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Granulomatous diseases of the oral tissues: differential diagnosis and update

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Granulomatous inflammation represents a unique form of the chronic inflammatory response [1]. A granuloma is a distinct, compact microscopic structure composed of epithelioid-shaped macrophages typically surrounded by a rim of lymphocytes (Fig. 1). Fibroblasts and collagen also are seen immediately surrounding the lymphocytes. The epithelioid macrophages represent activated cells that upon coalescing produce multinucleated giant cells. The nuclei in these giant cells may be arranged either haphazardly (foreign body-type) or peripherally, often in the shape of a horseshoe (Langhans-type) [1]. In some instances, granulomas also may exhibit a central area of caseous necrosis.

Granulomatous inflammation of the oral soft and hard tissues is an uncommon occurrence. Although isolated granulomas may be identified in biopsies from a variety of infectious and noninfectious disease processes, granulomatous inflammation is characteristically associated with a relatively limited number of conditions (Table 1) [1–12]. The most common causes of granulomatous inflammation involving the oral tissues include foreign body reactions, infection, Crohn's disease, sarcoidosis, and orofacial granulomatosis (OFG). Because of the relatively nonspecific clinical findings associated with a variety of granulomatous diseases, a microscopic diagnosis of granulomatous inflammation often presents a diagnostic dilemma for the clinician. A variety of other conditions may be associated with granuloma formation. Rare granulomas may be identified in variants of T-cell lymphoma [13]. In rare cases, granulomas may also be identified in Wegener's granulomatosis [14] and chronic granulomatous disease [1]. Despite their names, however, neither Wegener's granulomatosis nor chronic granulomatous disease represents true granulomatous disease [1,2,14], and they are not discussed furthering this article.

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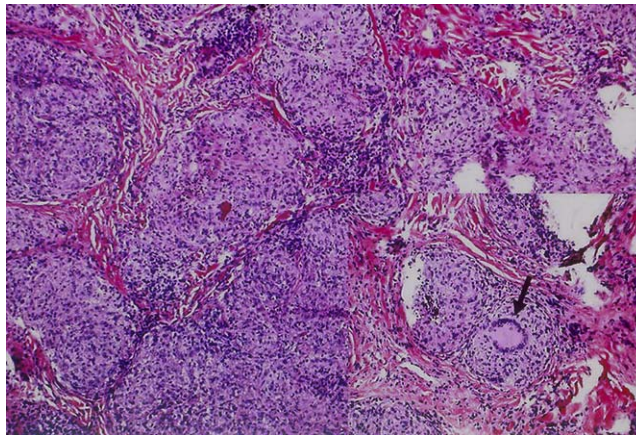

Fig. 1. Granulomatous inflammatory reaction in sarcoidosis (hematoxylin-eosin, original magnification × 40). (*Inset*) Granuloma composed of epithelioid macrophages, multinucleated giant Langhans-type cells (*arrow*), and scattered lymphocytes (hematoxylin-eosin, original maginificaiton × 100).

There are two types of granulomas, foreign body granulomas and immune granulomas [1]. The pathogenesis of granuloma formation differs between the two forms. This article highlights the etiology, clinical manifestations, current diagnostic modalities, and treatment of the various true granulomatous diseases that may be encountered in clinical practice.

Foreign body reactions

Foreign bodies or materials are the most common source of granulomatous inflammation in the oral cavity [2]. Foreign bodies may be endogenous

Table 1
The most common true granulomatous inflammatory conditions involving the oral and perioral tissues*

Disease	Cause
Foreign body reaction	Suture, hair, amalgam endodontic sealers, hyaluronic acid, etc
Tuberculosis	*Mycobacterium tuberculosis*
Leprosy	*Mycobacterium leprae*
Cat-scratch disease	*Bartonella henselae*
Tertiary syphilis	*Treponema pallidum*
Histoplasmosis	*Histoplasma capsulatum*
Cryptococcosis	*Cryptococcus neoformans*
Blastomycosis	*Blastomyces dermatitidis*
Paracoccidiodomycosis	*Paracoccidioides brasiliensis*
Sarcoidosis	Unknown
Crohn disease	Unknown
Orofacial granulomatosis	Unknown

* Other infectious organisms can also induce a granulomatous inflammatory reaction.

or exogenous. In either case, the foreign material is composed of particles that are usually too large to be phagocytosed by macrophages. Because the material is typically inert, it usually does not evoke an immune response. Instead, in an attempt to eliminate the foreign substance, steady streams of macrophages are recruited to the site. There they become activated, transform into epithelioid macrophages, and organize into granulomas. Microscopically, the granulomas are usually seen enveloping the foreign particles. In some cases, foreign material also may be identified within the cytoplasm of the giant cells, representing an effort by the giant cells to phagocytose and eliminate the material. Whereas some foreign substances, such as glass, suture material, hair fibers, and silica, may be easily visible under the microscope, other substances may require the use of polarized light to be visualized. If there is no identifiable foreign material, other causes of the granulomatous inflammation must be considered, as discussed later.

There is an extensive list of substances, including common dental materials, that may induce foreign body reactions in the oral cavity. Retained impression material, amalgam, pumice, gutta percha, zinc phosphate cement, various endodontic sealers, and suture material have all been associated with granulomatous inflammation [2,12,15–17]. Often these materials are iatrogenically implanted in the mucosa or bone during routine dental procedures or, in the case of suture or impression material, are inadvertently left for extended periods of time. Recently, there have been reports of foreign body reactions to hyaluronic acid, a material commonly used for lip augmentation [18].

Most foreign body reactions present with nonspecific clinical findings, usually in the form of discrete, nondescript masses or swellings [2]. Ulcerations or a diffuse, generalized mucosal swelling also have been identified in occasional patients, but these are uncommon presentations. In most cases, the oral lesions and granulomatous inflammation resolve following removal of the foreign substance. Nonetheless, a subset of patients may demonstrate persistent lesions warranting additional clinical and laboratory testing, specifically to rule out sarcoidosis [19]. Patients with sarcoidosis may have easily identifiable foreign material within mucocutaneous granulomatous lesions [19], but these granulomas typically persist despite removal of the foreign material. Thus, it is apparent that in some patients a diagnosis of a foreign body reaction should not preclude a clinician from evaluating the patient for more systemic disease, especially when lesions are persistent.

Immune-mediated granulomatous inflammation

Immune-mediated granulomatous inflammation represents a distinct form of delayed-type (cell-mediated) hypersensitivity [1]. Immune granulomas typically develop in response to infection by various mycobacterial and

fungal organisms [1–8]. Upon initial exposure to a nondegradable antigen derived from an organism (usually a protein), there is an accumulation of predominantly CD4-positive T-lymphocytes around blood vessels in the area where the antigens lie. Over time, the T cells differentiate, become activated T-helper (Th) cells, and begin secreting various cytokines that recruit macrophages to the site of the foreign antigen. If the antigens persist and remain nondegradable, the recruited macrophages eventually transform into epithelioid cells, organize, and form granulomas [1].

In general, the immune response to infectious and environmental agents is characterized by either a Th1 or Th2 cellular response [1,20,21]. Th1 and Th2 immune responses are differentiated by the specific expression and secretion of various cytokines by activated Th cells. Whereas Th2 cells express a variety of cytokines that are typically involved in antibody-mediated and allergic responses, Th1 cells produce cytokines, including interleukin (IL) 2, interferon-γ, IL-12, and IL-18, that are important in promoting cellular immunity [1,20,21]. Thus, immune granuloma formation is essentially a Th1 cellular response. For a more detailed discussion of Th1 and Th2 immune responses, the reader is directed to excellent reviews by Delves and Roitt [20,21].

Tuberculosis (TB) is the prototypical example of immune-mediated granulomatous disease. TB is caused by infection with *Mycobacterium tuberculosis* [4], but other mycobacterial infections, including those caused by *M leprae* (leprosy), *M bovis*, and *M avium intracellulare*, also can induce granulomatous inflammation [4,5]. A variety of fungal organisms, including *Histoplasma capsulatum, Cryptococcus neoformans,* and *Paracoccidioides brasiliensis*, can also induce granulomatous inflammation [1,2,6,7]. Tertiary syphilis, which is caused by *Treponema pallidum* [1], and cat-scratch disease, which is caused by *Bartonella henselae* [8], also are examples of granulomatous disease. Because the scope of this article is limited, the interested reader is directed to a number of articles outlining the diseases associated with these various organisms [2–8].

Tuberculosis

TB remains the most common cause of infection-related death in the world [4,5]. In North America, however, the annual incidence of TB, which had increased during the 1980s and early 1990s, seems to be declining again [4]. Nonetheless, TB remains an important cause of life-threatening disease, especially in individuals infected with HIV. The mode of transmission is usually airborne, from infected persons coughing or sneezing infectious droplets containing the bacillus [4]. In most cases, those who live in crowded, poorly ventilated areas are at greatest risk for inhaling the droplets and contracting disease. Unprotected individuals, including health care practitioners, who come in close contact with an infected patient, also are at

risk. The relative virulence of the organism and the number of bacilli in the inoculum are the main determinants in the successful transmission of disease. The level of host immunosuppression dictates who will ultimately contract the disease [5].

Genetic factors, including various HLA subtypes, also seem to influence disease susceptibility [22]. Recently, the *NRAMP1* gene has also been implicated in the susceptibility to and acquisition of TB and other infections, including Leishmania and leprosy [23,24]. The gene, which maps to chromosome 2q35, encodes a membrane protein that is expressed exclusively in the lysosomes of monocytes, macrophages, and neutrophils [23]. After phagocytosis of the organism, the protein is targeted to the membrane of the microbe-containing phagosome. There it plays a role in modifying the intraphagosomal milieu, thereby affecting microbial replication [23]. Mutations in the protein decrease the ability of the host phagocytic cells to limit the microbial replicative potential [23,24]. Thus, the organism is allowed to persist and propagate for an extended period of time.

Clinical findings

The lungs typically represent the site of primary infection [1,4]. Thus, pulmonary findings, including dyspnea, emphysema, and a productive cough, are often the initial manifestations of the disease. The bacilli usually come to rest in the middle or lower portions of the lung [1]. There, they evoke an immune response in the form of granulomatous inflammation. Often, Langerhans'; giant cells and a central area of caseous necrosis are seen within the granulomas. Although characteristic of TB, neither of these two microscopic findings is pathognomonic for the disease, and they may be seen in other granulomatous diseases [1,3,4]. Special histochemical stains are typically needed to detect the organism. A Zeihl-Neelsen acid-fast stain highlights mycobacterial bacilli, including *M tuberculosis*, magenta [1]. In some cases, however, the organisms may remain elusive. Thus additional clinical tests may be required to diagnose TB.

Following resolution of the primary infection, the organisms may lie dormant for an indefinite period of time, only to become reactivated years later. Although secondary TB also may be restricted to the pulmonary tissues, the severity of the disease varies depending on the extent of the renewed mycobacterial proliferation. Often patients with secondary TB present with various constitutional signs and symptoms before the onset of a cough or shortness of breath. If the organism spreads diffusely throughout the lung, tuberculous pneumonia may ensue.

In rare cases, primary TB may involve organ systems other than the lungs [1,4,5,25]. Dissemination of the organism through the vasculature may potentially seed any tissue or organ, including the oral cavity. Asymptomatic cervical or supraclavicular lymphadenopathy represents the most common extrapulmonary manifestation of TB and may be identified in up

to 10% of cases. Less than 1% of patients exhibit primary TB of the head and neck [4,25]. Scrofula is a limited form of primary TB characterized by tuberculous lymphadenitis of the cervical nodes. Scrofula is acquired by drinking infected milk. Although exceedingly rare in North America, cases of scrofula are still encountered in poorly developed countries around the world [5].

Although oral TB lesions may be identified as a manifestation of extrapulmonary TB, primary oral TB is extremely unusual [2,4,25]. Nonetheless, such patients may be encountered in clinical practice. Any oral site may be involved, but most patients present with gingival or vestibular involvement. Most cases of oral TB are caused by direct mucosal contact with infected sputum [2,4]. It is thought that sites of recent mucosal trauma allow the organism to invade the submucosal tissues directly. Most oral lesions take the form of a persistent ulceration (Fig. 2) or, less commonly, a discrete mass or swelling [25]. The clinical features of these lesions are nonspecific, however, and may be associated with a variety of disease processes, including neoplastic and traumatically induced lesions [2–5].

Intraosseous TB is extremely rare [25], but extraction sockets may provide a route for the organism to extend directly into the surrounding bone [2,4,25]. In some cases, periapical radiographs may demonstrate alveolar bone loss, thus mimicking periodontal bone loss. Some patients may present with multiple apical radiolucencies, thereby mimicking endodontic pathology. In other cases, more diffuse, poorly defined radiolucent or mixed radiolucent-radiopaque lesions may be seen within one or both jawbones. Salivary gland involvement, although unusual, typically presents as unilateral parotid enlargement with or without pain or an associated facial palsy [25].

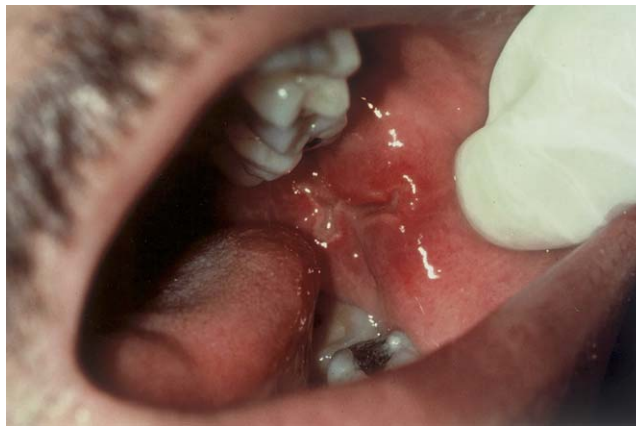

Fig. 2. Nonhealing ulceration of the buccal mucosa in a patient with acquired immunodeficiency syndrome. A biopsy and acid-fast stain revealed mycobacterial bacilli that were later confirmed as *M tuberculosis*.

Diagnostic tests

A biopsy exhibiting granulomatous inflammation and microscopic evidence of mycobacterial organisms is often suggestive of TB [1]. Because *M avium intracellulare* may also induce clinical signs and symptoms resembling those of TB, additional laboratory tests are required to diagnose TB accurately [5]. Sputum cultures and amplification of mycobacterial DNA through polymerase chain reaction are typically used to identify the TB bacillus. In patients with secondary TB, a chest radiograph typically demonstrates cavitational pulmonary lesions, with or without pleural effusion or hilar/paratracheal lymphadenopathy [1]. The tuberculin skin test also is used to identify individuals who have been previously exposed to TB, but individuals who have been previously immunized with the bacille Calmette-Guérin vaccine may exhibit a positive tuberculin test [4].

Treatment and prognosis

A variety of antimicrobial medications have been used to treat TB. The most commonly used medications include isoniazid, rifampin, and pyrazinamide [4,25]. A typical therapy consists of an 8- to 10-week course of the three medications combined, followed by an additional 16 to 18 weeks of isoniazid and rifampin [4,5]. A variety of multidrug-resistant strains of the bacillus have been identified in some parts of the world [5]. Patients infected with resistant strains often require longer treatment times and may need additional medications to combat the infection effectively. Despite a multipronged chemotherapeutic approach, an estimated 5% of patients remain infected [4]. A patient is considered cured if three consecutive sputum cultures are negative for the organism. For a more comprehensive review of TB the reader is directed to an excellent review by Rinaggio [4].

Sarcoidosis

Sarcoidosis is a relatively common, multisystem disease of unknown etiology [10,26]. A number of studies suggest that both host and environmental factors are important in the development of the disease [10,26–30]. Although unique environmental factors or infectious agents have yet to be identified, a number of studies have identified spatial, seasonal, and occupational clustering of sarcoidosis cases [27,28]. Moreover, there is ample data to suggest that sarcoidosis is a Th1 disorder, thus supporting a role for an external agent in the development of the disease [26,32]. In addition, oligoclonal expansion of T cells expressing specific T-cell receptors has also been identified through the sampling of affected tissues [32]. This finding suggests that sarcoidosis is an antigen-driven disease, thus further supporting a role for an external agent in its pathogenesis. Although there is continued interest in Mycobacteria and Proprionibacteria as possible

candidates in the pathogenesis of sarcoidosis [27,28], neither organism has been consistently associated with the disease.

Based on a number of studies, sarcoidosis also seems to be a genetically heterogeneous disease [29,30,33–35]. Recent large, multicenter studies have demonstrated that an individual has a significantly elevated risk for developing sarcoidosis if a first-or second-degree family member has the disease [29,30]. A number of candidate genes have been identified that may influence disease susceptibility, most of which are clustered within a region on chromosome 6 that contains the class II major histocompatibility (MHC) alleles [33]. Moreover, there is evidence that polymorphisms in various non–MHC class II genes, including the genes that encode for tumor necrosis factor-α (TNF-α) and angiotensin-converting enzyme (ACE), may influence disease progression and severity [34,35]. Additional studies are needed to define further the association between specific gene expression and disease susceptibility and severity.

Clinical findings

The prevalence and severity of the disease differ among various races, ethnicities, and geographic location. In the United States, blacks are 10 times more likely to develop sarcoidosis than whites, and females are more commonly affected than males [26,27,30]. Sarcoidosis may present at any age, but most cases are identified in persons between the ages of 20 and 40 years. When the disease develops in persons over the age of 40 years, it is often persistent and progressive [10].

The signs and symptoms associated with the disease often wax and wane over time, with or without treatment [10,26]. An estimated 30% to 60% of patients with sarcoidosis may be entirely asymptomatic [10]. In a number of cases, these patients are appropriately diagnosed only following a chest radiograph obtained for other reasons. Pulmonary involvement is characteristic of the disease, with most symptomatic patients presenting with a persistent dry cough, dyspnea, or chest pain [1,10,26]. Lymph node involvement is also typical, with most patients exhibiting hilar or mediastinal nodal involvement. Tonsillar lymphoid tissue is affected in 25% to 33% of patients [1]. A variety of nonspecific clinical findings may also be identified, including constitutional symptoms such as fever, malaise, arthralgia, and weight loss; ocular inflammation and visual changes; peripheral lymphadenopathy; and hepatosplenomegaly [26]. In rare cases, neurologic deficits, seizures, recurrent syncope, or life-threatening arrhythmias may be the presenting signs of the disease [10]. Cutaneous manifestations of sarcoidosis are identified in 33% to 50% of patients (Fig. 3) [1,26]. In most cases, the skin findings are nonspecific and may present as erythema nodosum, erythematous scaling plaques, papules, or nodules. In rare cases, especially in black patients, diffuse erythematous papular eruption (lupus pernio) is often associated with a negative prognosis [26].

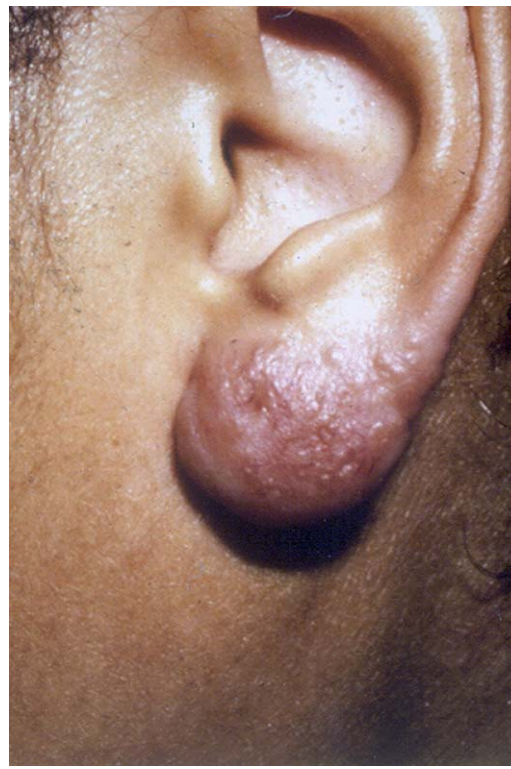

Fig. 3. Sarcoid nodule of the earlobe. (Courtesy of Rose Elenitsas, MD, Philadelphia, PA.)

Oral involvement in sarcoidosis is rare [2,36–38]. Although in some patients the oral lesions may be the initial manifestations of the disease, most patients typically have other signs and symptoms of sarcoidosis [36]. Oral sarcoid lesions are nonspecific. Any mucosal site may be affected, and occasionally multiple oral sites are involved. Most lesions present as painless, submucosal nodular or multinodular growths or swellings [36]. Sarcoidosis of the gingiva typically presents as a diffuse enlargement [2]. Involvement of the jawbones has also been reported [36,37], with the most characteristic presentation being that of an ill-defined radiolucency involving a tooth-bearing region (Fig. 4). In these cases, the patients may present with progressive bone loss and increasing mobility of the adjacent teeth, thus mimicking periodontal disease or Langerhans'; cell disease (eosinophilic granuloma) [2,37].

Sarcoidosis may also involve minor or major salivary gland tissue [36,38]. In some patients a labial gland biopsy may be useful in the diagnosis of generalized sarcoidosis, even if there is no clinically evident disease intraorally [38]. Although unilateral or bilateral parotid gland enlargement may be identified in some patients, other causes of the enlargement should

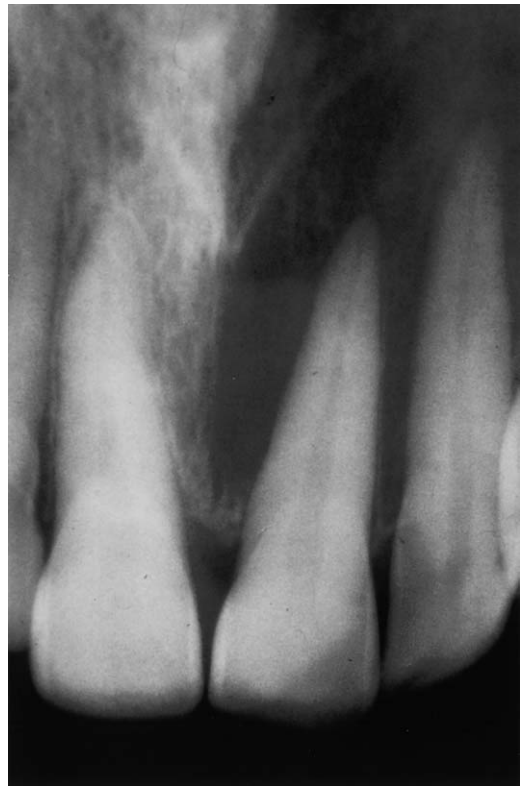

Fig. 4. Ill-defined radiolucency of the anterior maxilla in a patient with sarcoidosis. A biopsy revealed numerous granulomas.

also be considered in the differential diagnosis [2], which includes salivary gland neoplasms, Sjögren's disease, benign lymphoepithelial lesions, sialadenosis, and cat-scratch disease. In rare instances, the submandibular or sublingual glands may also be involved [2,3,8]. An unusual clinical variant of sarcoidosis known as Heerfordt's disease (uveoparotid fever) is characterized by parotid gland enlargement, fever, uveitis, and facial palsy [2].

Diagnostic tests

Because there are no specific tests that can accurately be used to diagnose the disease, sarcoidosis is often a diagnosis of exclusion [1–3,36]. Although a microscopic finding of granulomatous inflammation is necessary for sarcoidosis to be considered as a clinical diagnosis, granulomas may also be associated with a variety of other conditions. Chest radiographs are typically used to identify pulmonary involvement and bilateral hilar lymphadenopathy; however, neither finding is specific for sarcoidosis

[10,26]. Pulmonary- and kidney-function tests also may be warranted in some patients. The use of CT or MRI scans as routine diagnostic tools remains controversial, because neither technique has demonstrated significant benefit over traditional chest radiographs [26]. Nonetheless, MRI scans may be useful for identifying neurologic or soft tissue involvement. Thrombocytopenia, leukopenia, eosinophilia, and elevation of various serum markers, including calcium, alkaline phosphatase, and erythrocyte sedimentation rate (ESR), have been identified in association with sarcoidosis [10,26,36]. None of these laboratory findings has proven to be specific for the disease, however.

Although elevated serum ACE levels were once thought to correlate well with disease activity, more recent studies have not demonstrated consistent associations between sarcoidosis and ACE levels [10,26]. In chronic patients only, serum levels of IL-2 and IL-8 do seem to correlate with disease activity and progression [10,26,39,40]. Elevated levels of macrophage inflammatory protein 1 and TNF-α, obtained from bronchoalveolar lavage (BAL), may also be associated with chronic and persistent disease [40]. A higher proportion of CD4-positive T cells in BAL also has been identified in some patients, especially those with the acute form of the disease (Löfgren's syndrome—bilateral hilar lymphadenopathy, erythema nodosum, and uveitis) [10,26,39].

Treatment and prognosis

The decision to treat a patient with sarcoidosis should be based upon the extent of the disease and the organs and tissues involved, the stability of the disease over a period of continued observation, and the likelihood of therapeutic benefit [10,26,31]. Patients with only mild symptoms or stable disease often do not require any treatment. These patients should be followed on a regular basis, however. A relatively brief course of low-dose systemic corticosteroids, ranging from weeks to months, often is prescribed for patients with more severe or progressive disease [10]. Although an estimated 60% of patients exhibit resolution of their disease within 2 to 5 years after the initial presentation, a subset of patients demonstrates persistent symptoms and requires long-term therapy (>1 year) with immunosuppressive medications [26]. Chronic disease has been associated with a relatively poor prognosis. Long-term immunosuppressive therapy is indicated for patients who exhibit central nervous system, cardiac, ocular, or marked hepatic involvement, lupus pernio, or severe hypercalcemia [10,26]. Despite therapy, these patients typically have a worse overall prognosis.

Although systemic corticosteroids are often the medication of choice, other immunosuppressive drugs have been used with varying degrees of success [31,41]. Antimalarial medications, such as chloroquine, are often more effective than steroids in treating mucocutaneous sarcoidosis [26,31]. Recently, medications aimed at neutralizing TNF-α, including thalidomide,

infliximab, and etanercept, have also been used to treat sarcoidosis [31,41]. There are currently little data about their effectiveness as first-line therapy; thus routine usage of these medications remains controversial. Nonetheless, thalidomide has been used successfully in a number of patients with marked mucocutaneous disease [41].

Crohn's disease

Crohn's disease is a chronic granulomatous disorder that may involve any portion of the gastrointestinal tract, including the oral cavity [11]. Environmental and genetic factors seem to play a role in the pathogenesis of Crohn's disease [11,42–45], but the exact etiology remains unknown. Like sarcoidosis, Crohn's disease is a Th1 disorder [42], thus supporting a role for an external agent in the development of the disease. Although there is continued interest in Mycobacteria and other infectious agents as possible candidates in the pathogenesis of Crohn's disease, no organism has been consistently associated with the disease.

A number of studies have demonstrated familial clustering of Crohn's disease [43–45]. Moreover, if one twin has the disease, the second has a measurably increased risk for developing the disease. Recently, mutations in the *CARD15*/*NOD2* gene on chromosome 16 also have been identified in up to 25% of patients with Crohn's disease, with a predilection for patients with ileal disease [43–45]. Mutations in the gene seem to alter the innate immune response to the normal flora of bacteria lining the gastrointestinal tract. *CARD15* encodes a protein that acts as an intracellular receptor for bacterial components [43]. How defects in this protein actually induce the clinical manifestations associated with the disease remains unclear. Nonetheless, individuals with a mutation in the gene seem to have more penetrating mucosal lesions and to develop measurable levels of antibodies to various organisms, including *Saccharomyces cerevisiae* [43–45]. A variety of HLA subtypes have also been weakly associated with disease susceptibility and risk [45].

Clinical findings

Crohn's disease can develop at any age, but most cases are identified in the second and third decades of life [11,46]. There is no sex predilection, but males tend to be affected at a younger age than females. Overall, about 10 in 100,000 individuals are affected in North America [46]. There are distinct racial and ethnic distributions of the disease. Crohn's disease is much more prevalent in whites than in other races, and individuals of Jewish ancestry have a significantly increased risk of developing the disease than other groups [11,46].

The clinical manifestations of the disease are highly variable. The classical presentation is that of a patient complaining of various

constitutional signs and symptoms, abdominal pain, and repeated bouts of diarrhea [2,46]. Occasionally, the abdominal symptoms may be confused with acute appendicitis. Over time, the gastrointestinal symptoms often worsen because of bowel obstruction. Some patients may also develop a palpable abdominal mass, a perianal abscess, or fistula. Arthralgia and nonspecific skin findings, including erythema nodosum and pyoderma gangrenosum, may also be identified [46]. A number of studies have demonstrated that cutaneous findings may be quite common in patients with Crohn's disease [11,46]. Growth retardation may occur in 15% to 20% of pediatric patients [46].

Oral lesions are identified in up to 60% of patients and may be the initial manifestation of disease in 5% to 10% of affected individuals [11,46]. Some studies suggest that the earlier the onset of the disease, the greater the incidence of the oral manifestations [11]. A number of oral findings are associated with Crohn's disease, but linear ulcerations embedded within the base of linear hyperplastic tissue folds are the only pathognomonic findings associated with the disease (Fig. 5) [2,11,46]. These ulcerations are found within the mucobuccal folds and may be multifocal. Multiple papular or polypoid lesions involving the buccal mucosa and vestibules also are characteristic but are not pathognomonic for oral Crohn's disease [46]. Because these lesions are often closely aligned, they may give the mucosa a cobblestoned or corrugated appearance. A number of patients also present with manifestations that are more typical of OFG, as discussed later [11,46–48]. Over time, an estimated 20% to 40% of patients with OFG develop the classic signs and symptoms of Crohn's disease [2,11,46]. Thus, it has been suggested that oral Crohn's disease may represent an oligosymptomatic form of OFG [48]. OFG-like features include a persistent, firm, painless

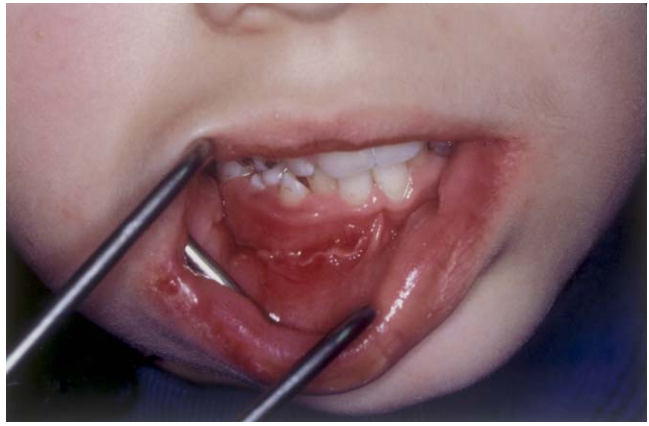

Fig. 5. Linear ulceration in the mucobuccal fold in a patient with oral Crohn's disease. (Courtesy of Paul Freedman, DDS, Flushing, NY.)

swelling of the lips, buccal mucosa, or face [46–48]. Vertical fissuring often develops within the swollen lips. Gingival lesions, usually in the form of generalized edema, erythema, and hyperplasia, are common. In most cases, the attached gingiva is involved, usually in the anterior facial regions [11,46]. In rare cases, rapid periodontal bone loss has also been reported [49]. Angular cheilitis may also develop in some patients. Pyostomatitis vegetans is another rare mucosal disorder that develops in association with inflammatory bowel disease, including Crohn's disease [46]. Some patients may also report a metallic taste, burning mouth, xerostomia, or recurrent aphthous stomatitis [46,48]. The clinical manifestations of Crohn's disease may wax and wane over extended periods of time [11,46].

Diagnostic tests

The diagnosis of Crohn's disease is often made through confirmatory biopsies of specific gastrointestinal lesions, abdominal radiographs with barium contrast, and laboratory findings [2,11,46]. Only about 50% of biopsies obtained from Crohn's disease patients reveal noncaseating, granulomatous inflammation, however [1,2,46]. In the remaining cases, a nonspecific, perivascular lymphocytic infiltrate is typically seen. A gut biopsy characteristically shows transmural inflammation [1]. This finding differentiates Crohn's disease from ulcerative colitis (UC). Moreover, a colonoscopy often reveals skip lesions, which can also be used to differentiate Crohn's disease from UC. In ulcerative colitis, the inflammatory changes are continuous and can extend over a significant length of the intestine [1]. In Crohn's disease, the inflammatory changes tend to involve different regions of the gastrointestinal tract, with the intervening areas of normal, unaffected tissue.

Laboratory tests often reveal a variety of elevated serum markers, including ESR, C-reactive protein, and α-1-antitrypsin [1,2,11,46], but these findings are nonspecific and may be associated with any number of inflammatory conditions. Because of diminished intestinal absorption, some patients may also exhibit signs of anemia, as evidenced by decreased iron or vitamin B_{12} levels [46]. About 40% to 60% of patients with Crohn's disease also exhibit elevated levels of anti-*S cerevisiae* antibody [45,50]. This serologic finding seems to have a relatively high specificity for the disease. Anti-*S cerevisiae* antibodies are more commonly identified in patients who have *CARD15* mutations [50].

Treatment and prognosis

Treatment depends on the extent of the disease [11,46]. If the disease is restricted to the oral cavity, high-potency topical or intralesional steroids may be sufficient [46]. In general, however, systemic corticosteroids, sulfasalazine, and other steroid-sparing immunosuppressive medications

such as methotrexate and azathioprine are often required to treat mild to moderate Crohn's disease [51,52]. Budesonide has been recently approved in the United States for the treatment of mild to moderate Crohn's disease [51,52]. This orally administered corticosteroid is designed so that it is released selectively in the small intestine. Budesonide has far fewer side effects than other corticosteroids because it undergoes little systemic absorption [52]. In severe cases of Crohn's disease, infliximab, a monoclonal antibody directed against TNF-α, has proven effective [42,51]. This medication is typically used in association with more traditional immunosuppressive agents. Antibiotics, including metronidazole or ciprofloxacin, may be necessary in patients with abscesses [46]. For those who do not respond to therapy or who have obstructive bowel disease, surgery is often necessary [51]. The most severely involved portions of the bowel are often removed. As a result, nutritional supplementation, electrolyte replacement, and increased iron and vitamin B_{12} intake may be required to counteract the imbalances created by the disease [46]. Crohn's disease is associated with an increased risk for cancer of the small intestine, so long-term follow-up is highly recommended for patients with the disease [1].

Orofacial granulomatosis

OFG is a nonspecific, descriptive term encompassing a variety of conditions that exhibit similar clinical and microscopic features [9,48]. If all possible causes have been ruled out, OFG is used as a clinical diagnosis of exclusion [9,48,53]. OFG may develop at any age, and there is no sex predilection. Although the incidence of OFG seems to have increased in recent years, the exact cause of the disease remains unknown. Infectious agents and genetic factors have been proposed as possible causes [9,48], but neither has proven to be consistently associated with the disease. An estimated 12% to 60% of patients with OFG are atopic, suggesting that OFG may represent an unusual form of allergic or hypersensitivity reaction [48].

Clinical findings

OFG may be associated with a variety of clinical manifestations. The most consistent finding is a persistent, painless swelling the orofacial tissues [9,48,53]. The lips are the most frequent sites of involvement (see Fig. 4). One or both lips may be involved, and the swelling may be unilateral or bilateral and symmetric [9,48]. Often a vertical fissure develops within the involved lip. Over the course of the disease most patients experience facial swelling that may also involve the eyelid [48]. Intraorally, the clinical findings are nonspecific and may include generalized edema and erythema (Fig. 6), superficial ulcerations, and papules. Dysgeusia has also been

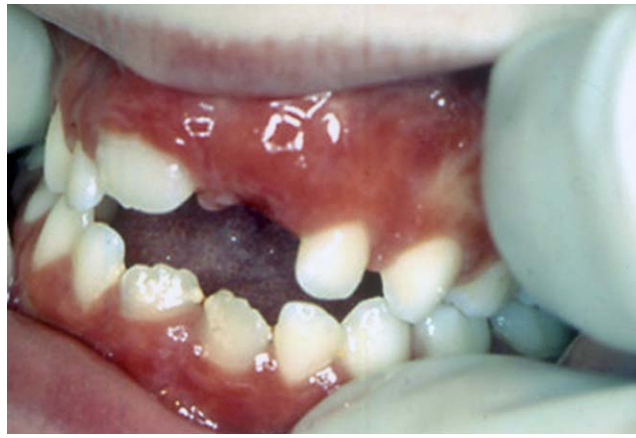

Fig. 6. Generalized erythema and edema of the maxillary and mandibular gingiva in a patient with orofacial granulomatosis. (Courtesy of Thomas Sollecito, DMD, Philadelphia, PA.)

reported in a number of cases [48,53]. In rare cases, autonomic signs and symptoms may be identified including hypo- or hypersalivation and abnormal lacrimation [48].

If the swelling is restricted to the lips, the disease is characterized as cheilitis granulomatosa of Miescher [9,53]. Melkersson-Rosenthal syndrome represents a more generalized presentation of OFG [9,48,53]. Classic Melkersson-Rosenthal syndrome is characterized by orofacial swelling, facial palsy, and, less commonly, fissured tongue (lingua plicata) [9]. In rare cases, small, superficial, lymphangiomalike amber vesicles develop on the labial or buccal mucosa [2]. The facial palsy tends to be unilateral and may be indistinguishable from Bell's palsy. It often develops over a period of time, usually after other OFG manifestations appear. In rare cases, areas beyond the orofacial region may be involved, including the hands, feet, chest, and buttocks [48].

Diagnostic tests

OFG is characterized by noncaseating granulomas; thus foreign bodies and infectious causes must be initially ruled out. Crohn's disease and, to a lesser degree, sarcoidosis may present with clinical manifestations indistinguishable from OFG [3,36,47,48]. Therefore, a number of laboratory and radiographic studies are often necessary to eliminate sarcoidosis and Crohn's disease from the differential diagnosis. Finally, patch testing or an elimination diet may be needed to rule out an allergic cause [2,48,53]. Although allergic reactions may induce clinical manifestations resembling OFG, in most cases they do not exhibit histologic evidence of granuloma formation.

Treatment and prognosis

Treatment of OFG is often challenging. Although systemic and intralesional corticosteroids are typically the treatment of choice, most patients eventually develop recurrences [9,48,53]. Steroid-sparing medications may be used, especially in patients who present with refractory or chronic disease.

Summary

A variety of conditions may be associated with granuloma formation in the oral cavity. The most common differential diagnosis includes foreign body reactions, infection, Crohn's disease, sarcoidosis, and OFG. Because of the relatively nonspecific clinical findings associated with these granulomatous diseases, a microscopic diagnosis of granulomatous inflammation often presents a diagnostic dilemma for the clinician. Thus, often, an extensive clinical, microscopic, and laboratory evaluation may be required to identify the source of the granulomatous inflammation. If the cause is correctly identified, and the condition is appropriately treated, a patient who presents with granulomatous disease may have a good to excellent prognosis.

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