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Oral Manifestations of Systemic Diseases: Exploring Diagnostic Challenges and Implications for Clinical Practice

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Abstract

Background: Oral and maxillofacial manifestations of systemic diseases are critical indicators of underlying health issues, often serving as the first signs detectable by healthcare providers. The recognition of these manifestations is essential for early diagnosis and intervention.

Methods: This review examines various systemic diseases with significant oral manifestations, focusing on conditions such as actinomycosis, tuberculosis, human immunodeficiency virus (HIV) infection, and autoimmune disorders. A comprehensive analysis of clinical presentations, diagnostic criteria, and differential diagnoses was conducted based on current literature and case studies.

Results: The findings highlight a diverse array of oral symptoms linked to systemic diseases, including localized infections, lesions indicative of autoimmune responses, and malignancies. For instance, actinomycosis may present as purulent lesions, while HIV-related conditions often manifest as candidiasis or hairy leukoplakia. The diagnostic process typically involves clinical examinations, cytological scrapes, biopsies, and serological tests to confirm the underlying systemic condition.

Conclusion: The oral cavity is a vital site for the early detection of systemic diseases. Dentists and general practitioners play a crucial role in recognizing oral manifestations, which can guide timely referrals and management. Enhanced training in the recognition of these symptoms is necessary to improve patient outcomes and reduce diagnostic delays.

Keywords: Oral manifestations, systemic diseases, diagnostic challenges, autoimmune disorders, human immunodeficiency virus.

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1. Introduction

The oral and maxillofacial manifestations of systemic illnesses constitute a comprehensive and intriguing field of research, primarily grounded on the understanding that many signs and symptoms of several systemic ailments may first appear as or be recognized via alterations in head and neck tissues. Dentists and general practitioners are crucial for early detection; hence, a thorough clinical examination of the mouth cavity must be conducted meticulously, ensuring no areas are overlooked, and a comprehensive medical history must be acquired without exception [1,2]. Suspicious lesions of the oral mucosa, lips, facial and cervical skin, cervical and submandibular swellings, atypical radiological findings, unusual coloration and morphology of teeth, unexplained or sudden mobility of one or more teeth, and unexplained bleeding from the gingiva, oral mucosa, and nasal cavity must always be thoroughly investigated and monitored to attain a medical explanation. A cytological scraping, incisional biopsy of suspected lesions, or fine needle aspiration of uncertain swellings, followed by cyto-histological investigation, must be conducted as required to get a conclusive diagnosis [3].

We examine the prevalent and challenging oral and maxillofacial manifestations potentially linked to or emerging at the outset of systemic disorders in both adult and pediatric patients, including diagnostic criteria and guidance on differential diagnosis.

2. Contagious Illnesses

Actinomycosis is a rare chronic bacterial illness that is often misinterpreted by seasoned practitioners. It is supported by Actinomyces (mostly *Actinomyces israelii* or naeslundii), a saprophytic element of the mouth cavity's endogenous flora, and is morphologically and clinically categorized into three types: cervico-facial, pulmonary, and abdominal-pelvic [1,2]. The cervicofacial form is the most prevalent and may induce, particularly in immunocompromised persons, suppurative and granulomatous inflammatory lesions characterized by locally aggressive and destructive activity [3,4]. Soft tissue edema (Figure 1) or osteomyelitis accompanied by purulent discharge and sinus tract development are prevalent clinical manifestations, mirroring the typical signs of abscesses, acute sialoadenitis, and lymphadenitis. Periapical localization may resemble ordinary periapical lesions (granulomas, cysts) on an X-ray, although it remains fundamentally resistant to medicinal and technical interventions. Microbiological cultures and histopathological examination are essential for diagnosing this condition, which, if left untreated, may progress to pulmonary, cerebral, and para-pharyngeal dissemination [3-5].

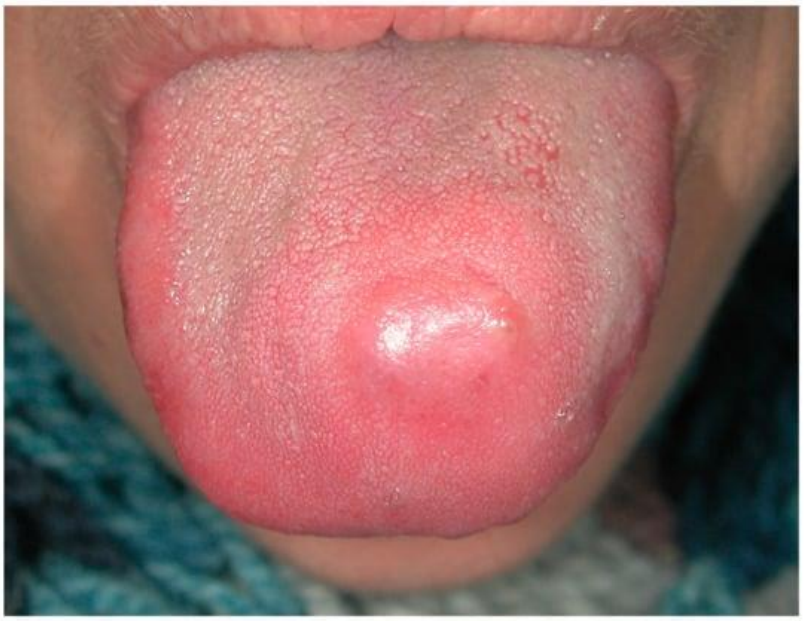


Figure 1. Tongue edema with purulent exudate identified as actinomycosis by fine needle/core needle biopsy.

Tuberculosis is a chronic granulomatous illness mostly affecting the lungs, however it may include numerous bodily systems. It is more prevalent in impoverished nations and among immunocompromised individuals, and it has a significant fatality rate. Extrapulmonary involvement mostly arises from the endogenous dissemination of the infection from the initial location. The primary form originates from the direct inoculation of infecting pathogens at susceptible sites without systemic involvement, such as the soft tissues of the oral cavity and the mandible, where potential infection routes include recent dental extractions, mucosal wounds or lacerations, as well as systemic hematogenous and/or lymphatic dissemination. Tuberculosis may clinically mimic periodontal or periapical lesions or abscesses, with or without intra- or extra-oral drainage, or present as significant ulceration of the oral mucosa, perhaps accompanied by cervical lymphadenopathy [6-8].

Human immunodeficiency virus infection now ranks as the fourth greatest cause of mortality globally, with oral symptoms sometimes serving as the first indicators, particularly in asymptomatic individuals, or observable in 30%–80% of people already diagnosed. Oropharyngeal candidiasis and hairy leukoplakia are the predominant first manifestations in undetected patients [9-11]. Oro-maxillo-facial signs may encompass manifestations of bacterial, viral, and fungal infections (primarily caused by Mycobacterium, HPV, HSVs, CMV, Cryptococcus, Histoplasma, Aspergillus, Mucoraceae, etc.), pseudo-tumoral lesions (such as necrotizing gingivitis or periodontitis, unilateral/bilateral lympho-epithelial cysts of the major salivary glands, cancrum oris, etc.), and neoplasms (including Kaposi's sarcoma and Non-Hodgkin's lymphoma) [12-15]. Despite a significant reduction in the general prevalence of such symptoms due to the implementation of HAART treatment, regular oral examinations of infected individuals are highly recommended for meticulous disease monitoring.

Human papillomavirus infection can lead to various benign clinically papillary lesions in the oral cavity, including squamous papilloma, condyloma acuminatum, verruca vulgaris, and multifocal epithelial hyperplasia (Heck's disease). Additionally, it may be linked to the development of potentially malignant lesions and oro-pharyngeal squamous cell carcinoma. More than two hundred human papillomaviruses may be transmitted vertically (from mother to fetus), horizontally (between humans via sexual contact, skin-to-skin contact, skin-to-mucosa contact, or mucosa-to-mucosa contact), and by autoinoculation [16]. Virus entry may be enhanced by mucosal disruptions or micro-abrasions, leading to the infection of basal stem cells, which subsequently differentiate into keratinocytes, accompanied by genomic amplification, immune evasion, and viral dissemination through desquamation from the superficial layers [16-18]. The clinical and differential diagnosis of squamous papilloma, condyloma acuminatum, and verruca vulgaris is rather straightforward; nevertheless, it must necessarily include giant cell fibroma, verruciform xanthoma, papillary squamous cell carcinoma, and sialoadenoma papilliferum [19-22]. The diagnosis of multifocal epithelial hyperplasia is primarily based on clinical observation, particularly in pediatric cases; however, Cowden's syndrome, neurofibromatosis type 1, and multiple endocrine neoplasia type 2B must always be included in the differential diagnosis, alongside other benign clinically papillary lesions of the oral mucosa.

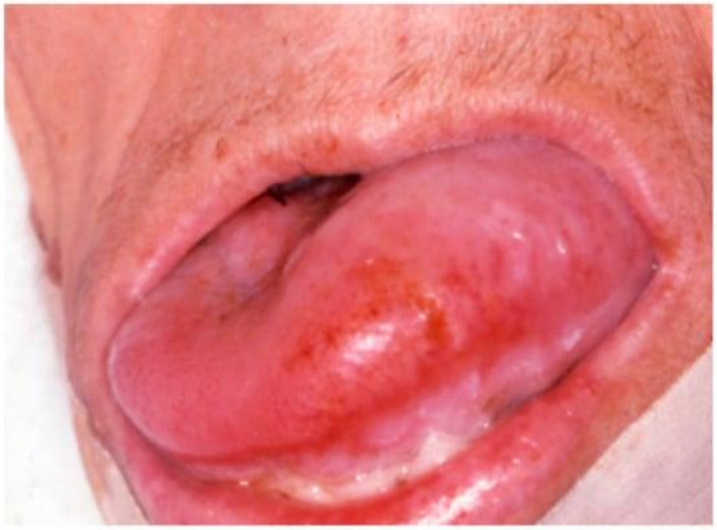
The Epstein–Barr virus (EBV) infection often manifests in early childhood and, like other human herpesviruses classified as HHV-4, is mostly characterized by viral latency in the B-cells of the majority of adults after first infection. EBV induces infectious mononucleosis and hairy leukoplakia in otherwise healthy individuals, and through an inadequately elucidated tumorigenesis pathway involving human oral epithelial or lymphoid tissue, it is associated with various epithelial and non-epithelial neoplasms or tumor-like lesions in the head and neck, predominantly in immunocompromised patients. These include Burkitt's lymphoma, Hodgkin's and non-Hodgkin's lymphoma in the context of immunodeficiency, post-transplant lymphoproliferative disorder, lymphoepithelioma-like carcinoma of the parotid gland, and nasopharyngeal carcinoma. Aside from infectious mononucleosis and hairy leukoplakia, which are common and readily identifiable through clinical examination, all other EBV-related lesions and neoplasms pose a significant challenge; they are often diagnosed at an advanced stage when located in the oro-maxillo-facial region due to their rarity and the nonspecificity of clinical and radiological manifestations [23-26].

3. Autoimmune and Dysimmune Disorders

Amyloidosis is an uncommon condition characterized by the accumulation of insoluble aggregates of misfolded fibrillary proteins (amyloidogenic proteins) in the extracellular matrix of diverse tissues and organs, manifesting in various forms (primary, multiple myeloma-associated, and secondary) [27-29]. It occurs in the head and neck in approximately 40% of patients with systemic disease [30,31], primarily affecting the larynx, orbit, sinuses, and salivary glands. In the oral cavity, the tongue (Figure 2) is the most commonly affected site, exhibiting nodular or diffuse enlargement, with potential ulceration or hemorrhage, followed by the palate and gingiva [32-36]. Oro-facial lesions often serve as the first clinical indication and often signify a poor prognosis [37]. Diagnosis must be unequivocally validated by tissue biopsy, and therapy is contingent upon the illness stage.

fIgure 2. The first indication of primary amyloidosis is macroglossia along with a nodular enlargement.

Sjögren's syndrome is an autoimmune disorder of unknown origin, predominantly affecting women (female:male ratio 9:1), and involves the exocrine glands, specifically the salivary and lacrimal



glands. It is categorized as primary or secondary, with the latter often associated with rheumatoid arthritis and other autoimmune conditions such as lupus erythematosus, scleroderma, and vasculitis. Typical manifestations include keratoconjunctivitis sicca and xerostomia, characterized by thick, ropey, mucinous saliva or its complete absence, atrophy of the papillae, fissuring of the tongue, and angular cheilitis, frequently linked to Candidiasis in these patients. Furthermore, various symptoms related to the qualitative and quantitative reduction of saliva may be present, including dysphagia, taste disturbances, and difficulties in speaking and chewing. Diagnosis relies on clinical, serological (the presence of serum autoantibodies anti-SS-A/Ro and anti-SS-B/La), and histological (assessment of lymphocytic infiltration around salivary ducts in labial minor salivary gland samples) findings [38,39]. Nonetheless, the majority of cases remain either untreated or discovered at a later stage. The potential development of MALT lymphoma in over 30% of patients with Sjögren syndrome, along with the decline in quality of life associated with later clinical stages, underscores the critical need of early illness diagnosis to avert consequences [40].

Autoimmune blistering illnesses are mostly categorized into the Pemphigus and Pemphigoid groups. Pemphigus comprises a collection of chronic autoimmune disorders characterized by autoantibodies that attack specific desmosomal proteins on epithelial cell surfaces. In pemphigus vulgaris, these autoantibodies predominantly target desmoglein-3 and, in approximately 50% of cases, may also target desmoglein-1, which is exclusively targeted in pemphigus foliaceus. This leads to acantholysis and frequently results in intraepithelial blistering. Oral cavity manifestations are typically severe and often serve as the initial clinical indication of disease, commonly presenting as painful, flaccid vesicles primarily

on the gingiva, tongue, and palate, which rapidly progress to erosion and ulceration, exhibiting classic positivity to the Nikolsky sign [41-44]. Histological analysis, supplemented by direct immunofluorescence of the tissues, is essential for differential diagnosis, alongside blood tests for BP180 and BP230. Paraneoplastic pemphigus is a clinical variant commonly linked to an undiagnosed neoplasm, primarily non-Hodgkin lymphoma, leukemia, or multiple myeloma. It is characterized by intra- and sub-epithelial bullae, with an unclear relationship between the malignancy and autoimmunity. An immune dysregulation characterized by the generation of autoantibodies (targeting desmoglein-3, as well as desmoplakins I and II, periplakin, envoplakin, BP230 [BPAg1], and a 170-kd membrane protein) likely arises as a consequence of the neoplasm rather than as a fundamental etiology.

The pemphigoid group primarily comprises bullous pemphigoid, dermatitis herpetiformis, mucous membrane pemphigoid, herpes gestationis, linear IgA bullous dermatosis, and epidermolysis bullosa acquisita; however, the two conditions most affecting the oral cavity are bullous pemphigoid and mucous membrane pemphigoid [45]. Bullous pemphigoid is the most prevalent condition, with oral involvement often occurring concurrently with skin lesions. In 10–20% of patients, gingival erosion, erythema, or serous/hemorrhagic blisters may manifest. Conversely, the clinical start of mucous membrane pemphigoid exhibits significant variability. Patients, mostly female, may exhibit oral lesions, particularly desquamative gingivitis, as early or solitary manifestations, or in conjunction with skin or other mucosal sites, including conjunctival irritation, photophobia, ulceration, and scarring-symblepharon. Bioptic tissues reveal a sub-epithelial bulla with sparse inflammatory cells on H&E and linear deposits of IgG and C3 at the epithelial-connective junction, indicative of autoantibody synthesis, primarily targeting Antigen BPAG2 (180 kD). Early diagnosis is crucial in these situations to avoid problems and for the prompt initiation of appropriate treatment.

Behcet's syndrome is a chronic inflammatory condition marked by the traditional trio of oral, genital, and ocular ulcers; moreover, cutaneous, vascular, central nervous system, and gastrointestinal involvement may be variably present. Oral lesions sometimes represent the first presentation of the illness (such as recurrent aphthous major, ischemic necrosis of the gingiva, etc.) [46]. As there are no relevant serological or biochemical indicators for diagnosing and monitoring the condition, the process relies mostly on the examination of lesions, symptoms, and a comprehensive medical history [47-49]. Numerous measurement systems (both scores and indices) for patient-reported outcomes are available to enhance the management of Behcet's syndrome. Some are validated as disease-specific (Total Activity Index, Behcet's Disease Current Activity Form, Behcet's Syndrome Activity Scale), while others are organ-specific (Oral Ulcer Severity Score, Genital Ulcer Severity Score, Composite Index for oral ulcers, and Muco-cutaneous Index) [50]. The presence of mucocutaneous lesions, typically observed in women and diminishing with age, alongside musculoskeletal involvement signifies a milder form of the disease; oral ulcer activity, often persistent particularly in young males, frequently precedes involvement of other organs.

Psoriasis is a chronic inflammatory mucocutaneous disorder primarily impacting the skin, with many clinical manifestations. The intraoral manifestation, whether concurrent with cutaneous lesions or as isolated oral lesions, is infrequently documented in the literature; involvement of the oral mucosa and other mucous membranes may arise, particularly in conjunction with generalized pustular or erythrodermic variants of psoriasis [51]. Prevalent observations in the oral cavity include leukoplakia-like lesions mostly located on the face and palate, desquamative gingivitis, migratory glossitis, and geographic or fissured tongue. The presence of psoriasis lesions in the oral cavity remains contentious. It is widely acknowledged that patients with psoriasis exhibit oral lesions concurrently with skin manifestations, both displaying analogous histopathological characteristics and a corresponding clinical trajectory; however, a positive family history and affirmative HLA typing for genes B13, B17, B37, Cw4, or Cw6 are typically employed as diagnostic criteria. Oral lesions exhibiting definitive histological characteristics, in the absence of associated skin involvement, are often indicative of a remission phase of cutaneous psoriasis. Due to the absence of the specified diagnostic criteria, most writers classify suspicious lesions as psoriasiform mucositis instead of authentic oral psoriasis. The actual prevalence of oral involvement in psoriasis remains uncertain, likely because to its rarity, the ephemeral characteristics of oral lesions, and the lack of a clinical and histological

agreement about the diagnosis of oral psoriasis. Nonetheless, it cannot be ruled out since insufficient attention is often given to the oral cavity of patients with overt cutaneous psoriasis or even a familial history of psoriasis, and particularly, mucosal biopsies are conducted in relatively few instances [52].

Lichen planus (LP) is a prevalent mucocutaneous disorder that may be limited only to the oral mucosa or manifest in a more extensive manner [53,54]. It is an autoimmune/inflammatory disorder impacting the skin, oral mucosa, and tongue; in the oral cavity, it may present in several forms or subtypes often characterized as reticular or 'lace-like' (Wickham's striae), bullous, and erosive. LP lesions, particularly in the reticular variant, are often asymptomatic and are typically discovered during dental examinations. Symptoms are instead indicated by the patient exhibiting erosive lesions associated with LP. Patients with confirmed diagnoses by histological evidence should be watched to avoid malignant transformation as well [55,56]. Indeed, alterations in the clinical manifestation of intra-oral lesions throughout prolonged follow-up, which may extend over many years or even decades, need meticulous observation and often further biopsies to rule out dysplasia or cancer. Symptom management and/or reduction of oral lesions may be attained with the use of topical and/or systemic corticosteroids. While the clinical diagnosis is comparatively straightforward, the differential diagnosis encompasses a broad spectrum, including lichenoid drug reactions, oral psoriasis, graft-versus-host disease, discoid lupus erythematosus, frictional keratosis, candidiasis, erythroplakia, and early-stage oral carcinoma. Additionally, the potential association with other systemic diseases, particularly Hashimoto's thyroiditis, should always be explored in patients with lichen planus.

4. Granulomatous Disease

The term oro-facial granulomatosis refers to various conditions characterized by comparable clinical features (primarily persistent soft tissue enlargement in the oral and maxillofacial areas) and microscopic characteristics (presence of non-caseating granulomas upon histological analysis), frequently linked to systemic disorders such as sarcoidosis and Crohn’s disease [57-59].

Sarcoidosis is a multi-system granulomatous disorder of indeterminate etiology, often impacting the thoracic region of young and middle-aged people via bilateral hilar lymphadenopathy [59]. Skin, muscle, nerves, liver, heart, kidneys, and joints may be variously affected by the development of non-caseating giant-cell granulomas. Sarcoidosis in the head and neck may affect salivary glands and lateral neck lymph nodes, presenting as asymptomatic, slow-growing swellings. Additionally, single or multiple submucosal nodules, however nonspecific and uncommon, may be seen in the lip and cheek [60]. Lofgren's syndrome is an unusual clinical manifestation of sarcoidosis, distinguished by enlargement of the salivary and lacrimal glands, uveitis, and peripheral facial nerve palsy [58,59]. The diagnosis relies on chest radiography, hematological assessments including Angiotensin-Converting Enzyme levels, and incisional or core-needle biopsy of lesions that confirm the existence of non-caseating granulomas.

Melkersson-Rosenthal syndrome is an oro-facial granulomatous disorder often defined by a trio of symptoms: oro-facial edema, recurrent peripheral facial nerve paralysis, and a fissured tongue. These clinical symptoms may manifest either synchronously or metachronously, even after several years [61]. When just the swelling of the lower lip is seen, the condition is referred to as granulomatous cheilitis or Miescher’s illness. Additionally, there may be swelling of the tongue, cheek, and palate, along with generalized erythema of the gingiva that is refractory to medicinal or mechanical interventions. The diagnosis is often established by the identification of clinical signs and histological analysis of the affected tissue, which is beneficial for differentiating it from angioedema, Crohn’s disease, and amyloidosis [62].

5. Metastases to the Orofacial Tissues

Metastases to the oro-facial tissues are very uncommon, with a frequency of 1–8% among all oral malignant tumors, mostly occurring in individuals aged 50 to 70 years. The most prevalent primary tumors in men are located in the lung, kidney, prostate, and colon-rectum, while in females, they are found in the breast, lung, uterus, and ovary. Oro-facial metastases may affect the oral mucosa, jawbones, or salivary glands, perhaps serving as the first indication of an undetected malignancy or as a symptom of advanced

illness [63]. Furthermore, a tendency for metastases to localize to specific areas in the oro-facial region is widely acknowledged, particularly in the molar and premolar regions due to their enhanced vascularization and greater bone marrow density. This phenomenon is likely further influenced by unique clinical conditions of the oral hard and soft tissues, including periodontal tissues with inflammatory lesions in dentate individuals, gingival tissues in edentulous patients with prostheses, or post-extraction sites, potentially resulting from increased blood flow following the organization of the blood clot. Clinically, oro-facial metastases often present as quickly enlarging lesions of the gingiva, potentially involving bone, exhibiting radiological characteristics of aggressive neoplasms, or as face swelling when affecting the main salivary glands. Their identification, particularly in undiagnosed or occult primary cancers, poses a significant dilemma for clinicians, as the differential diagnosis (both clinical and radiological) is exceedingly complex. This challenge extends to pathologists in accurately defining the primary tumor through sample analysis, especially when the diagnostic evaluation is confined to the head and neck region.

6. Conclusions

The clinical presentation of oro-facial manifestations associated with systemic diseases is extensive, particularly given their potential to exhibit a concurrent or metachronous progression alongside systemic lesions, potentially preceding them and serving as the initial clinical indicator in patients who are unaware of or yet-to-be-diagnosed with their condition. Diagnostic delays are often linked to the treatment trajectory in these individuals, since clinical detection and accurate histological identification of sampling lesions may be challenging. Therefore, dentists and general practitioners must get clinical and academic training to facilitate prompt diagnosis by the recognition of prevalent or particular oro-facial symptoms indicative of systemic or generalized diseases.

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المظاهر الفموية للأمراض الجهازية: استكشاف التحديات التشخيصية وتداعياتها على الممارسة السريرية

الملخص

الخلفية :تعتبر المظاهر الفموية والوجهية للفم من الأمراض الجهازية مؤشرات حيوية على القضايا الصحية الكامنة، وغالبًا ما تكون العلامات الأولى القابلة للكشف من قبل مقدمي الرعاية الصحية. إن التعرف على هذه المظاهر أمر ضروري للتشخيص المبكر والتدخل.

الطرق :تستعرض هذه المراجعة مجموعة من الأمراض الجهازية التي لها مظاهر فموية كبيرة، مع التركيز على حالات مثل داء الفطريات، والسل، وعدوى فيروس نقص المناعة البشرية(HIV) ، والاضطرابات المناعية الذاتية. تم إجراء تحليل شامل للعروض السريرية، ومعايير التشخيص، والتشخيصات التفريقية بناءً على الأدبيات الحالية ودراسات الحالة.

النتائج :تسلط النتائج الضوء على مجموعة متنوعة من الأعراض الفموية المرتبطة بالأمراض الجهازية، بما في ذلك العدوى الموضعية، والآفات التي تشير إلى استجابات مناعية ذاتية، والأورام الخبيثة. على سبيل المثال، قد يظهر داء الفطريات كآفات صديدية، بينما تظهر الحالات المرتبطة بفيروس نقص المناعة البشرية غالبًا على شكل عدوى فطرية أو ليوكوبلاكيا الشعرية. تتضمن عملية التشخيص عادةً الفحوصات السريرية، والخدوش الخلوية، والخزعات، والاختبارات المصلية لتأكيد الحالة الجهازية الكامنة.

الاستنتاج :تعتبر تجويف الفم موقعًا حيويًا للكشف المبكر عن الأمراض الجهازية. يلعب أطباء الأسنان وممارسو الرعاية العامة دورًا حيويًا في التعرف على المظاهر الفموية، مما يمكن أن يوجه الإحالات والإدارة في الوقت المناسب. هناك حاجة إلى تعزيز التدريب في التعرف على هذه الأعراض لتحسين نتائج المرضى وتقليل التأخيرات في التشخيص.

الكلمات المفتاحية :المظاهر الفموية، الأمراض الجهازية، تحديات التشخيص، الاضطرابات المناعية الذاتية، فيروس نقص المناعة البشرية.