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An Update on Granulomatous diseases of the oral tissues

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Keywords

Type IV hypersensitivity; tuberculosis; Crohn disease; sarcoidosis; orofacial granulomatosis; biologic therapy

Introduction

Granulomatous inflammation is a unique form of chronic inflammation.[1] Granulomas are distinct structures composed of epithelioid-shaped macrophages, multinucleated giant cells, lymphocytes and fibroblasts. However, the clinical findings associated with granulomatous inflammation are usually variable and often indistinct. Granulomatous inflammation has a multifactorial etiology and may arise as a reaction to environmental or genetic factors, infectious organisms, or maybe idiopathic, for which there is no known trigger.[2] A typical differential diagnosis includes: foreign body reactions, infection, Crohn disease (CD), sarcoidosis and orofacial granulomatosis (OFG).[2] Less commonly, other systemic diseases may also be associated with granuloma formation.

Foreign substances are the most common source of localized granulomatous inflammation in the oral cavity.[3] There are numerous endogenous and exogenous substances which may trigger foreign body reactions. Relatively common endogenous sources include hair fibers, keratin aggregates and lipids derived from cholesterol deposits and fat emboli.[2] Exogenous materials may include an array of commonly-used dental materials, retained sutures, and cosmetic filler substances-such as hyaluronic acid, which are used for labial and peri-labial augmentation.[4-8]

Foreign body reactions are associated with non-specific clinical findings. These may include non-descript masses, erythema, localized or generalized edema, pain and/or ulceration.[2] A tissue biopsy is typically warranted for diagnosis and, in many cases, the foreign material is readily evident on microscopic examination. In general, the clinical manifestations will subside following removal of the foreign substance in conjunction with topical and/or intralesional corticosteroid treatment.

The persistence of signs and symptoms may warrant additional clinical and laboratory testing to identify other possible sources of the inflammation. This is particularly true if the

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patient exhibits manifestations that are diffuse and cannot be readily explained by the presence of localized foreign material. The absence of identifiable foreign material does not preclude a clinical diagnosis of foreign-body reaction; a detailed history and evaluation may help increase the index of suspicion. However, unless the foreign substance is identified in microscopic sections, histologic evidence of granulomatous inflammation often presents a diagnostic dilemma for the clinician. With new insights into the pathogenesis of specific granulomatous diseases, and with the advent of high-throughput genetic screening and availability of next-generation biologic therapies, clinicians now have several options at their disposal to help ensure accurate diagnosis and effective treatment. The discussion that ensues highlights some of the current knowledge about the more common granulomatous systemic diseases that may be encountered in clinical practice.

TUBERCULOSIS

Immune-mediated granulomatous inflammation represents a unique form of Type IV delayed-type hypersensitivity reaction.[1] While tuberculosis (TB) represents the prototypical example of infection-related granulomatous disease, any one of several different mycobacterial and fungal infections, including leprosy and histoplasmosis, are associated with a similar immune response (Table I). Since the scope of this review is limited, only TB is described here.

TB is one of the most common causes of infection-related death in the world.[9,10] Although epidemiologic studies suggest the number of new TB cases may be decreasing, the emergence of multi-drug resistant and even total-drug resistant TB is threatening disease control efforts.[9] *Mycobacterium tuberculosis* is primarily a pathogen of the respiratory tract and mode of transmission is usually airborne. Organismal virulence, the number of bacilli in the inoculum, host genetic factors and host immune status are the main determinants in the successful transmission and contraction of disease.[9-13]

Upon initial infection, macrophages phagocytose but do not kill the organism. Chemokines secreted by the macrophages recruit other cells and help promote the initial inflammatory response and tissue remodeling. Subsequent activation of T cells leads to granulomatous inflammation, thereby protecting host tissues and limiting organismal growth and dissemination.[14] However, while the organism may no longer replicate, it does survive encased within a granuloma and may become re-activated following granuloma disruption. Thus, individuals who become T-cell depleted or who cannot efficiently activate T cells are particularly at risk, not only for primary TB, but also re-activation of latent infection leading to disseminated disease.[1,14]

There are rare inherited immunodeficiencies which may increase infection risk.[15] More commonly, uncontrolled HIV infection is a significant risk for TB.[16] The emerging at-risk population that the dentist needs to also be familiar, includes patients who are taking a medications known as immune-suppressing biologics. This powerful class of drugs is being prescribed with increasing frequency and for a variety of cancers and common immune-mediated diseases, including rheumatoid arthritis, psoriasis and Crohn disease.[17-19] These individuals are at risk, not only for disseminated or extrapulmonary TB, but for other invasive mycobacterial and fungal infections.

Clinical findings

The manifestations of TB are variable and most commonly restricted to pulmonary complications.[2,9] While oral manifestations may be identified in extrapulmonary or disseminated TB, primary oral TB is uncommon.[20] Direct mucosal contact with infected sputum may be the most likely cause of oral TB. A non-healing ulceration is the most

common manifestation; localized masses or swellings may also be evident. In rare instances, infection may involve the alveolar bone and mimic periodontal disease.[20] Unilateral salivary gland enlargement with or without pain and facial palsy have also been reported. It is important to note that oral and perioral manifestations of TB are not specific and similar findings may be associated with a variety of other etiologies, including neoplasia and trauma.[2]

Diagnostic tests

A biopsy exhibiting granulomatous inflammation and microscopic evidence of mycobacterial organisms may suggest TB.[14] Additional laboratory investigations are typically required to confirm the diagnosis. This may include chest radiographs, sputum cultures, or PCR amplification of mycobacterial DNA.[10] The tuberculin skin test is used to identify individuals who have been previously exposed to TB. A tuberculin test is typically performed prior to initiating therapy with a biologic drug.[18] If a tuberculin test is positive, treatment of TB should be initiated prior to treatment with any biologic drug. Even if a tuberculin test is negative, all patients undergoing biologic therapy need to be closely monitored for the development of TB and other invasive infections.

Advances in the study of TB have led to a new class of commercially available diagnostic tests termed interferon-γ (IFN-γ) release assays (IGRAs).[21] The most current iterations of these IGRAs are QuantiFERON®-TB Gold In-Tube (QFT; Cellistis, Ltd. Carnegie, Australia) and T-Spot TB (Oxford Immunotec, Marlborough, MA).[21] QFT is an in vitro, enzyme-linked immunosorbent assay (ELISA) whereas T-Spot TB is an enzyme linked immunospot assay; both have received regulatory approval in the United States for diagnosis of TB. IGRAs can reliably detect active disease and latent TB infection, but they cannot differentiate between the two.[22-24] Therefore, a positive test result suggests that there is high risk for current or future active tuberculosis. Conversely, a negative result suggests that TB infection is unlikely.

The basis of IGRAs is that infected individuals have circulating effector T lymphocytes within their blood that recognize various *M. tuberculosis* antigens.[21] Recognition of these antigens leads to release of IFN-γ from these primed T cells which can then be quantified. Thus, for IGRAs to accurately measure IFN-γ activation, a fresh whole blood specimen that contains viable mononuclear cells is needed.

The QFT assay uses two synthetic partial peptides that simulate *M. tuberculosis* antigens ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein-10) thereby triggering IFN-γ release from the cells; ESAT-6 and CFP-10 are potent T-cell antigens.[21] The TB-Spot TB assay also uses these same antigens, except the mononuclear cells are incubated with synthetic proteins representing the entire amino acid sequences of ESAT-6 and CFP-10, respectively.[21] It is important to note that these antigens are very rarely expressed by nontuberculous mycobacteria. Thus, IGRAs are highly specific for TB.

Only a single patient visit is required for these assays whereas two visits are needed to perform and analyze a tuberculin skin test.[21-23] More importantly, the greatest advantage to using IGRAs rather than the tuberculin skin test is that they do not yield a positive result in patients who have been vaccinated against TB using the BCG vaccine (Bacillus Calmette-Guerin).[21] In some studies, IGRAs have been shown to be more reliable and more cost-effective than the skin test in identifying TB in certain population subsets, including health care workers.[24] Conversely, in third world countries, the cost of using IGRAs still exceeds that of the skin test.[22,23] Thus, widespread usage of IGRAs as a primary means of TB screening in third world countries remains a long term goal.

Treatment and prognosis

The most common medications used to treat new TB cases include isoniazid, rifampin, pyrazinamide and ethambutol.[9,10] A typical therapy consists of a two-month course of the four medications, followed by an additional four months of isoniazid and rifampin. In patients with previously treated TB, streptomycin is added to the initial regimen, and total therapy may last for at least eight months. Multi-drug resistant TB (MDR-TB) is emerging as a threat to human health and survival.[9] MDR-TB is defined by the resistance to the first line drugs isoniazid and rifampin. The second-line drugs are more expensive, less effective and are associated with significantly greater complications.[9] In MDR-TB, the actual drug regimens may vary depending on geographic location, but typically includes the addition of fluoroquinolone. Total duration of therapy is at least 18 months. A patient must have three consecutive negative sputum cultures in order to be considered cured of the disease. Despite extensive therapy, an estimated 5% of patients will remain infected.[1,9]

SARCOIDOSIS

Sarcoidosis is a multi-organ disease of unknown etiology that is typically associated with non-caseating granulomas.[25] In the US, African-Americans and women have significantly higher rates of sarcoidosis than Caucasians and males, respectively.[25,26] There is also ethnic variability with respect to age of disease onset. In most cases, the age of onset is typically between the ages of 20-39 years. However, women also have a second incidence peak with onset of disease occurring in the 7th decade of life.[21] The older the age at initial onset, the poorer the prognosis and greater the likelihood of persistent and progressive disease.[27]

Familial clustering, ethnic variations of disease prevalence and increased concordance in monozygotic twins suggest that sarcoidosis has a genetic basis of disease.[26,28] Several candidate genes have been identified and most of these are clustered within the major histocompatibility complex (MHC) on chromosome six. This region includes the human leukocyte antigens (HLA) class I and class II genes, and several other genes implicated in regulating immunity and inflammation. The expression of various HLA subtypes correlate with disease in specific subsets of patients. With the advent of genome-based analyses, additional genetic associations have also been identified. In particular, single-nucleotide polymorphisms (SNPs) in cytokine genes, including tumor necrosis factor-α (TNF-α), transforming growth factor-β_3 (TGF-β_3), interleukin-1A (IL-1A), interleukin-4 (IL-4), interferon-α (IFN-α), receptor genes including toll-like receptor-4 (TLR4) and chemokine receptor 2 (CCR2), and in other genes such as angiotensin converting enzyme (ACE) and vascular endothelial growth factor (VEGF), all appear to influence disease susceptibility in specific patient populations.[26,28] ACE is of clinical significance because serum ACE levels may be elevated in sarcoidosis[29], but ACE levels are not reliable either as a general diagnostic marker of disease or in predicting prognosis. Finally, genome-wide association studies (GWAS) have become the standard in candidate gene identification. A recent study in almost 500 patients and controls identified annexin A11 (ANXA11) as a novel disease susceptibility gene.[30] The Sarcoidosis Genetic Analysis is another GWAS aimed at identifying risk-conferring genes in African-Americans.[31] To date, several sarcoidosis susceptibility loci have been identified on chromosome five. Investigations for specific disease genes within these loci are ongoing.

Although a causal relationship between infectious or other environmental agents and sarcoidosis has yet to be established, a transmissible infectious agent has long been suspected in disease pathogenesis.[25,32,33] Mycobacterial organisms are the suspected culprits. In a recent meta-analysis examining 26 years of published data, of 847 sarcoidosis patients, 26% were positive for mycobacterial DNA and/or RNA.[34] In addition, some studies suggest a poor clinical prognosis if mycobacterial DNA can be identified from

sarcoidal lesions.[32] Conversely, other molecular-based investigations have not yielded similar associations between mycobacterial DNA and sarcoid. Identifying mycobacterial nuclei acid also raises the possibility that the initial diagnosis of sarcoidosis may have been incorrect.

A preponderance of data suggests that sarcoidosis is an antigen-driven disease.[25,32,35] It is for this reason that immune-based analyses have gained prominence in an attempt to identify a causative external agent. A specific mycobacterial protein, mycobacterial catalase-peroxidase (mKatG), was recently identified as a putative pathogenic antigen, and a target of the adaptive immune response in 50-80% of sarcoidosis patients.[36,37] This protein could be identified in sarcoidal granulomas. In addition, circulating mKatG-reactive T cells were shown to decrease in response to either systemic treatment or in patients who experienced disease remission relative to patients with active disease.[36] While mKatG may show promise in the potential identification of a causative organism, mKatG is not the only pathogenic antigen in sarcoidosis. Proprionibacterial organisms have also been implicated but specific antigens have not been consistently identified.[35] It is also likely that other unknown environmental factors may also influence disease pathogenesis.

Clinical findings

Sarcoidosis is a phenotypically heterogeneous disease.[25,38-41] Disease severity is influenced by racial and ethnic differences and geographic location. The disease manifestations will often wax and wane, with or without treatment. The vast majority of afflicted individuals will exhibit pulmonary involvement. If symptomatic, the most common complaints are persistent dry cough, dyspnea and/or chest pain. However, it is not unusual to encounter entirely asymptomatic patients even with objective evidence of disease in the form of characteristic findings, including bilateral hilar lymphadenopathy, observed on a chest radiograph.[25]

Cutaneous manifestations may be the initial signs of sarcoidosis in up to a third of all patients.[41] Most of the skin findings are non-specific and can vary from the relatively common (papular eruptions, erythematous scaling plaques, scar, erythema nodosum) to the relatively uncommon (hypopigmentation, ulcerations) to rare (alopecia). Lupus pernio is a cutaneous manifestation that is characterized by indurated, brownish-red plaques that typically affect the nose and cheeks, and progressively enlarge and become confluent.[41] This can cause significant disfigurement, and is often associated with systemic disease and a poor prognosis since it may be recalcitrant to treatment. Various ocular manifestations, life-threatening cardiac complications, neurologic manifestations, and/or visceral disease including involvement of the liver, kidneys and/or spleen have all been reported in subsets of patients.[40] Thus, it is not uncommon that sarcoidosis patients exhibit an array of non-specific clinical findings including: fever, malaise, arthralgia, and weight loss; ocular inflammation and visual changes; peripheral lymphadenopathy; and hepatosplenomegaly.[40,41] Oral lesions may also be evident in some patients and may represent the first clinical evidence of disease.[38,39] Oral sarcoidosis typically manifests as non-specific painless ulcerations and/or nodules, and any mucosal site may be affected. Sarcoidosis of the gingiva may present as a generalized enlargement. In rare cases, sarcoid affects bone and, in the orofacial region, may present as progressive alveolar bone loss, thereby mimicking aggressive periodontal disease.[38,42]

Salivary gland involvement may also be evident in sarcoidosis patients. The parotid gland is most commonly affected; submandibular and sublingual gland involvement are much less common. When the major glands are affected, the patients may present with either unilateral or bilateral enlargement. A clinical variant of sarcoidosis, known as Heerfordt disease (uveoparotid fever), is characterized by parotid gland enlargement, fever, uveitis and facial

palsy.[2] The minor salivary glands within the lips and oral cavity may also be affected.[38,43] A labial salivary gland biopsy may be useful in the diagnosis of generalized sarcoidosis, even if there is no clinical evidence of oral or perioral involvement.[44]

Diagnostic tests

A microscopic finding of granulomatous inflammation is necessary for sarcoidosis to even be considered as a clinical diagnosis.[25] A detailed history, including family history, thorough physical examination, chest radiographs and pulmonary function tests if deemed necessary, serum chemistries, ophthalmologic evaluation and complete blood cell counts are recommended in an initial screen for all patients with suspected or diagnosed sarcoidosis. However, it should be noted that no specific assays or analyses are diagnostic for this disease.[25] Thus, sarcoidosis is often a diagnosis of exclusion.

Treatment and prognosis

Patients with limited disease usually have a very good to excellent prognosis. Up to two-thirds of patients will exhibit spontaneous resolution of their disease within the first three years after the initial presentation.[25] Conversely, if left untreated, other patients will demonstrate persistent symptoms and chronic progressive disease that will require long-term immunosuppressive therapy. Patients with chronic sarcoidosis typically have a relatively poor prognosis. Overall, the decision to treat a patient with sarcoidosis should be made 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.[25,28,40,41]

Due to the complex nature of this disease, there are no standard therapies for sarcoidosis. Systemic corticosteroids remain the treatment of choice for systemic or generalized disease.[25,41] Steroid-sparing medications, including methotrexate, have also been employed, but with variable results. Hydroxychloroquine and chloroquine have shown some effectiveness in treatment of cutaneous disease, but toxicity of these medications can limit their use. Minocycline might be beneficial for limited skin disease. Although few studies have described treatments for oral sarcoidosis, the aforementioned medications have all been used with varying degrees of success.[39] Intralesional and/or topical steroids may also be sufficient for localized or limited mucocutaneous involvement. Recently, anti-TNF-α agents have been tested in clinical studies and specifically in patients with systemic disease. In particular, thalidomide, infliximab and adalimumab may be effective in the treatment of pulmonary and extrapulmonary sarcoidosis.[40,41,45,46] As noted earlier, use of these biologic agents significantly increases susceptibility to disseminated infectious diseases, including tuberculosis and deep fungal infections. Thus, the clinician should conduct a risk-benefit analysis prior to initiating therapy with a biologic drug.

CROHN DISEASE

Crohn disease (CD) is an inflammatory bowel disorder that mainly affects the gastrointestinal tract, including the oral cavity.[47,48] Extraintestinal manifestations and other immune disorders are also prevalent in CD patients. Like sarcoidosis, CD is a multifactorial disease with genetic and environmental factors, including diet, psychological stress and smoking, playing important roles in disease pathogenesis and/or exacerbation.[47,49-52] Although there is continued interest in mycobacteria and other infectious agents as possible candidates, no single organism has been consistently associated with the disease. Nonetheless, the surface of the gastrointestinal tract is colonized by a vast, biologically diverse microflora. Under normal circumstances, there is a symbiotic host-microbe relationship. In CD, this symbiotic relationship is impaired due to a weakened innate

immune response to the normal regional flora.[47,50] The evidence for this is based on the discovery of several disease-associated genes implicated in regulation of innate immunity.

Unlike sarcoidosis, the genetic link to CD is much better defined. Familial and ethnic clustering, concordance in monozygotic twins, and genetic anticipation (ie earlier disease onset in offspring of parents with the disorder), have all been experimentally confirmed.[52,53] GWAS have identified and confirmed at least 71 susceptibility loci on at least seventeen different chromosomes.[54] Intriguingly, a number of these loci also increase susceptibility to ulcerative colitis, which is another inflammatory bowel disorder. However, unlike CD, ulcerative colitis is not associated with granulomatous inflammation.

Several risk-conferring SNPs have been identified in CD patients. However, SNPs in the CARD15/NOD2 gene on chromosome 16 are the most strongly associated with CD.[50,55] CARD15 is an intracellular pattern recognition receptor protein that plays an important role in recognition of bacterial peptidoglycan muramyl dipeptide, which is a constituent of Gram positive and Gram negative bacteria. CARD15 is expressed in monocytes, macrophages, dendritic cells, epithelial cells, including Paneth cells. Paneth cells are found in the small intestine and are thought to play a critical role in microbial immunity and host defense.[56] CARD15 SNPs have been identified in 35-45% of Caucasian patients, not including subsets of Northern European patients, with a predilection for ileal disease.[51,57]

There are multiple distinct disease-associated CARD15 SNPs. They are all located within the coding region of the gene, and specifically within the region encoding the leucine-rich repeat ligand-binding domain of the protein. Alteration in CARD15 function results in decreased expression of antimicrobial peptides, decreased propagation of antibacterial T-helper lymphocytes, reduced transcription of critical cytokines, and impairs autophagy.[47]

Autophagy is a catabolic lysosomal degradative process whereby the cell degrades its own components, including proteins and organelles, as well intracellular pathogens as a means of ensuring its own survival.[50] Thus, autophagy plays an integral role in the innate immune response to intracellular microorganisms. To this end, SNPs in other autophagy-associated genes, including ATG16L1, CARD9, IRGM and LRRK2, have also been identified in subsets of CD patients.[47,50,52] Hence, an abnormal innate immune response to intracellular pathogens is thought to primarily underlie the pathogenesis of CD in at least a subset of patients. Other genes including those implicated in regulation of intestinal barrier function, lymphocyte differentiation, leukocyte migration, adaptive immunity and apoptosis have also been linked to CD; most still require detailed investigations.[47] However, irrespective of which protein may be implicated in disease pathogenesis, none of these currently explain the appearance of granulomatous inflammation within affected tissues. In addition, disease susceptibility loci only convey less than one third of the risk for CD.[49] This is why environmental factors are also thought to play an important role in development of CD.

Clinical findings

CD can develop at any age, but most patients develop disease by the age of 40 years.[53] CD is much more prevalent in whites than in other races. More than any other population group, white Ashkenazi Jewish ancestry is associated with significantly increased risk of developing the disease.[47] Overall, there is no sex predilection, but the younger the age of onset, the greater the likelihood that the disease will affect males. Recent epidemiologic studies suggest increasing incidence rates worldwide, including within pediatric populations.[47,53]

CD is a phenotypically heterogeneous disease. Like sarcoidosis, there are no standard criteria for diagnosis. A typical presentation is that of a patient complaining of various non-

specific constitutional signs and symptoms, abdominal pain, anemia, arthralgia, repeated bouts of diarrhea, and weight loss.[47] In most cases, an accurate diagnosis of gastrointestinal CD is rendered only following integration of a thorough history, physical findings, imaging data, laboratory analyses including microscopic studies and stool cultures, endoscopy, consultation with various medical specialists, and exclusion of other diseases that may mimic CD, including Behçet disease.[47,51,53] Once diagnosed, patients are stratified based on criteria established by the Working Party of the 2005 Montreal World Congress of Gastroenterology.[57]

The Montreal classification is useful in determining patient management and therapeutic strategy. The Montreal criteria also recommend thorough screening for extraintestinal manifestations and autoimmune diseases. To this end, oral lesions are commonly identified in CD, and may be the initial manifestation of disease in a subset of affected individuals.[48,51] Moreover, oral complications are more prevalent in children than in adults. Oral findings may include aphthous stomatitis, painless, swelling of the lips, oftentimes with vertical fissuring, papular lesions that give the oral mucosa a cobblestoned appearance, localized or diffuse erythema or edema, gingivitis, and mucosal tags. None of these manifestations are specific, but when considered in the proper context, are characteristic for CD. Deep linear ulcerations embedded within the vestibular folds are the only pathognomonic findings associated with the disease (Figure 1).[48,51] Similar to the intestinal manifestations, oral lesions of CD may wax and wane over extended periods of time. In rare cases, CD may trigger pyostomatitis vegetans, which is characterized by pustular mucosal lesions and superficial erosions, oftentimes with a concomitant peripheral eosinophilia.[58] Pyostomatitis vegetans can also be triggered by ulcerative colitis and gastrointestinal adenocarcinomas.

Diagnostic tests

The diagnosis of Crohn disease is typically made through the cumulative interpretation of several different clinical, radiographic and laboratory analyses.[47] Tissue biopsy is an important diagnostic test, and histopathologic analysis may reveal non-caseating granulomatous inflammation. However, only about 50% of CD biopsies reveal granulomas.[2] In the intestine, CD is characterized by the appearance of ‘skip lesions’ and gross and histologic evidence of transmural inflammation. This helps to differentiate CD from ulcerative colitis.

In general, serologic markers have questionable value in a routine diagnostic work-up for CD.[47,53,59] In contrast, at least some of these biomarkers may have potential value in predicting long-term disease course. Markers including elevated C-reactive protein levels and anti-*Saccharomyces cerevisiae* antibodies are frequently observed in CD patients.[59,60] Both factors exhibit a positive correlation with severity of CD. However, up to 30% of CD patients do not exhibit C-reactive protein. Moreover, C-reactive protein levels may also increase in several other inflammatory conditions. In addition, serum anti-*S. cerevisiae* antibodies levels remain unchanged after curative intestinal resection. Anti-*S. cerevisiae* antibodies are more commonly identified in patients who have CARD15 SNPs.[60]

Calprotectin is a fecal granulocyte protein that has emerged as a promising marker of gastrointestinal inflammation.[61] Fecal calprotectin levels are significantly increased in CD and may have predictive value in identifying active CD in adults and children.[47] In other studies, calprotectin levels also had value in predicting disease relapse. Calprotectin levels return to normal following CD treatment. It is important to note that calprotectin levels also increase in other inflammatory bowel diseases. Similarly, anti-neutrophil cytoplasmic antibodies (ANCA) may also be elevated in inflammatory bowel diseases including CD and ulcerative colitis.[59,62] However, studies suggest that ANCA may be more commonly

increased in ulcerative colitis than CD. Thus, its usefulness as a diagnostic marker for CD is limited.

Treatment and prognosis

Like sarcoidosis, the primary goal of CD treatment is to suppress the inflammation, promote mucosal healing, and interrupt disease progression to obviate disease morbidity.[47,51,53] The actual initial drug of choice will be dependent upon the extent of the disease, disease activity, and associated comorbidities. Corticosteroids and anti-TNF-α biologic therapies, including infliximab, have proven effective in acute phase treatment.[47] This may be combined with immunomodulatory drugs, such as methotrexate or a thiopurine like azathioprine, for long-term maintenance. If the manifestations are restricted to the oral cavity, high-potency topical or intralesional steroids may be sufficient. Antibiotics, including metronidaloze or ciprofloxacin, may be necessary in patients with abscesses or fistulae. Sulfasalazine and the 5-amino-salicylates (mesalamine) are another common class of medications used to treat CD. For those who fail to respond to pharmacologic therapy, or who have obstructive bowel disease, surgery is often necessary. Long-term follow-up is recommended for patients with CD; these patients have an increased risk for cancer of the small intestine.[51]

OROFACIAL GRANULOMATOSIS

Orofacial granulomatosis (OFG) is a rare, non-caseating granulomatous inflammatory disorder that is restricted to the oral and perioral tissues.[63] OFG may develop at any age, there is no sex predilection, and its etiology remains unknown. Infectious agents and genetic factors have been proposed, however, neither have proven to be consistently associated with the disease.[63] It has been suggested that OFG may represent an unusual allergic reaction to foods, dental materials or some other environmental agent.[63-65] Importantly, onset of OFG during childhood may predict future development of CD.[66,67] Thus, there is still no consensus as to whether OFG is a distinct clinical disorder or simply the initial manifestation of CD or possibly sarcoidosis.

Clinical findings

Affected patients typically present with persistent painless swelling of the lips (cheilitis granulomatosa).[63] Less commonly other oral mucosal sites, including the buccal mucosa, are affected (Figure 2). One or both lips may be involved; vertical fissuring is a common finding If left untreated, most patients will also eventually experience painless facial swelling. *Melkersson-Rosenthal syndrome* (MRS) is characterized by orofacial swelling, facial palsy, and less commonly, fissured tongue.[68] The facial palsy tends to be unilateral and may be indistinguishable from Bell's palsy. The occurrence of oral ulceration and abnormalities in serologic or hematologic parameters, including elevated C-reactive protein, may be less commonly a feature of OFG than CD.[66]

Diagnostic tests

Although OFG is characterized by non-caseating granulomas, foreign-body reaction, infectious disease, CD and sarcoidosis must all be reliably ruled out prior to rendering a diagnosis of OFG. Thus, OFG is a diagnosis of exclusion.

Treatment and prognosis

Systemic or intralesional corticosteroids are typically the treatment of choice.[63,69] Steroid-sparing medications may be used, especially in patients who present with refractory or chronic disease. Anti-TNF-α therapy may be beneficial for short-term therapy but long-term benefits remain unclear.[69,70] Spontaneous remission is rare and most patients will eventually

develop recurrences. Long-term follow-up is recommended since progression to systemic disease in the form CD or possibly even sarcoidosis may occur.[63,66,67]

SUMMARY

Granulomatous inflammation may manifest in the oral cavity and usually with an array of non-specific clinical findings. The differential diagnosis includes foreign-body reaction, infectious disease, CD, sarcoidosis and OFG. Thus, an extensive clinical, microscopic and laboratory evaluation may be required in order to identify the source of the granulomatous inflammation. However, if the etiology is correctly identified and appropriate therapy rendered, prognosis of the condition is significantly improved.

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Key points

1. Granulomatous inflammation often presents as a diagnostic dilemma for the clinician.
2. Granulomatous inflammation often has a multifactorial etiology including environmental or genetic factors, infectious organisms, or maybe idiopathic, for which there is no known trigger.
3. A typical differential diagnosis includes: foreign body reactions, infection, Crohn disease, sarcoidosis and orofacial granulomatosis.

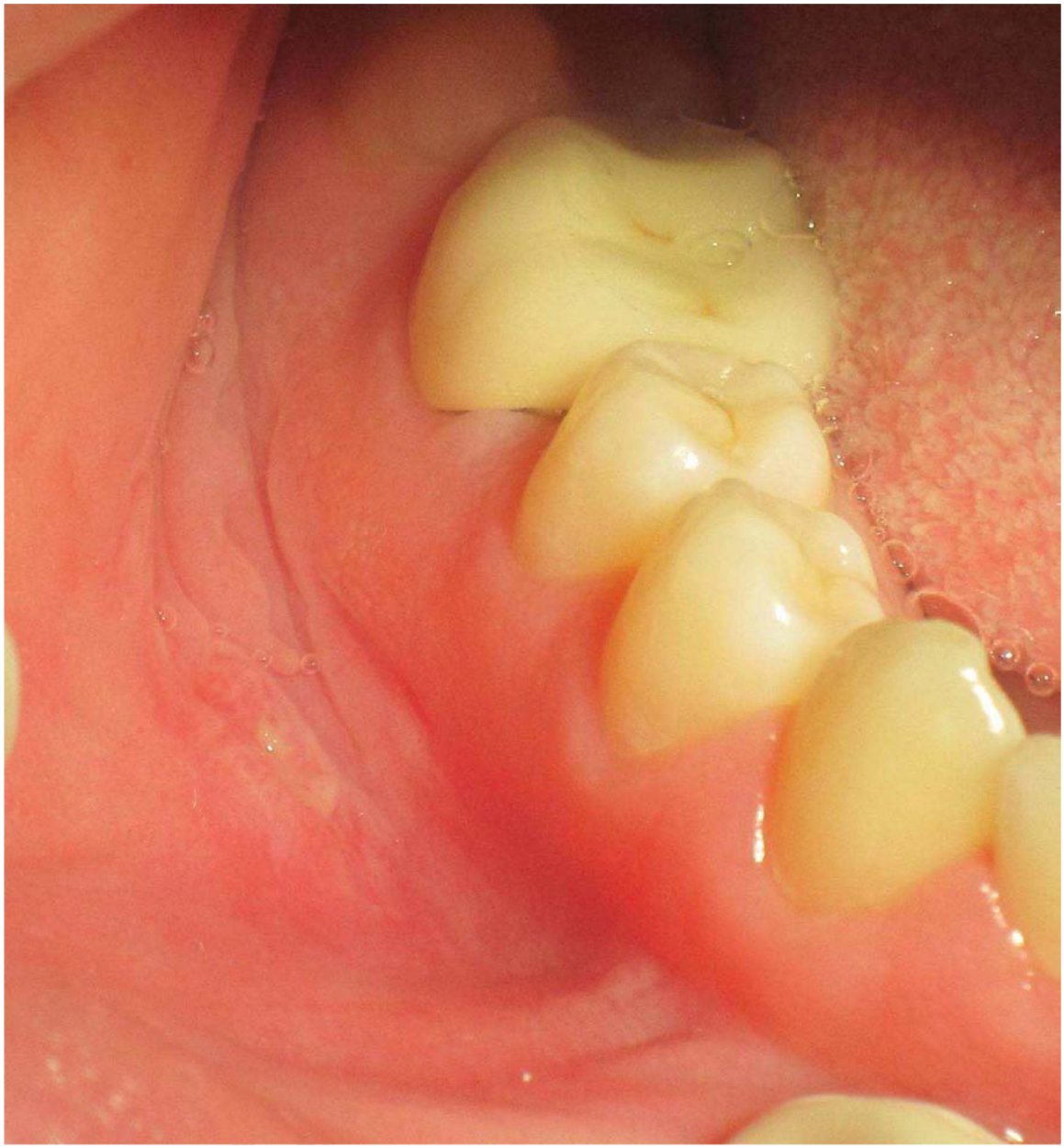

Figure 1.
Corrugated vestibular mucosa with linear ulceration consistent with Crohn Disease. (Courtesy of Dr. Eric T. Stoopler, Philadelphia, PA.)

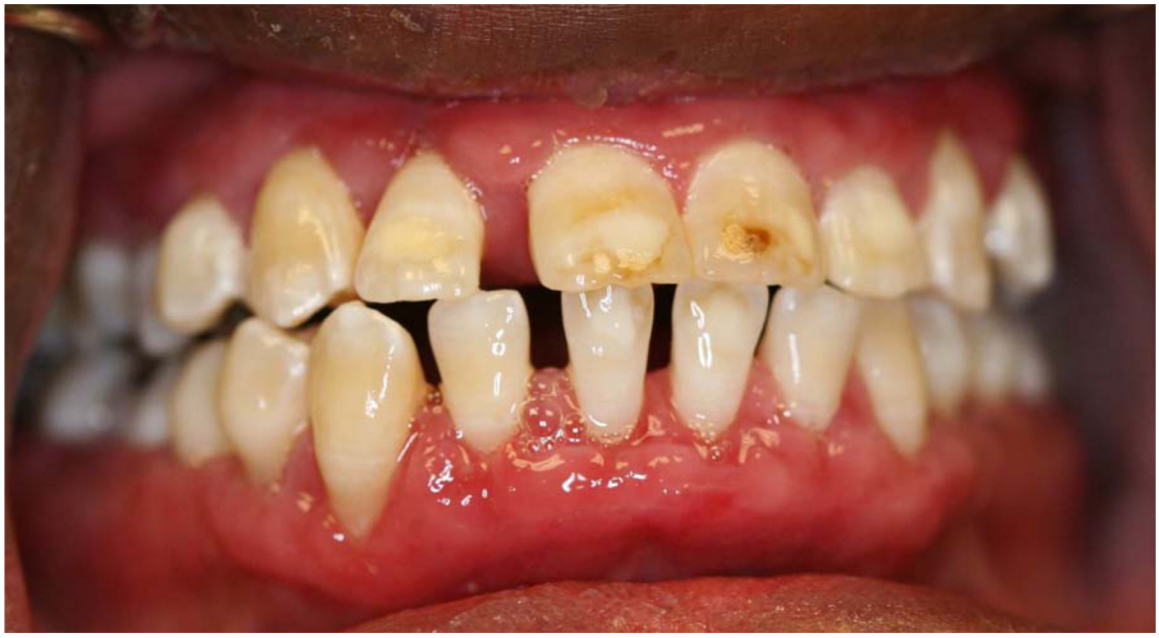

Figure 2.
Generalized gingival erythema and edema representative of orofacial granulomatosis. (Courtesy of Dr. Eric T. Stoopler, Philadelphia, PA.)

Table I

Infectious organisms known to induce granulomatous inflammation

Mycobacterial organisms
M. tuberculosis
M. leprae
M. avium complex
M. marinum
Fungal organisms
Histoplasma capsulatum
Cryptococcus neoformans
Coccidioides imitis
Blastomyces dermatitidis
Paracoccidioides brasiliensis