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Granulomatous Diseases: Oral Manifestations

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Abstract

Oral granulomatous disease presents with varied manifestations due to wide variety of infections. It is complex and difficult to diagnose various granulomatous diseases due to similar appearing clinical lesions. However, the emergence of numerous diagnostic techniques has now made it easier to scrutinize the granulomatous diseases. A very thorough and exhaustive clinical, microscopic and laboratory evaluation is required to diagnose oral granulomatous diseases.

The present review article aims to highlight etiology and oral findings of various granulomatous diseases affecting the oral cavity.

Keywords: Granulomatous inflammation; Granulomatous diseases; Oral granulomatous lesions

Introduction

The protean manifestation of granulomatous diseases is characterized by granuloma formation which is a focal accumulation of inflammatory cells, commonly formed as a result of continual existence of a non-degradable product or hypersensitivity reactions [1,2]. They form due to strong defense mechanism and present inflammatory processes to destroy the invading infectious agents leading to formation of giant cells or transform into epithelioid cells [3].

The etiology is multifactorial and includes infections, vasculitis, immunological upset, hypersensitivity, neutrophil oxidase defect, chemicals and neoplasia [2]. The antigen presenting cells release cytokines and cause chemoattractants that attract neutrophils and lead to activation of monocytes and engulfment by macrophages. *Via* MHC class II and CD1 molecules, they present to T antigens. The naïve T cells activate Th1 cells which produce IL-2 leading to attraction of chemokines and formation of granuloma [4].

They have multifaceted appearances such as sessile, lobulated with or without erythema. With the passage of time, they may show central ulceration and present as squamous cell carcinoma. The lesions depending upon their clinical presentation can be treated accordingly [5,6]. Clinically, it can involve the oral hard and the soft tissues and pose a diagnostic dilemma.

In the present review article, we aim to summarize the details of granulomatous lesions that affect the soft and hard tissues.

Orofacial Granulomatosis

The term was introduced by Wiesenfeld et al. in 1985 which is characterized by oral granulomas without any recognizable systemic cause and can affect any gender at any age [7,8].

The disease involves facial swelling, ulceration of the oral mucosa, cobblestone appearance of the buccal mucosa and gingival hypertrophy [9]. With the involvement of facial paralysis and fissured tongue, it is known as Melkerson-Rosenthal syndrome. When only the lips are involved, it is cheilitis granulomatosa [7].

Orofacial granulomatosis is characterized by chronic, non-caseating granulomas. Studies have shown higher prevalence of *S. salivarius* is found in these patients [9,10].

Treatment involves topical agents like corticosteroids, calcineurin inhibitors; intralesional corticosteroids and systemic agents like azathioprine, thalidomide and metronidazole [11].

Sarcoidosis

Sarcoidosis is a granulomatous condition of unknown etiology, characterized by granulomatous inflammation affecting any organs but most commonly involving the lungs [12,13].

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It is a disease of multiple etiological factors characterized by non-caseating granulomas. Patients show a strong association with HLA A1, B8, and -DR3, few infectious microorganisms like pollen, silica, and occupational exposures [13].

Th1 lymphocytes play an integral role in granuloma due to accumulation of poorly soluble antigenic material. In case of no resolution, granuloma is converted to avascular and acellular connective tissue further leading to hyalinization and fibrosis [14]. It is a delayed type hypersensitivity response which is due to regulatory T cells (Treg). They accumulate at the periphery of a granuloma causing anti proliferative action by suppression on TNF-α, therefore promoting granuloma formation. These non-caseating granulomas eventually join and form multinucleated giant cells [15-17].

Oral findings: Oral involvement is very uncommon, but can present as gingival enlargements or swellings of the salivary glands, buccal mucosa, lips, tongue [18-20].

Some other tests findings are involvement of the bone that radiographically appear similar to eosinophilic granuloma or periodontal disease [13,18,20-22].

Diagnostic tests: An extensive history, physical examination, chest radiographs and pulmonary function tests, serum chemistry, eye evaluation and complete hematological counts need to be done with suspected or diagnosed sarcoidosis [17].

Management: Infliximab has shown good response in the management of sarcoidosis [17].

Tuberculosis

Tuberculosis (TB) is a chronic infectious granulomatous disease caused mostly by *Mycobacterium tuberculosis* [23]. Despite the large numbers of bacilli contacting the oral cavity mucosa in a typical case of pulmonary tuberculosis, oral lesions are rare (0.05% to 5%). This could be due to saliva acting as a protective agent [24,25].

Oral Findings: The oral lesions can be primary or secondary. The former is less common and mostly present on the gingival, mucobuccal vestibule or any extraction site [26-28]. The latter involve vestibule, corner of the mouth, tongue and the lip and presents as a single, non-healing, painful ulcer covered by inflammatory exudates [29]. Patients may also present as pain while eating sometimes accompanied by dysphonia [30]. In rare circumstances, infection may involve the alveolar bone and mimic periodontal disease and sometimes may lead to painless or painful salivary gland enlargement with facial palsy [23].

Diagnostic tests: Chest radiographs, sputum cultures and PCR amplifications of mycobacterial DNA. A tuberculin test can be done to identify the exposure to TB. Other tests are interferon–γ release assays and QuantiFERON TB Gold In-Tube (QFT). This requires only a single visit whereas 2 visits are needed for tuberculin skin test [31-33].

Management: New cases are treated by isoniazid, rifampin, pyrazinamide and ethambutol. An accepted regime involves two-month course of the listed drugs followed by an additional four months of isoniazid and rifampin. Older cases require addition of streptomycin [34].

Leprosy

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae* (Hansen's bacillus). It can present as lepromatous (low resistance) or tuberculoid leprosy (highly resistant) [35].

Oral findings: Oral lesions are most frequently seen in the areas of mouth with lower surface temperature and are seen as multiple nodules (lepromas) that can lead to necrosis and ulceration. Most affected areas are hard and soft palate of the uvula, on the lips and gums and the ventral side of the tongue [35,36].

Diagnosis: As the oral presentations are very nonspecific, the diagnosis is based on the confirmation with histopathological examination [37].

Syphilis

Syphilis is caused by *Treponema pallidum*, a spirochaete microorganism that is transmitted by sexual intercourse [38].

Clinical staging of the syphilitic infection can be divided into primary, secondary and tertiary syphilis [38].

Primary syphilis: It presents as chancre of the oral mucosa due to urogenital sexual practice and appears as painless ulcers.

Secondary syphilis: Characterized by a rash that appears from 2 to 8 weeks after the chancre develops and sometimes before it heals and is the most contagious stage.

Tertiary syphilis: Tertiary syphilis refers to gumma, cardiovascular syphilis, psychiatric manifestations (e.g., memory loss or personality changes), or late neurosyphilis.

Diagnosis: The confirmation of primary or secondary syphilis is done by Dark Field Microscopy [39]. Nontreponemal tests can show false positive tests [40].

Treatment: The disease is managed with the use of Benzathine Penicillin G [40].

Cat Scratch Disease

Cat scratch disease is known as regional granulomatous lymphadenitis which only occurs in humans that are scratched or bitten by kittens [41].

Oral findings: A case report by Walsch et al. showed submandibular swelling in a patient with cat scratch disease. Regional lymphadenopathy develops within 2 weeks. The nodes are initially firm and tender, later becoming fluctuant, and may drain with fistula formation. Fever, malaise, headache, and anorexia may accompany lymphadenopathy [41].

Investigations: It is identified by PCR Hybridization and indirect fluorescent antibody assay [29].

Histoplasmosis

It was first described by Samuel Darling in 1905 by *H. capsulatum*, a dimorphic fungus that is known to grow at ambient temperature [42,43].

Oral findings: The oral involvement can appear as papillary, ulcerated, granulomatous lesion involving the tongue, palate and buccal mucosa [44].

Diagnosis: It is done by clinical signs and symptoms, histopathology, culture, serological and histoplasmic skin test [45].

Blastomycosis

It is a fungal disease caused by *Blastomyces dermatitidis* [42]. The transmission is by spore inhalation involving the lungs most commonly.

Oral findings: Skin and mucosal lesions can appear as proliferative verrucous growth, may also show evidence of ulceration and scarring [42,43].

Diagnosis: Cytological or histopathological examination of tissue with identification of organism is important with culture of sputum or fresh biopsy material as additional methods for diagnosis.

Aspergillosis

Aspergillosis, caused by *Aspergillus* causes life threatening disease in patients with immunosuppression [42].

Oral findings: The second most commonly seen fungal infection is usually seen as a yellow or black ulcer with necrotic base mostly present on the palate and posterior tongue [42].

Diagnosis: Clinical, microbiological and histological characteristics are required for diagnosis of oral aspergillosis. Other methods are polymerase chain reaction and galactomannan detection [46].

Langerhans Cell Histiocytosis

Langerhans Cell Histiocytosis (LCH) is a rare multisystem disease of unknown pathogenesis [47]. Previously known as histiocytosis X and it involves 3 different clinical conditions: Eosinophilic granuloma, Hand-Schuller-Christian disease, and Abt-Letterer-Siwe disease [48].

Oral findings: Oral manifestations are the earliest signs of the disease and shows gingival recession, oral ulceration and gingival bleeding. The radiograph presents "scooped out" appearance in the region of crestal bone [47-53].

Investigations: As the lesion involves the periodontal tissues, hence the role of a periodontist remains vital to diagnose LCH at the earliest [54].

Management: Oral lesions need to be curetted and the non-restorable teeth need to be extracted. The mucosal lesions are treated with Intralesional interferon injections [54].

Wegener's Granulomatosis

Wegener's Granulomatosis (WG) is a lethal inflammatory systemic disease characterized by a triad of systemic vasculitis of small arteries and veins, necrotizing glomerulonephritis and necrotizing granulomatous inflammation of the lower and upper respiratory tract [55,56]. It was first diagnosed as a distinct syndrome by Friedreich Wegener in 1936 [57].

The American College of Rheumatology developed classification criteria for the diagnosis of WG, requiring the presence of at least 2 of the following: (1) Oral or nasal ulcers or discharge, (2) specific chest radiographs, (3) certain urine sediment abnormalities, and (4) granulomatous inflammation in biopsies [58].

The initial clinical symptoms are nonspecific such as fatigue, loss of appetite, weight loss, fever, and night sweats [58].

Oral findings: A characteristic sign of Wegener's granulomatosis is strawberry gingivitis [59-63]. It clinically appears as an exophytic gingival hyperplasia with petechial and a red granular friable appearance that usually begins in the interdental papillae then spreads to involve other areas of the gingiva [63].

Patients may also complain about tooth mobility, pain and bleeding on the affected site [63].

Some studies have also stated that it may manifest as parotid gland enlargement and oroantral fistulas [62].

Diagnosis: According to Manchanda et al. [61], the presence of an irregular form of gingival inflammation with symptoms of otitis and sinusitis should be thoroughly investigated. Histopathologically, very few deposits of immune complexes are typically provable during biopsy, WG is classified as vasculitides. Therefore, a thorough clinicopathological correlation work up along with serological evaluation should help in diagnosing of WG.

Treatment: Dentists play an integral role in the active management of patients with Wegener's granulomatosis. All the dental foci of infection should be removed before starting of immunosuppressive therapy [58]. Antiseptic/antimicrobial mouth rinses should be prescribed and patients should be kept at regular follow up and all the elective procedures should be postponed while ongoing chemotherapy. The management of gingival lesions have been seen to be highly effective with the intralesional steroid injections [64].

Conclusion

In this review manuscript, various granulomatous diseases have been thoroughly described as oral health care providers can consider these diseases and find the related differential diagnosis in the management of patients with suspicious lesions.

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