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Case Report

Orofacial sarcoidosis: report of three cases

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Abstract – Introduction: Sarcoidosis is a systemic non-caseating granulomatous disorder of unknown etiology that may affect multiple organ systems. Head and neck involvement can present in unusual and often nonspecific ways. **Observations:** We report three cases of sarcoidosis with orofacial manifestations: one African American patient with an existing diagnosis who presented with perioral cutaneous involvement by sarcoidosis, and two Caucasian patients with cases where the initial oral presentation – diffusely affected gingiva in one and intraosseous jaw involvement with resultant dental implant failure in the other – led to workup and establishment of the diagnosis of sarcoidosis. The patients were referred to rheumatology and dermatology for appropriate treatment. **Conclusion:** Although oral lesions of sarcoidosis are not common, they may be the first clinical manifestation of sarcoidosis. The practitioner should be aware of the possible manifestations and be able to formulate an informed clinical differential diagnosis.

Introduction

Sarcoidosis is a systemic non-caseating granulomatous disorder of unknown etiology that may affect multiple organ systems. As a systemic disease, it is well documented in existing literature. However, the rarity and the often non-specific manifestation of oral sarcoidosis emphasizes the need to reinforce the literature with clinical case examples and draw additional attention to clinical features that general practitioners may encounter. This report aims to expand the literature surrounding orofacial sarcoidosis and support oral health practitioners in recognizing its head and neck manifestations by providing three clinically different presentations that all lead to a diagnosis of sarcoidosis.

Case series

Case 1

A 59-year-old African American female patient presented to an oral medicine specialist for evaluation of a lip lesion present, which she stated has been present for at least 5 years. She denied any change in lesion size during this time. On initial examination, the patient only reported a past medical history of gastroesophageal reflux disease (GERD), hypothyroidism, and hypertension. Extraoral examination revealed a nontender, pink, indurated, somewhat plaque-like lesion with a corrugated surface on the lower lip. The lesion extended onto the oral labial mucosa and had an erythematous border (Fig. 1). The remainder of the clinical examination was non-contributory.

Histologic examination of an incisional biopsy of the lesion revealed non-caseating tight aggregates of histiocytes and multinucleated giant cells against a diffuse lymphocytic infiltrate (Fig. 2). Polarization studies and special stains for acid fast bacilli (AFB) and fungal microbes (Periodic Acid-Schiff [PAS], Grocott's Methenamine Silver [GMS]) were negative, and a broad diagnosis of non-caseating granulomatous inflammation was rendered. A comment was included recommending further evaluation to rule out chronic granulomatous diseases such as Crohn's disease and sarcoidosis.

When discussing the biopsy findings and possible etiologies with the patient, she recalled being diagnosed with stage 2 sarcoidosis at an outside hospital six years prior to the current visit. The lesion thus was interpreted as cutaneous involvement by sarcoidosis. The patient was subsequently referred to dermatology for treatment with intralesional corticosteroid injections.

Case 2

A 50-year-old Caucasian female was referred to an oral medicine specialist for evaluation of persistent gingival erythema and ulcerations after seeking general dental care for increasing tooth mobility. She reported previous treatment of the gingival erythema with prednisone but has had minimal response to azathioprine and methotrexate in the past. She currently endorsed recent worsening of her gingival disease

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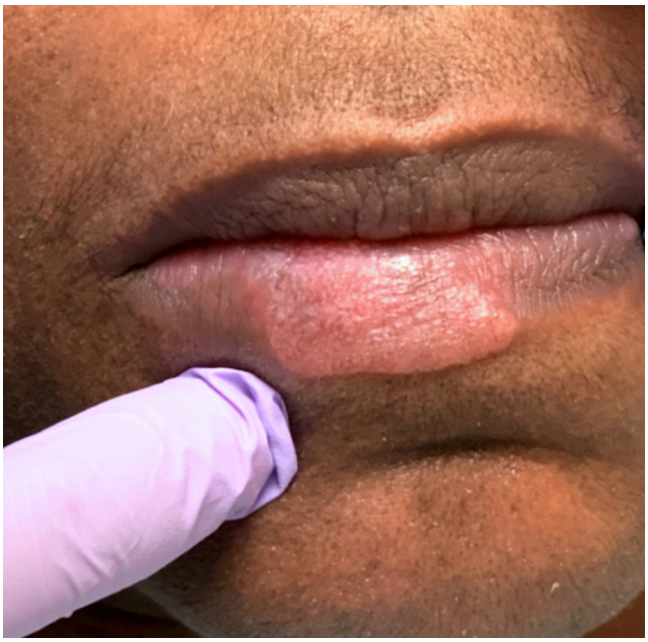

Fig. 1. Lower lip lesion. Pink plaque-like lesion with a corrugated surface is noted on the lower lip.

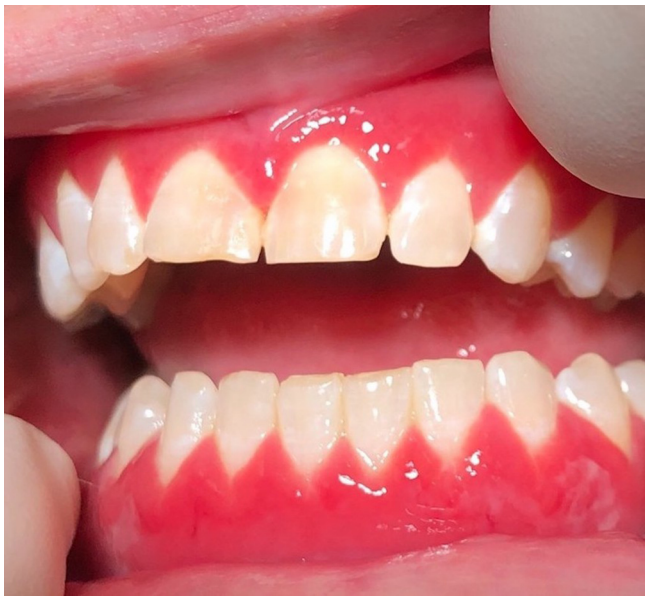

Fig. 3. Erythematous maxillary and mandibular gingivae. Maxillary gingivae are enlarged and erythematous. Mandibular gingivae are diffusely enlarged, erythematous, and focally ulcerated.

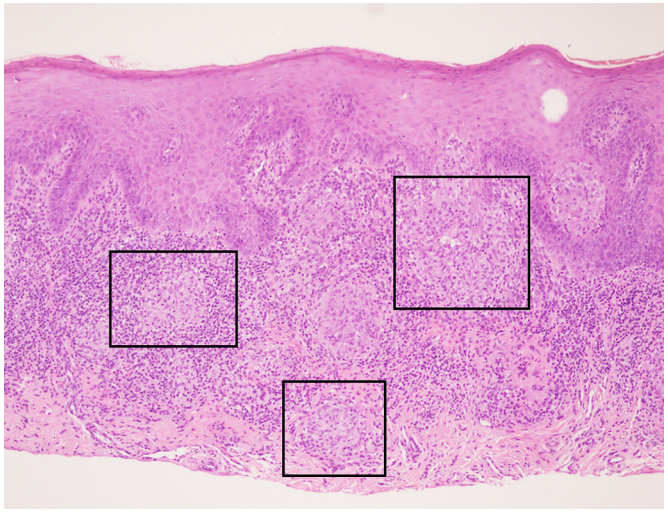

Fig. 2. Histological section of lower lip lesion. On medium power, tight granulomata are noted against a diffusely lymphocytic background; hematoxylin-eosin, 100×.

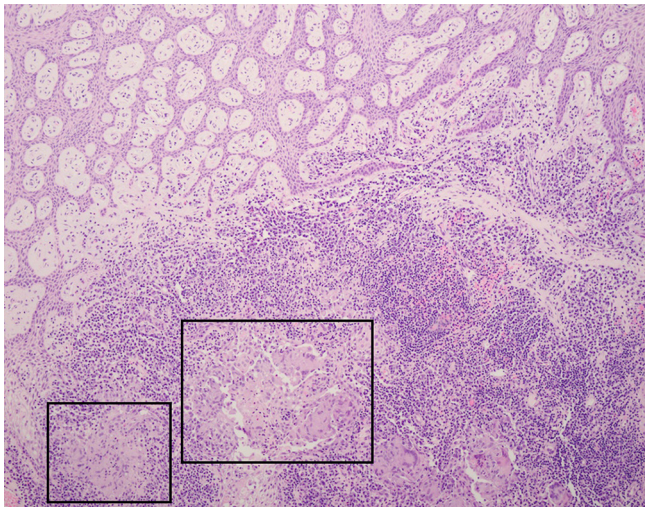

Fig. 4. Histological section of gingiva. Granulomata can be appreciated against a brisk lymphoplasmacytic infiltrate; hematoxylin-eosin, 100×.

activity. The family history was notable for inflammatory bowel disease, although the patient's recent screening colonoscopy was negative.

Intraoral examination revealed a generalized bright red appearance of maxillary and mandibular gingiva with focal ulcerations (Fig. 3) and increased mobility of mandibular premolar teeth. A two-week course of topical dexamethasone and tacrolimus application did not result in clinical improvement, and an incisional biopsy was obtained.

Microscopic examination revealed brisk chronic mucosal inflammation with granuloma formation (Fig. 4) without microscopic evidence of embedded foreign body and with negative special stains for acid fast bacilli or fungal microbes. The patient was referred to a rheumatologist for evaluation, and further work-up led to the diagnosis of sarcoidosis. The patient was started on a course of tumor necrosis factor (TNF) inhibitor injections.

Case 3

A 38-year-old Caucasian male was referred to a periodontist for evaluation of failing mandibular implants and "bone loss beyond redemption" with "increased breakdown" that showed little improvement after a course of antibiotics. He reported

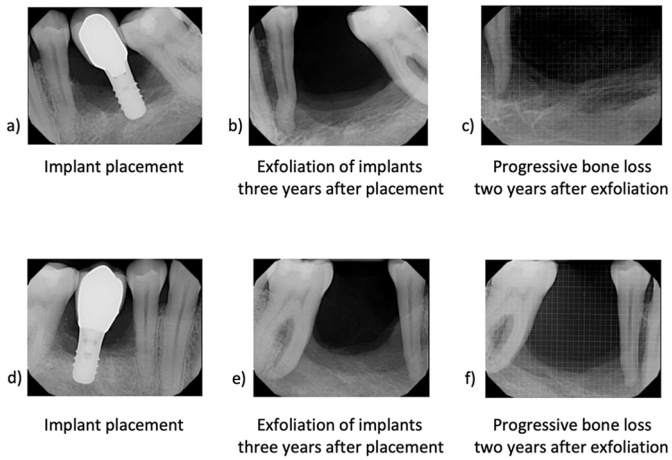

Fig. 5. Periapical radiographs of implant site and exfoliation. (a) Implant placement, (b) exfoliation three years later, and (c) progression of bone loss two years after implant exfoliation at the site of the left mandibular second premolar. (d) Implant placement, (e) exfoliation three years later, and (f) progression of bone loss two years after implant exfoliation at the site of the right mandibular first molar.

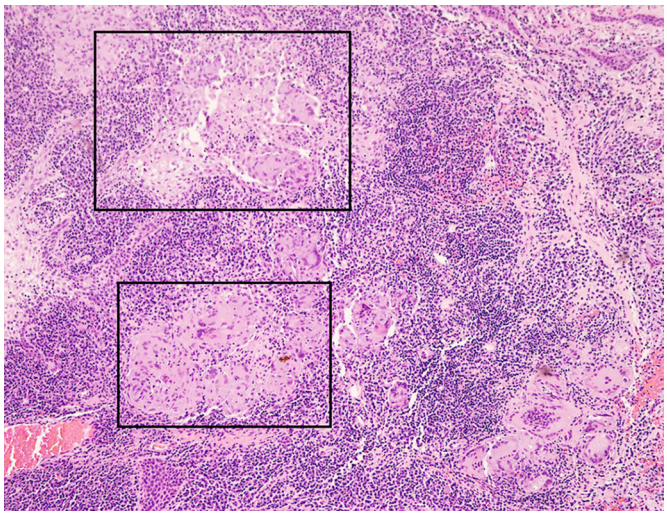

Fig. 6. Histological section of affected bone. Medium power reveals granulomatous inflammation consisting of tight aggregates of histiocytes and multinucleated giant cells in the background of diffuse plasma-lymphocytic infiltrate; hematoxylin-eosin, 100×.

that he had several teeth extracted in the past due to "bone loss" and that the dental implants placed at these sites subsequently exfoliated three years later. He denied any pertinent medical history. His surgical history was significant for recent kidney donation.

Intraoral examination revealed a generally stable maxillary dentition with probing depths ranging from 2 mm to 4 mm. Examination of the mandibular arch revealed hypermobility of the teeth and significant bone loss in the areas of the left mandibular second premolar and the right mandibular first molar, which corresponded to the previous extraction and implant sites. Progressive bone loss not responsive to conservative periodontal treatment or local antibiotic therapy was observed two years later (Fig. 5).

Surgical exploration of these areas revealed brittle bone with reduced density which was submitted for histopathologic examination. Microscopic examination revealed non-caseating granulomatous inflammation (Fig. 6). The granulomas were arranged in tight aggregates reminiscent of sarcoidosis. Polarization studies and special stains for acid fast bacilli (AFB) and fungal microbes (PAS, GMS) were negative. These findings were relayed to the treating clinician, who referred the patient to a rheumatologist for evaluation, and further work-up led to the diagnosis of sarcoidosis.

Discussion

Sarcoidosis is a systemic non-caseating granulomatous disorder of unknown etiology that can affect multiple organ systems [1,2]. In the United States, the rates of sarcoidosis vary with race, with one study citing 35.5–64 cases per 100,000 African American and 10–14 cases per 100,000 Caucasian individuals [3]. Another study found African American females to be at highest risk for developing sarcoidosis at 39.1 cases per 100,000 [4]. Population-wide genome studies have found that sarcoidosis may be in part related to the ANXA11 gene on chromosome 10 and to the HLA gene on chromosome 6, specifically HLA-DRB1 alleles such as 11:01, 12:01, and 15:03, which may contribute to higher prevalence among African American populations [5].

Although no direct inciting factor has been attributed to the onset of sarcoidosis, immunologic studies have shown that the disease is associated with elevated levels of CD4+ T cells, Th1 helper T cells, and macrophages at disease sites and circulating immune complexes [6]. In recent years, sarcoidosis has been linked to bacterial antigens from *Mycobacteria* and *Propionibacteria*, as well as MHC-II activating auto-antibodies against vimentin, β-actin, hemoglobin, and macroglobulin antigens, supporting an autoimmune pathogenesis theory [7,8]. Studies have also shown that even inhaled materials such as silicone, inorganic dust, and copy machine emissions can trigger an autoimmune response and the onset of local and systemic symptoms of sarcoidosis. Formation of giant cell granulomas containing exogenous material has been found in predisposed patients [9].

While initial presentation of sarcoidosis varies with race, sex, and age, the clinical manifestations most commonly involve persistent cough, disease localization in the skin, eye, and peripheral lymph nodes, erythema nodosum, fatigue, and incidental abnormal chest radiograph of bilateral hilar lymphadenopathy with or without pulmonary infiltration [1,10]. About half of all cases resolve spontaneously, while others persist, leading to classification of the disease into acute (≤2 years) or chronic (≥3–5 years) [1].

The lungs are considered to be the most commonly involved organ and are affected in more than 90% of sarcoidosis patients. About one third to one half of patients may

experience dyspnea, dry cough, and retrosternal chest pain. Hemoptysis, digital clubbing, and lung crackles, on the other hand, are rare. Because pulmonary involvement is so frequently seen in sarcoidosis, a five-stage staging system has been developed for categorizing different radiographic patterns of involvement. Stage 0 indicates normal chest radiographic findings, Stage 1 indicates a finding of bilateral hilar lymphadenopathy, Stage 2 has bilateral hilar lymphadenopathy accompanied by lung parenchymal infiltration, Stage 3 is limited to parenchymal infiltration, and Stage 4 indicates advanced irreversible pulmonary fibrosis [10]. The prognosis of patients with bilateral hilar lymphadenopathy in Stage 1 is generally unfavorable, with a resolution rate of about 60%. Stage 2 and Stage 3 have been noted to have a lower rate of resolution at about 46% and 12%, respectively [11].

Cutaneous involvement also occurs in sarcoidosis and can be specific, with findings of non-caseating granulomatous inflammation on biopsy, or nonspecific. Common specific findings include subcutaneous nodules and papules or plaques. Papules or plaques can be of a variety of colors and hypopigmented or hyperpigmented. The most common nonspecific lesion is erythema nodosum, an inflammation of subcutaneous fat that appears as tender red nodules on the skin, and lupus pernio, indurated bluish-red nodules typically found on the nose and cheeks [12]. Cutaneous involvement is a useful prognostic indicator, as subcutaneous nodules have been associated with greater disease remission while plaques and lupus pernio are more indicative of chronic disease [2,10]. Because spontaneous remission of skin lesions is common, treatment is generally not indicated unless the lesions are particularly distressing. Topical or intralesional glucocorticoids are considered the first line of treatment due to their relatively limited toxicity [2].

Osseous lesions in sarcoidosis are usually asymptomatic, but some patients present with symptomatic dactylitis, especially in the second and third phalanges. Radiographically, multiple cystic lesions can be seen, revealing a classic "lacy" pattern [13]. Long bone and axial skeleton involvement is rare.

While sarcoidosis can involve the head and neck, and bone and skin involvement has been reported to be as high as 40% and 25%, respectively, oral involvement of sarcoidosis is considered rare [2]. The rare oral manifestations of sarcoidosis are variable and may be the first presenting sign of the disease [2]. Among those, some oral soft tissue manifestations are lesions of the buccal mucosa, gingiva, lips, floor of mouth, tongue, palate, and salivary glands including the parotid, submandibular, and sublingual glands. The lesions typically present as localized swelling, nodules, ulcers, gingivitis, gingival hyperplasia, or gingival recession [6,10,14]. The tongue has been reported to be affected most often, followed by the lips, oral mucosa, palate, and the gingiva [14].

Intraosseous manifestations in the maxilla and mandible commonly present as lytic lesions, which can result in tooth mobility, pain localizing to the ears, or non-healing sockets [2]. Several cases have been documented in the literature describing patients presenting with loose teeth as initial manifestations of sarcoidosis. Clinicians should be aware of the rare possibility of sarcoidosis mimicking aggressive periodontitis, as reported in our case. Intraosseous granulomatous inflammation has also been documented to cause alveolar bone destruction, destabilizing the bony housing of the teeth [10]. Non-healing sockets can be a result of local granulomatous inflammation or progress to oro-antral fistulas [10]. Corticosteroid therapy (prednisone) along with infliximab has been reported to prevent progression of these lesions and should be considered in managing osseous manifestations of sarcoidosis [15].

Establishing the diagnosis of sarcoidosis typically involves demonstrating the presence of noncaseating granulomas with epithelioid histiocytes on histological examination concurrent with pulmonary involvement, evidenced by hilar lymphadenopathy on imaging [16]. Several diseases are characterized by the presence of granulomas and must be ruled out, including Crohn's disease, lymphoma, granulomatosis with polyangiitis, primary biliary cirrhosis, hypersensitivity pneumonitis, drug reactions, berylliosis, and tuberculosis. Ruling out other causes of noncaseating granulomas such as local foreign body reactions is important. Elevated angiotensin converting enzyme levels, hypercalcemia, leukopenia, and elevated serum lysozyme levels may be helpful in supporting a diagnosis of sarcoidosis, but these findings are nonspecific [16]. Recent literature also suggests that sarcoidosis may co-occur with other autoimmune conditions. Patients receiving the diagnosis of sarcoidosis should therefore be evaluated for the presence of associated diseases such as Sjogren's syndrome and systemic lupus erythematosus [9].

Imaging of soft tissue lesions is typically not indicated due to the clinically apparent nature of mucosal and gingival involvement. Magnetic resonance imaging (MRI) can be used to detect enhancing soft tissue lesions in the buccal mucosa, tongue, floor of mouth, and palate, while the lytic involvement of the jaws can be detected as radiolucent lesions on panoramic radiographs or computerized tomography (CT) scans [6,15].

Conclusion

We report three cases of oral manifestations of sarcoidosis – a single lower lip lesion, diffuse gingival involvement, and osteolytic lesions of the mandible. While oral lesions of sarcoidosis are rare and not fully understood, they are often the first clinical manifestation of sarcoidosis. Clinicians and pathologists should be aware of these clinical presentations and use them to formulate an informed clinical differential diagnosis. Ultimately, oral health practitioners should be aware of the multitude of systemic diseases with oral manifestations.

Authors contributions

N. Koutrakis: Writing original draft, Reviewing and Editing; A. Sahu: Writing, Reviewing and Editing; D. Vasilyeva: Conceptualization, Methodology, Writing, Reviewing and Editing; S. Peters: Conceptualization, Methodology, Reviewing and Editing.

Conflict of interest

"The authors declare that they have no conflicts of interest in relation to this article."

Informed consent

"The authors declare that informed consent not required."

Ethical committee approval

The authors declare that Ethical approval not required.

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