REVIEW ARTICLE

Granulomatous diseases: Oral manifestations and recommendations

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Abstract Granulomatous diseases may present with oral manifestations that are detectable by dental care providers. In certain cases, oral manifestations may precede systemic signs and symptoms. Dentists managing patients with these conditions may modify the dental treatment plan and possibly retain the support of other health professionals. This review gives an update on granulomatous diseases that can be faced by the dental practitioner.

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1. Introduction

Granulomatous diseases encompass a wide variety of conditions characterized by a histological denominator of granuloma formation. A granuloma is a focal accumulation of inflammatory cells, commonly formed as a result of stimulation of the immune system by several agents (Coash et al., 2012; James, 2000).

The etiology of granulomatous diseases includes infections, vasculitis, immunological upsets, hypersensitivity, neutrophil oxidase defect, certain chemicals, and neoplasia (James, 2000). Chronically, foreign body granulomas that affect the oral soft and hard tissues are uncommon, but when present, they may represent a diagnostic dilemma (Alawi, 2013). In this review, the most common granulomatous disorders affecting the oral soft and hard tissues will be discussed (Table 1).

2. Foreign body granulomas

Foreign body granulomas are the most common granulomatous inflammatory lesions encountered in the oral cavity. They may be incited by a variety of inert endogenous or exogenous substances; therefore, an immune response is not evoked. Furthermore, foreign body granulomas are too large to be ingested by macrophages (Alawi, 2013). Examples of dental materials that have been associated with granulomatous inflammation include amalgam, impression material, zinc phosphate cement, endodontic sealers, gutta percha, and suture materials (Alawi, 2013; Bernath and Szabo, 2003; Matthew et al., 1993; Stewart and Watson, 1990). The clinical presentation of foreign body granulomas is generally non-specific and may appear as discrete swellings or ulcerations.

3. Chronic granulomatous disease

Chronic Granulomatous Disease (CGD) is a rare condition that was first described in the 1950’s (Holland, 2010). It is caused by a genetic disorder in one of the 4 genes encoding for the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Seger, 2010; Towbin and Chaves, 2010). This leads to the failure of phagocytic cells to produce the reactive oxygen species required to kill ingested pathogens, resulting in the host’s increased susceptibility to bacterial and fungal infections (Seger, 2010; Towbin and Chaves, 2010). The most common form of the disease is X-linked, but other types are autosomal-recessive (Holland, 2010). The disease affects at least 1/200,000 to 1/250,000 of live births (Winkelstein et al., 2000). Excessive inflammation, recurrent infections, granuloma formation, lung fibrosis, and gastrointestinal symptoms mimicking Crohn’s disease are common among CGD patients (Rieber et al., 2012; Seger, 2010; Towbin and Chaves, 2010).

Oral findings include ulcerations, periodontal disease, and mucositis (Dar-Odeh et al., 2010). Oral health may be neglected in patients with CGD, which aggravates their periodontal situation, and thus periodontal treatment and maintenance are of extreme importance (Dar-Odeh et al., 2010). It is imperative that dental treatment be coordinated with the patient’s primary care, since prophylactic antibiotics may be needed (Seger, 2008).

4. Orofacial granulomatosis

The term “orofacial granulomatosis” (OFG) was introduced by Wiesenfeld and colleagues in 1985 to describe orofacial granulomas in the absence of recognizable systemic causes (Grave et al., 2009; Wiesenfeld et al., 1985). It is a rare condition that most commonly affects the lips (Wiesenfeld et al., 1985). In addition to facial swelling, oral ulceration, a cobblestone-like appearance of the buccal mucosa, and gingival enlargement may occur (Grave et al., 2009; Zbar et al., 2012). When clinical features of OFG are associated with facial paralysis and fissured tongue, the condition is called Melkerson-Rosenthal syndrome (Grave et al., 2009). When only lips are affected, it is called cheilitis granulomatosa (Grave et al., 2009).

The etiology of OFG is not clearly understood, and management can be challenging for both patients and clinicians. Exclusion of any systemic conditions that may cause the clinical appearance of OFG is the first and most important step in management. Sanderson and co-workers (Sanderson et al., 2005) examined 35 patients with OFG but without gut symptoms. Interestingly, upon endoscopy, 54% of those patients had intestinal abnormalities, and two of them had features of Crohn’s disease. The authors also reported that intestinal abnormalities were more common among younger individuals.

5. Tuberculosis

Tuberculosis (TB) is a chronic infectious granulomatous disease caused mostly by *Mycobacterium tuberculosis*, and less frequently by other species. Oral TB lesions are rare, involving only 0.05–5% of total TB cases, and can be either primary or secondary (Mignogna et al., 2000). Primary oral TB lesions are less common and usually involve the gingiva, mucobuccal vestibule, or extraction sites, although other sites within the mouth can be infected (Eng et al., 1996; Mignogna et al., 2000; Rinaggio, 2003).

| Table 1 Granulomatous diseases and their oral manifestations. |
|---------------------------------------------------------------|
| **Granulomatous diseases**                                      | **Oral findings**                                      |
| Foreign body granulomas                                       | Swellings; ulcerations                                 |
| Chronic Granulomatous Disease                                 | Ulcerations; periodontal disease; mucositis            |
| Orofacial granulomatosis                                      | Facial swelling; oral ulceration; cobblestoning of the mucosa; gingival enlargement |
| Tuberculosis                                                   | Ulcers; fissures; swellings; gingival enlargement       |
| Sarcoïdosis                                                   | Gingival enlargement; swelling; severe alveolar bone loss |
| Wegener’s granulomatosis                                      | Strawberry gingivitis; oral ulceration; painful cobblestoning of oral mucosa; failure of extraction socket to heal; parotid gland enlargement; oro-antral fistulas |
| Langerhans cell histiocytosis                                  | Severe alveolar bone loss                              |
Secondary TB lesions are more common and have been most frequently reported in the palate, the buccal mucosa, lip, gingiva, tongue, retromolar area, and floor of the mouth; they may also involve salivary glands and cervical lymph nodes (Eng et al., 1996; Gill et al., 2010; Mignogna et al., 2000; Rao et al., 1977).

Oral TB lesions appear as ulcers, fissures, swellings, or gingival enlargement. (Gill et al., 2010; Karthikeyan et al., 2006; Mignogna et al., 2000; Rinaggio, 2003) Tuberculous osteomyelitis of the jawbone has also been reported (Bhatt and Jayakrishnan, 2001; Chaudhary et al., 2004; Sheikh et al., 2012).

Although oral TB is rare, it should be considered in differential diagnosis, especially in cases of non-healing lesions. A periodontist may aid in early diagnosis by taking a biopsy of a suspected oral lesion (Gill et al., 2010; Karthikeyan et al., 2006). He/she should also ensure that there is no drug interaction with the patient’s TB regimen (Rinaggio, 2003).

6. Sarcoïdosis

Sarcoïdosis is a granulomatous condition of unknown etiology, characterized by granulomatous inflammation affecting any organs but most commonly involving the lungs (Culver, 2012)

Oral involvement in sarcoïdosis is uncommon, (Blinder et al., 1997) but, if present, it may potentially affect any oral structures. Sites most commonly affected are: the salivary glands, buccal mucosa, gingiva, lips, floor of the mouth, tongue, and hard and soft palates (Antunes et al., 2008; Blinder et al., 1997; Makris and Stoller, 1983). Oral lesions may appear as gingival enlargements or swelling of the affected area, or they may have a nodular appearance. (Blinder et al., 1997).

Jawbone involvement has been reported, and lesions may have the radiographic appearance of eosinophilic granuloma, or a presentation similar to that of periodontal disease (Antunes et al., 2008; Culver, 2012; Makris and Stoller, 1983; Moretti et al., 2007; Suresh et al., 2004).

7. Wegener’s granulomatosis

Wegener’s granulomatosis (WG) is a lethal systemic condition characterized by vasculitis, glomerulonephritis, and necrotizing granulomatous inflammation of the lower and upper respiratory tract (Ponniah et al., 2005). WG is often challenging to diagnose when involvement is limited, and therefore, recognition of a distinctive sign would help in early diagnosis (Lourenco and Nico, 2006; Manchanda et al., 2003).

WG is one of the vasculitis conditions characterized by the circulation of antibodies, called anti-neutrophil cytoplasmatic antibody (ANCA) (Weeda and Coffey, 2008). Prevalence of WG is about 3 cases per 100,000 people, with no gender predilection (Weeda and Coffey, 2008).

The disease may be of limited involvement or it may run an aggressive course that could lead to multiple organ failure (Hoffman et al., 1992; Ponniah et al., 2005; Weeda and Coffey, 2008). Patients with the generalized form of the disease usually have shorter life expectancy (Ponniah et al., 2005).

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. (Leavitt et al., 1990)

The initial clinical manifestations of WG may entail nonspecific symptoms such as fatigue, loss of appetite, weight loss, fever, and night sweats (Weeda and Coffey, 2008).

Most WG patients seek medical care for respiratory symptoms, with sinusitis being the most common (Hoffman et al., 1992; Lilly et al., 1998; Weeda and Coffey, 2008). Otitis media with possible altered hearing is seen in about 25% of cases (Weeda and Coffey, 2008). Oral lesions are reported to occur in less than 13% of patients, and are the initial feature in only 2% of cases (Duna et al., 1995). Strawberry gingivitis is a highly characteristic sign of WG, and although rarely reported, it can be one of the earliest manifestations of this disease (Lourenco and Nico, 2006; Ruokonen et al., 2009; Siar et al., 2011). Strawberry gingivitis 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, potentially leading to periodontal attachment loss and tooth mobility; patients may complain of pain and bleeding in that area (Manchanda et al., 2003; Weeda and Coffey, 2008). Other oral findings may include ulceration, a painful cobblestone-like appearance of oral mucosa, failure of extraction sockets to heal, and, less commonly, parotid gland enlargement and oro-antral fistulas (Hernandez et al., 2008; Manchanda et al., 2003; Stewart et al., 2007; Virendra Singh, 2012; Weeda and Coffey, 2008).

The medical management of WG involves the combination of prednisone and cyclophosphamide (Weeda and Coffey, 2008). Other medications, such as rituximab, have also been used as an adjunct treatment (Staines and Higgins, 2009).

The dentist may have a unique opportunity to participate in diagnosing WG when it is suggested by medical history and clinical presentation (Ponniah et al., 2005; Stewart et al., 2007). The presence of an irregular form of gingival inflammation, accompanied by symptoms such as otitis and sinusitis, should raise a red flag (Manchanda et al., 2003). In fact, dentists may actively participate in the management of WG patients. Before the patient begins immune-suppressive therapy, he/she should be dentally evaluated to remove any foci of dental infection (Ponniah et al., 2005; Stewart et al., 2007). During chemotherapy, elective dental treatment should be postponed (Stewart et al., 2007; Weeda and Coffey, 2008). Antiseptic mouth rinses may be prescribed and recall visits for dental prophylaxis should be regularly scheduled and performed (Stewart et al., 2007; Weeda and Coffey, 2008). An improvement in gingival lesions may be seen with only medical treatment (Hernandez et al., 2008; Stewart et al., 2007). Surgical removal of gingival lesions could be performed for biopsy (Hernandez et al., 2008; Stewart et al., 2007). Intralelosional steroid injections have been reported to aid in the healing of gingival lesions (Lilly et al., 1998; Weeda and Coffey, 2008).

8. Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a rare multisystem disease of unknown pathogenesis. (Madrigal-Martinez-Pereda et al., 2009) It was previously known as histiocytosis X and encompasses three different clinical conditions: eosinophilic granuloma, Hand-Schuller-Christian disease,
and Abt-Letterer-Siwe disease (Annibali et al., 2009). Involvement of the jawbones and oral soft tissues is common and may be the earliest sign of disease, (Erdem et al., 2013; Madrigal-Martinez-Pereda et al., 2009) since it may cause bone resorption in the form of intra-bony lesions, “scooped out recession” lesions, or crestal lesions resembling periodontal defects. Periodontal soft-tissue involvement is frequent and may be in the form of recession, oral ulceration, and gingival bleeding (Artzi et al., 1989; Erdem et al., 2013; Hartman, 1980; Madrigal-Martinez-Pereda et al., 2009; Rapp and Motta, 2000). LCH may initially affect the periodontal tissues and thus, periodontists may play a vital role in the early detection of LCH. When LCH is suspected based on clinical examination, a biopsy should be taken to confirm the diagnosis (Muzzi et al., 2002).

Management of LCH patients is multidisciplinary, since extra-oral involvement must be verified and treated. Accessible oral lesions are to be curetted and non-restorable teeth extracted (Klein et al., 2006; Madrigal-Martinez-Pereda et al., 2009). Mucosal lesions can be treated by intralesional interferon injection (Annibali et al., 2009).

9. Conclusion

In this appraisal, common granulomatous diseases that could be encountered by dentists were highlighted. Oral health care providers should be aware and consider these diseases in the differential diagnosis when managing patients with suspicious lesions.

Declaration of Competing Interest

We declare that we have no conflict of interest.

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