regarding the dynamic interaction between inflammation and epithelial alterations in OPMDs, while highlighting the importance of careful clinicopathological correlation during biopsy planning and follow-up.

Author Contributions

Gerardo Gilligan: Conceptualization, literature review, manuscript drafting, clinical data interpretation, and supervision.

Federico Garola: Literature review, data interpretation, manuscript review, and editing.

María Fernanda Galíndez-Costa: Literature review, manuscript review, and editing.

Jerónimo Lazos: Conceptualization, critical revision of the manuscript, and interpretation of clinical findings.

Eduardo Piemonte: Conceptualization, critical revision of the manuscript, and scientific supervision.

René Pánico: Conceptualization, manuscript review, supervision, and final approval of the submitted version.

All authors critically reviewed the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

The manuscript is original and has not been published or submitted elsewhere.

All clinical cases were managed according to institutional and international ethical standards. Patients provided informed consent for the use of clinical images and information.

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