ARC Journal of Dermatology
Volume 8, Issue 5, 2025, PP 42-51
ISSN No. (Online) 2456-0022
DOI: https://doi.org/10.20431/2456-0022.0805005
www.arcjournals.org

Oral Crohn's Disease in the Differential Diagnosis of Chronic Orofacial Inflammation

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Received: 14 July 2025 Accepted: 29 July 2025 Published: 20 August 2025

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Abstract

Chronic orofacial inflammation reflects a diagnostically heterogeneous spectrum of mucosal pathology characterized by shared clinical features, convergent immune mechanisms, and variable systemic associations. Oral Crohn's disease, a localized granulomatous manifestation of Crohn's pathology, often presents with subtle or mischaracterized signs that escape early detection in the absence of gastrointestinal symptoms. Clinical features such as indurated labial swelling, mucosal tags, angular fissuring, linear vestibular ulcerations, gingival hyperplasia, and a cobblestone pattern of the buccal mucosa represent surface correlates of deeper lympho-granulomatous activity and mucosal immune dysregulation. Histopathologic samples may reveal noncaseating granulomas, perivascular lymphoplasmacytic infiltrates, and mucosal edema, yet frequently fall short of definitive diagnosis when evaluated in isolation or in early disease. Diagnostic complexity increases in the presence of overlapping entities such as orofacial granulomatosis, Melkersson–Rosenthal syndrome, sarcoidosis, granulomatosis with polyangiitis, and delayed hypersensitivity reactions. Integration of oral findings with immunologic, serologic, and radiologic data enables higher diagnostic precision, particularly in pediatric or adolescent patients in whom oral lesions may predate intestinal involvement by months to years or remain the exclusive disease manifestation. Salivary cytokine profiling, mucosal microbiome shifts, and epithelial barrier dysfunction are emerging as valuable biomarkers reflecting systemic inflammatory burden. Reframing oral Crohn's lesions as active immunologic interfaces rather than secondary mucosal changes provides a foundation for early therapeutic intervention and longitudinal disease tracking. Recognizing oral Crohn's disease as an active and autonomous expression of systemic inflammation enables earlier intervention, alters disease trajectory, and reinforces the mouth's diagnostic and prognostic value in chronic immune-mediated pathology.

1. INTRODUCTION

Chronic orofacial inflammation presents a diagnostic challenge due to its overlapping clinical features, heterogeneous histopathologic findings, and multifactorial etiologies, including infections, autoimmune processes, and granulomatous diseases [1, 2]. These lesions may manifest as swelling, ulceration, mucosal irregularity, or architectural changes that often obscure their underlying pathogenesis, making early recognition difficult [3].

Among these conditions, oral Crohn's disease (OCD), a localized, granulomatous expression of systemic Crohn's pathology, poses a unique challenge. In children and adolescents especially, OCD may precede gastrointestinal involvement by months or even represent the sole manifestation of disease [4, 5]. Clinical signs

such as indurated labial swelling, mucosal tags, gingival hyperplasia, linear ulcerations, and cobblestoning of the buccal mucosa can be subtle and are often misattributed to benign or reactive conditions [1, 6].

Histopathologic findings such as noncaseating granulomas, perivascular lymphoplasmacytic infiltrates, and mucosal edema, while consistent with Crohn's disease, are nonspecific and may overlap with other granulomatous conditions including orofacial granulomatosis, sarcoidosis, granulomatosis with polyangiitis, and Melkersson–Rosenthal syndrome [7, 8]. As such, isolated histology offers limited diagnostic utility without integration of systemic and immunologic data. Recent advances in salivary cytokine profiling and mucosal microbiome analysis have demonstrated promise as non-invasive biomarkers of systemic inflammatory burden in Crohn's disease [9, 10]. These tools may enable earlier detection and more accurate disease monitoring, especially in patients with minimal or absent intestinal symptoms.

Importantly, reframing oral Crohn's lesions as autonomous immunologic events, rather than secondary mucosal sequelae, emphasizes their diagnostic and prognostic significance in the broader inflammatory landscape [6, 11]. Early identification of oral findings offers a critical opportunity for timely intervention, especially in pediatric populations vulnerable to nutritional and developmental complications [12, 13].

This review aims to contextualize oral Crohn's disease within the differential diagnosis of chronic orofacial inflammation, highlight its clinical and histologic hallmarks, and explore emerging diagnostic tools. Recognizing OCD as a primary site of disease expression enhances diagnostic precision and underscores the mouth's role as a vital immunologic interface in systemic inflammatory disease.

2. Clinical Features of Oral Crohn's Disease

Oral Crohn's disease (CD) presents with a variety of clinical features that may occur in isolation or simultaneously in the same patient [14]. These lesions are typically classified as *specific* or *non-specific*, based on the presence or absence of non-caseating granulomas on histopathological examination, a hallmark of CD [15]. The reported prevalence of oral involvement in CD varies widely, from 0.5% to 50%, and in some cases, oral lesions may precede gastrointestinal symptoms, making them valuable for early diagnosis [16,17,18]. Notably, oral manifestations are more common in patients with proximal or perianal gastrointestinal involvement [17]. Due to their intermittent nature, these oral lesions are often overlooked, yet when identified, they may serve as early clinical signs of systemic disease. Specific oral lesions include indurated mucosal tags, cobblestone buccal mucosa, mucogingivitis, deep linear ulcerations, and labial swelling with vertical fissures. Mucosal tags, typically found in the vestibule and retromolar region, appear as white, polypoid, fringe-like folds [14]. Cobblestoning results from granulomatous swelling and presents as nodular, hyperplastic mucosa, often causing discomfort during eating or speaking [15,19]. This cobblestone appearance is also pathognomonic in gastrointestinal CD. Gingival involvement may present as hyperplastic, granular tissue that can extend to the mucogingival margin [20]. Deep linear ulcerations, commonly located in the buccal sulci, can be particularly painful. Labial swelling involves chronic lip enlargement with vertical fissures and crusting of the vermillion border, often leading to facial disfigurement and impacting quality of life [21]. These lesions can significantly affect patients' daily functioning and should be actively incorporated into treatment planning and disease monitoring.

Non-specific oral manifestations**,** such as aphthous stomatitis and angular cheilitis, are less diagnostically specific and can be seen in both CD and ulcerative colitis (UC). However, they occur more frequently in CD patients [22]. Aphthous ulcers typically present as recurrent, shallow lesions with well-defined margins and a surrounding erythematous halo [23,24]. Angular cheilitis appears as fissured, erythematous plaques at the corners of the mouth and surrounding skin [24]. Though nonspecific, these lesions warrant clinical attention given their frequency and potential to reflect systemic disease activity.

The pathogenesis of oral CD mirrors the broader immunologic dysregulation characteristic of the disease. It involves a complex interplay of genetic, environmental, and microbial factors that lead to an aberrant immune response. Specific oral lesions are often associated with moderate-to-severe disease activity and may serve as external indicators of systemic inflammatory burden [25]. Central to this immune response is the activation of T-helper 1 (Th1) and T-helper 17 (Th17) cells, which secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α),

interleukin-12 (IL-12), and interleukin-23 (IL-23) [26]. These cytokines drive the chronic inflammation and granuloma formation characteristic of both gastrointestinal and oral manifestations of CD [26]. Thus, oral findings in Crohn's disease not only reflect localized inflammation but also serve as clinically significant markers of systemic immune activity and disease severity.

3. Histopathologic and Immunologic Findings

Endoscopic evaluation combined with histopathological analysis is essential for confirming a diagnosis of Crohn's disease. The most common histopathological findings observed during endoscopy include non-caseating granulomas, perivascular lymphoplasmacytic infiltrates, and mucosal edema. The presence of epithelioid non-caseating granulomas has been described as a hallmark of Crohn's disease [27]. These granulomas are composed of epithelioid cells, lymphocytes, macrophages, and multinucleated giant cells, and are mediated by immune system dysregulation leading to a Th1-dominant response [27]. Granulomas are identified in approximately 10–50% of patients with Crohn's disease [27, 28].

In one study involving 56 newly diagnosed Crohn's disease patients, researchers found that 44.6% exhibited granulomas [28]. This study also suggested that granulomas are more likely to be present in patients with more severe disease, as those with granulomas demonstrated elevated severity markers [28]. These findings support the potential utility of non-caseating granulomas as a prognostic indicator in Crohn's disease.

In addition, due to immune system dysfunction in Crohn's disease, perivascular lymphoplasmacytic infiltrates may also be observed on endoscopic evaluation. These infiltrates can appear in a heterogeneous distribution within the mucosa, occurring as small patches or well-circumscribed lymphoid aggregates [29]. The presence of the perivascular lymphoplasmacytic infiltrates reflect the dysregulation leading to the activation of the immune system. Additionally, mucosal edema is another histological feature frequently encountered during endoscopy. This edema is associated with active inflammation and crypt abscess formation, which can progress to aphthous ulcers and subsequently evolve into deep longitudinal and transverse ulcers with intervening edematous mucosa [30]. These findings highlight the variable nature of histopathological and immunologic findings seen in Crohn's disease that may aid in the diagnosis process.

Although endoscopic findings may be indicative of Crohn's disease in its later stages, they are less reliable for detecting early-stage disease. Chronic inflammation often requires time to significantly alter the gut lining in ways that are discernible endoscopically. Consequently, a delay typically exists between the onset of mucosal inflammation and the appearance of endoscopic abnormalities [31]. Moreover, histological findings are often non-specific to Crohn's disease, as similar features may be present in other gastrointestinal disorders. In early disease, patients commonly present with irritable bowel syndrome (IBS)-like symptoms, which can lead to misdiagnosis and delayed initiation of appropriate treatment [31]. The chronic inflammation characteristic of Crohn's disease is ultimately driven by dysregulation of the immune system [31]. Therefore, early diagnosis of Crohn's disease remains a challenge and further reveals the importance of a comprehensive evaluation of patients to differentiate Crohn's disease from other gastrointestinal disorders that have similar manifestations.

4. Differential Diagnosis and Diagnostic Challenges

When diagnosing nummular dermatitis in skin of color (SOC), there are complications in clinical overlap with various inflammatory and granulomatous dermatoses. Overlapping conditions, such as Orofacial granulomatosis, Melkersson–Rosenthal syndrome, Sarcoidosis, Granulomatosis with polyangiitis, and Delayed hypersensitivity reactions, can present with certain lesions that mimic nummular dermatitis.

Orofacial granulations present with the enlargement of soft tissue and oral ulceration. For the differential diagnosis to be accurate, it is essential to have histopathological confirmation of non-caseating granulomas [32]. Melkersson-Rosenthal Syndrome (MRS) is a neurological disease which is characterized by a triad of face swelling, tongue furrowing, and facial paralysis [33]. The facial erythema and swelling may superficially resemble nummular dermatitis. Sarcoidosis presents as a multisystem disease that affects any organ, but mainly the lungs, eyes, and lymphatic system [34]. The cutaneous presentation of sarcoidosis is reactive, non-specific lesions, which are similar to erythema nodosum. The annular and plaque-like lesions that are present on the extremities may present

like nummular dermatitis, but lack the intense pruritus that characterizes nummular dermatitis [35].

Granulomatosis with polyangiitis (GPA) is a type of rare vasculitis that affects the small vessels of the body and is linked to an array of disorders classified as antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitides. The defining features of this disease consist of necrotizing granulomas and pauci-immune vasculitis, primarily affecting the lungs, kidneys, and upper respiratory tract. A diagnostic challenge that arises with diagnosing GPA is that there is an observed overlap in symptoms with microscopic polyangiitis (MPA), which includes alveolar hemorrhage and necrotizing glomerulonephritis [36].

Delayed hypersensitivity reactions present in various clinical forms, but the common cutaneous presentations include contact dermatitis, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, and Acute Generalized Exanthematous Pustulosis [37]. The coin-shaped plaques with scaling and vesiculation slightly mimic acute nummular lesions.

Given the overlapping clinical presentations of many dermatologic conditions, relying solely on histopathology or morphology can be insufficient for accurate diagnosis. A more comprehensive, multimodal diagnostic approach is necessary, one that incorporates a detailed patient history, including potential triggers and the timing of symptom onset; a thorough dermatologic examination that captures lesion morphology, progression, and palpation findings; histopathologic evaluation; allergy testing to assess for potential contact or food allergens; and a systemic workup employing multiple diagnostic modalities to identify or exclude underlying systemic conditions [38].

5. Pediatric and Adolescent Considerations

Although Crohn's disease is predominantly diagnosed in adults, the incidence of young onset CD has been increasing recently, particularly in the western world due to a complex interaction of genetic, environmental, and dietary factors. The typical age of onset in the younger population falls between 10 and 20 years, with a slight male predominance [39]. Notably, the clinical presentation of CD in younger patients often differs from that in adults, with oral manifestations representing a significant and sometimes primary feature. A seminal study by Pittock et al. (2001) reported that oral lesions are present in approximately 50–80% of pediatric patients with CD, with nearly 30% presenting initially with oral involvement [40]. The most commonly observed lesion is aphthous stomatitis, while less frequent findings include mucosal cobblestoning, gingival hyperplasia, and labial swelling [40,41]. These lesions can be nonspecific and mimic those of other conditions, such as viral infections, canker sores, or other forms of oral mucosal inflammation making the diagnosis of oral CD very challenging.

Frequently, oral manifestations of CD emerge as the initial complaint without accompanying gastrointestinal (GI) symptoms and patients often seek care for recurrent mouth ulcers, gingival inflammation, or discomfort during eating, which may require further evaluation [42]. This temporal disconnect between the oral and GI symptoms poses diagnostic difficulties, as oral lesions are frequently subtle and easily misinterpreted as benign conditions such as nutritional deficiencies or viral infections, particularly when GI signs are absent [43]. Consequently, early detection of these oral findings through comprehensive clinical assessment is vital, enabling earlier diagnosis of CD and intervention. The clinical importance of early recognition of oral CD in the younger populations cannot be overstated. In pediatric patients, untreated CD can lead to significant developmental and nutritional challenges due to the effect of oral lesions on eating habits and consequently nutritional intake [44].

Furthermore, early diagnosis of oral CD also helps clinicians monitor for the development of extra-intestinal manifestations, which are quite common in pediatric IBD patients. These include joint involvement, eye inflammation (e.g., uveitis), skin rashes, and liver disease. Recognizing these manifestations early allows for a more comprehensive treatment approach, addressing both the gastrointestinal and extra-intestinal manifestations [45]. Finally, the psychological and social impact of CD on pediatric and adolescent patients cannot be overlooked. Oral CD, due to its visible nature, can significantly affect a child's self-esteem, body image, and social interactions, especially during critical periods of adolescence. Chronic oral ulcers and discomfort can lead to difficulties in speaking, eating, and socializing, which can affect the overall quality of life [46]. Early interventions and management can alleviate these psychosocial burdens, allowing patients to lead more normal lives.

6. Emerging Diagnostic Biomarkers

Traditional diagnostic methods for Crohn's disease (CD), such as endoscopies and biopsies [47], are often invasive, costly, and burdensome for patients. Consequently, there is growing interest in non-invasive tools that support earlier diagnosis and more accessible monitoring. Recent advances in immunology and microbiology have led to the identification of several emerging biomarkers with the potential to improve early detection, risk assessment, and disease tracking. Among the most promising are salivary cytokine profiling, mucosal microbiome alterations, and epithelial barrier dysfunction. These approaches may be especially valuable in identifying and monitoring oral manifestations of CD, which are often under-recognized and challenging to diagnose using conventional methods. Salivary cytokine profiling has emerged as a promising non-invasive diagnostic tool, particularly given the frequent occurrence of oral inflammation in CD patients. This inflammation is associated with altered cytokine levels. Recent studies have focused on the Th-17 family of cytokines, which play a crucial role in immune response and inflammation. Ulvi et al. (2024) found significantly higher salivary Th-17 cytokine levels in Crohn's patients alongside increased periodontal inflammation, indicating Th17 as a potential biomarker. [48].

Beyond cytokines, saliva contains a wide range of biomarkers with diagnostic and monitoring potential. These include oxidative stress indicators like malondialdehyde, elevated proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, specific microRNAs with altered expression patterns, and proteins like calprotectin and α-amylase. While these findings highlight saliva's potential as a non-invasive source of diagnostic biomarkers, further research is essential to validate and expand these candidates for routine clinical application [49]. In addition to molecular biomarkers, microbial shifts in the oral cavity have emerged as potential indicators of Crohn's disease activity. The oral microbiome is highly diverse, second only to the gut, and evidence suggests that oral bacteria may translocate to the gut, potentially contributing to disease progression [50]. These microbial imbalances, particularly in specific bacterial populations, may serve as diagnostic signatures and non-invasive indicators of disease activity [51]. One study comparing microbiota from the oral cavity, sputum, and ileum in CD patients found significantly reduced microbial diversity in the oral cavity and sputum compared to healthy controls. Specifically, Crohn's patients showed a decreased relative abundance of *Firmicutes* and *Actinobacteria* and an increased abundance of *Fusobacteria*, *Porphyromonas*, and *Haemophilus*, particularly during active disease. These patterns in oral microbiota suggest that microbial imbalances in the mouth may mirror and even influence gut inflammation and could serve as non-invasive biomarkers for disease monitoring [52].

In one pediatric case, gingival erythema and swelling were the initial signs of CD, preceding intestinal symptoms and prompting diagnosis. This example underscores the diagnostic value of oral tissue as an immunologically active site [53]. The shared pathophysiology between oral and intestinal tissues, particularly disruptions in mucosal immunity and epithelial barrier integrity, supports further investigation into oral biomarkers for CD. Salivary changes in cytokine levels, microbiota composition, and markers of epithelial barrier function offer an accessible and non-invasive means to detect and monitor the disease. Salivary biomarkers and oral microbial signatures represent an emerging frontier in Crohn's diagnostics. These tools offer accessible, non-invasive, and potentially early indicators of systemic inflammation. Continued research, standardization, and integration into clinical practice are needed to fully realize their potential in personalized disease management and longitudinal monitoring.

7. Reconceptualizing Oral Crohn's Lesions

Traditionally, oral lesions observed in Crohn's disease (CD) were viewed as secondary effects, peripheral extensions of a predominantly gastrointestinal pathology. They were often seen as localized complications resulting from systemic inflammation or nutritional deficiencies. However, evolving research on mucosal immunology and disease phenotyping increasingly supports a paradigm shift: oral manifestations in CD may serve as *primary immunologic expressions* of the disease, with both diagnostic and prognostic significance [54, 55]. This reconceptualization challenges clinicians to move beyond a gut-centric model of Crohn's disease and recognize the oral cavity as an active participant in systemic immune dysregulation.

From a pathophysiologic standpoint, the oral mucosa demonstrates similar patterns of immune activation seen in the gastrointestinal tract of CD patients. As mentioned previously, elevations in

pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), and interleukin-23 (IL-23), have been found in both gut and oral tissues, implicating Th-1 and Th-17 pathways in shared granulomatous processes [56,57]. Noncaseating granulomas, lymphoplasmacytic infiltrates, and epithelial barrier dysfunction, hallmarks of intestinal CD, are also present in oral biopsies, reinforcing the concept that oral lesions reflect the same immunologic terrain as their gastrointestinal counterparts [58].

Moreover, oral tissue offers a unique diagnostic advantage: accessibility. Biopsy of oral lesions is less invasive than intestinal endoscopy and may allow for earlier histopathologic confirmation, especially in patients who have yet to develop gastrointestinal symptoms. This is particularly relevant in pediatric and adolescent populations, where oral manifestations may predate gastrointestinal disease by months or even years [59,60]. Recognizing oral Crohn's disease (OCD) as a harbinger of systemic disease could allow for earlier intervention, potentially altering disease trajectory and improving long-term outcomes. In addition to histopathology, novel diagnostic approaches have highlighted the value of oral biomarkers in CD. Studies have shown that patients with IBD exhibit significant dysbiosis in their salivary microbiome, with increased pathogenic bacteria and decreased commensals, changes that often mirror intestinal microbial shifts [61]. Salivary cytokine profiling has also emerged as a promising tool for non-invasive disease monitoring. Increased levels of IL-1β, IL-6, and TNF-α in saliva correlate with disease activity and may serve as early indicators of subclinical inflammation [62]. These findings suggest that oral tissues are not merely reflective of systemic disease but are themselves immunologically active sites capable of revealing systemic pathology.

Therapeutically, this reconceptualization demands that oral lesions be treated as part of the systemic disease burden rather than isolated mucosal issues. Patients with refractory or extensive oral involvement may benefit from systemic immunosuppressive therapies, even in the absence of overt gastrointestinal disease, to prevent escalation or extraintestinal complications [63]. In this context, interdisciplinary care models incorporating gastroenterologists, dermatologists, oral medicine specialists, and pediatricians are essential for holistic disease management. Moreover, persistent oral lesions in treated patients may signal incomplete disease control or an impending flare, reinforcing their utility in longitudinal disease surveillance.

Beyond clinical practice, recognizing oral lesions as primary immunologic events opens avenues for research. Oral mucosal biopsies and salivary assays could be used in clinical trials as accessible sites for studying mucosal immunity, drug response, and disease biomarkers. Because of their visibility and ease of sampling, oral lesions offer a non-invasive window into systemic immune dynamics, presenting opportunities to explore early pathogenesis, therapeutic efficacy, and personalized treatment approaches.

Finally, oral Crohn's lesions may hold prognostic significance. Some studies suggest that patients who present with early or severe oral involvement may exhibit more aggressive disease courses or increased risk of developing extraintestinal manifestations [64,65]. Therefore, routine oral examinations in patients with known or suspected CD could contribute meaningfully to risk stratification and therapeutic decision-making. Reconceptualizing oral Crohn's lesions as active immunologic sites reshapes their role in the diagnostic, therapeutic, and research framework of inflammatory bowel disease. This approach underscores the importance of early recognition, integrated care, and continued investigation into the oral-gut immune axis. Acknowledging the oral cavity as a frontline interface in Crohn's disease not only enhances diagnostic precision but also affirms its value as a window into the systemic burden of this complex, immune-mediated condition.

8. Conclusion

At present, chronic orofacial inflammation remains an enigmatic condition wherein overlapping surface pathology, histology, and immune dysregulation patterns render it difficult for practitioners to arrive at a definitive diagnosis. In this review article, we emphasize the need to strongly consider Oral Crohn's disease in the differential and the implications for doing so regarding early diagnosis, active disease surveillance, and prognostic utility in the management of Crohn's disease. Of importance is the early detection of Crohn's Disease in patient populations such as children and adolescents in whom oral pathology may precede gastrointestinal involvement by years or is the sole manifestation of their illness. Diagnostic biomarkers such as salivary cytokines, oral mucosa microbiome changes, and dysfunctions to epithelial barrier integrity are emerging as

potential tools for arriving at an early diagnosis and the longitudinal monitoring of disease. Future research should aim to investigate the utility and efficacy of these biomarkers in detecting Oral Crohn's disease as well as predicting clinical severity and trajectory. Moreover, further investigation should be geared towards understanding how these biomarkers can be weaved into multi-modal diagnostic approaches in everyday clinical care. Coupled with histopathological data, imaging, and serology, increased attention toward oral lesions in clinical practice may be a promising tool for providers to precisely diagnose Oral Crohn's disease, assess treatment responses, and refine therapeutic regimens.

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Citation: *Abigail Beard et al. Oral Crohn's Disease in the Differential Diagnosis of Chronic Orofacial Inflammation. ARC Journal of Dermatology. 2025; 8(5):42-51. DOI: https://doi.org/10.20431/2456-0022.0805005*