Sarcoidosis is a common systemic granulomatous disease affecting multiple organs. Oral involvement is relatively rare and, to our knowledge, there have been only 64 cases reported in the English literature. Most cases of oral sarcoidosis present with mobility of the teeth due to rapid alveolar bone loss. Other oral manifestations include asymptomatic swelling of the involved mucosa, gingivitis and ulcers. Diagnosis of sarcoidosis is by exclusion as no specific test is available. Radiographic, biochemical and histological findings are non-specific, but helpful. All cases of sarcoidosis do not require treatment. Corticosteroids are the treatment of choice in patients requiring treatment. Other drugs such as chloroquine, methotrexate, infliximab and thalidomide are also used in the treatment of sarcoidosis. In most of the oral cases reported, systemic steroids and surgery were the preferred treatment.

Etiology and pathogenesis

Although the etiology of sarcoidosis is unknown, genetic, infectious and environmental factors have been postulated as possible causes. The recent progress in epidemiological and laboratory studies in sarcoidosis has considerably narrowed down the field of probable causes (Moller and Chen, 2002). A putative genetic pathogenesis has been suggested due to the presence of familial clusters in sarcoidosis (Rybicki et al, 1996). In addition, positive association with HLA-A1, HLA-B8 and HLA-DR3 has been identified. Studies confirm a genetic predisposition for sarcoidosis and presents evidence for the allelic variation at the HLA-DRB1 locus as a major contributor (Rossmann et al, 2003). The genetic variations that promote susceptibility to the disease may reside in loci that influence the immune response (English et al, 2001).

Infectious agents such as mycobacterium, propionobacteria, Epstein–Barr virus (EBV), and human herpes virus-8 (HHV-8) have been considered as possible etiological agents but so far the scientific results have been inconsistent and inconclusive (Richter et al, 1996; Kon and du Bois, 1997; Popper et al, 1997; Vokurka et al, 1997; English et al, 2001; Moller and Chen, 2002). Similarly, environmental factors (wood dust, pollen, clay, mold, silica) and occupational exposure (farmers, fire fighters, military) have been suggested as etiological agents. The possible role of these agents was explored in a randomized age, gender and race matched case–control study (Moller and Chen, 2002). Preliminary results from this study showed a positive association of sarcoidosis with environmental exposure to mold, musty odors and workers in agriculture,
insecticides and pesticides. There was a negative association with animal dusts and tobacco smoking, and no association with wood dust, pine pollen, silica, metals, and health care workers and the evidence was inconclusive in fire fighters and military personnel (ACCESS Research Group, 1999; Moller and Chen, 2002).

Reported evidence indicates an immunological response resulting from one or a combination of factors mentioned above. The T-helper 1 (Th1) lymphocytes play a central role (Moller and Chen, 2002) in granuloma formation, which is thought to be the result of deposition of poorly soluble antigenic material in the tissue. This antigenic material is taken up by antigen presenting cells such as macrophages or dendritic cells, which then expose it to T-lymphocytes. In response to these antigens, a local amplification of the cellular immune reaction takes place. In addition, mononuclear phagocytes and other inflammatory cells migrate to the site of the antigenic deposition under the influence of the chemokines and cytokines produced by Th1 cells. This results in the formation of a granuloma (English et al, 2001; Moller, 2003).

Clinical features

Sarcoidosis is a multiorgan disorder. The clinical symptoms depend on the ethnicity, chronicity of illness, site and extent of involvement of the organ and activity of the granulomas (Wilcox et al, 2000). One-third of the patients with sarcoidosis can present with non-specific constitutional symptoms such as fever, fatigue, malaise or weight loss (English et al, 2001). The most common presentation of sarcoidosis consists of pulmonary infiltration and hilar lymphadenopathy (Figure 1), dermal, and ocular lesions (Hunninghake et al, 1999). The organ involvement and their clinical features are summarized in Table 1.

Diagnosis

Sarcoidosis is a diagnosis of exclusion. No diagnostic tests or specific markers have been established yet (Muller-Quernheim, 1998; Hunninghake et al, 1999). The diagnosis is based upon history (occupational or environmental exposure), pulmonary function tests (forced expiratory volume, vital capacity), haematology (complete blood count, erythrocyte sedimentation rate), biochemical investigations (liver and renal function tests, serum calcium, and serum angiotensin converting enzyme levels), chest radiograph, and histological studies.

Pulmonary function tests including forced expiratory volume, vital capacity and diffusing capacity are all diminished. Haematological and biochemical tests may show anemia, lymphocytopenia, elevated ESR, increased liver enzymes, hypercalcemia and hypercalcaemic nephropathy (Rizzato, 1998; Johns and Michelle, 1999). The serum angiotensin converting enzyme (ACE) level is elevated in 50–80% of patients with sarcoidosis (Turton et al, 1979; Khan et al, 1998). It is useful in monitoring the disease progression and effectiveness of therapy (DeRemee and Rohrbach, 1980). When serum ACE is used to diagnose sarcoidosis, it has a 10% false positive and a 40% false negative rate. The ACE level is also elevated in diabetes mellitus, cirrhosis, leprosy and many other conditions. Therefore, ACE level has to be used as an adjunct, and a clinical correlation must be made for a specific diagnosis and disease progression or remission of sarcoidosis (English et al, 2001) (Figs 2 and 3).

![Figure 1 Posterior–anterior view of the chest X-ray shows bilateral hilar lymphadenopathy and cavities in a patient with sarcoidosis](image)

**Table 1** Organ involvement in sarcoidosis

<table>
<thead>
<tr>
<th>Organs</th>
<th>Frequency (%)</th>
<th>Signs and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung/lymphnode</td>
<td>90</td>
<td>Dry cough, dyspnea, Lofgran syndrome</td>
</tr>
<tr>
<td>Liver/spleen</td>
<td>50–80</td>
<td>Hepatosplenomegaly, abnormal liver function</td>
</tr>
<tr>
<td>Eyes</td>
<td>50</td>
<td>Uveitis, iritis, photophobia, dry eyes</td>
</tr>
<tr>
<td>Bone and marrow</td>
<td>40</td>
<td>Osteolytic lesions</td>
</tr>
<tr>
<td>Skin</td>
<td>25</td>
<td>Indurated purple plaques (lupus pernio),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>erythema nodosum</td>
</tr>
<tr>
<td>Heart/nerves</td>
<td>5–10</td>
<td>Cardiac arrhythmias, congestive heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>facial nerve palsy</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>4–6</td>
<td>Parotitis, Herefordt syndrome</td>
</tr>
</tbody>
</table>

Lofgran syndrome: bilateral hilar lymphadenopathy with erythema nodosum; Herefordt syndrome: uveoparotitis and facial palsy.
Depending on the involvement of the lungs and the lymph nodes, sarcoidosis in the chest radiographs may be staged as follows (Johns and Michelle, 1999):

- **Stage 0**: Normal chest radiograph.
- **Stage I**: Bilateral hilar lymphadenopathy without pulmonary infiltrates.
- **Stage II**: Bilateral hilar lymphadenopathy with pulmonary infiltrates.
- **Stage III**: Pulmonary infiltrates without hilar lymphadenopathy.
- **Stage IV**: End-stage fibrosis, cystic cavities, and honeycombing.

Biopsy of the involved tissues is helpful in the diagnosis of sarcoidosis. The histology of sarcoidosis will show non-caseating granulomas (Figure 4A). The center of the granulomas usually contains epitheloid macrophages surrounded by a rim of lymphocytes (Gal and Koss, 2002). Occasional multinucleated Langhans type giant cells are also seen (Figure 4B). The giant cells result from the fusion of the epitheloid mononuclear cells and may occasionally contain many inclusion bodies such as Schumann bodies or stellate asteroid bodies (Black and Epstein, 1974; Elgart, 1986; Gal and Koss, 2002). Schumann bodies are basophilic, calcified, and laminated bodies derived from lysosomes found in about 48–88% of sarcoidosis patients (Sheffield, 1997). Stellate or asteroid bodies are found in 2–9% of the cases. They are spiculated in shape and represent entrapped collagen (Elgart, 1986). Some lymph nodes may contain distinctive small yellow brown bodies measuring 1–15 \( \mu m \) in the sub-capsular sinus called Hamazaki–Wessenberg bodies. They represent large lysosomes and stain black with methamine silver and red with periodic acid-Schiff stain (Gal and Koss, 2002). The histological findings are not specific to sarcoidosis and may be found in other infectious granulomatous disorders. Nevertheless, the findings should raise the suspicion of sarcoidosis.

Skeletal involvement shows lytic lesions with tunneling of the involved bone, which is best, assessed by gallium bone scan (Rizzato, 1998) and positron emission tomography (PET scan), but these tests are expensive.

A test of historical value, but no longer used because of its low specificity and sensitivity, is the Kveim–Slitzbach test. This test involved the intradermal injection of a spleen extract from a known sarcoid lesion. Patient with sarcoidosis developed a nodule in 4–6 weeks. The biopsy of the nodule was done to confirm the diagnosis (Hong and Farish, 2000). This test is no longer employed due to the concerns regarding transmission of spongiform encephalopathy diseases (Ho and Blair, 2003).

**Treatment**

Treatment is not required for all patients with sarcoidosis. The American Thoracic Society, European Respiratory Society and World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) have identified several specific conditions, which require treatment (Hunninghake et al, 1999). These include the sarcoidosis of the heart and nerves, hypercalcemia, and ocular involvement that do not respond to local therapy. Asymptomatic pulmonary involvement does not require treatment, while treatment is indicated in symptomatic pulmonary sarcoidosis with worsening pulmonary function tests (Baughman and Lynch, 2003).

Corticosteroids have remained as the mainstay in the treatment of sarcoidosis. Randomised controlled trials by the British Thoracic Society have found that corticosteroid therapy is superior to no treatment (Gibson et al, 1996) and a recent meta-analysis has confirmed these findings (Paramothayan and Jones, 2002). A major problem in treatment of sarcoidosis patients is relapse (Baughman and Lower, 1998). More than 70% of patients treated with corticosteroids relapsed within a 2 year period (Gottlieb et al, 1997).

Antimalarial drugs such as chloroquine and hydroxychloroquine have been particularly useful in the treatment of cutaneous and mucosal sarcoidosis, including sinus and laryngeal sarcoidosis (Johns and Michelle, 1999). They are used in combination with low dose corticosteroids. Ocular and hepatic toxicity is associated with chloroquine, therefore, periodic eye examination and monitoring liver function are recommended (Baughman and Lynch, 2003).
Immunosuppressant drugs such as methotrexate, cyclophosphamide and azathioprine have been shown to be beneficial in the treatment of sarcoidosis. These drugs should be used with caution for their adverse side effects. Drugs inhibiting TNF-alpha such as etanercept, infliximab, pentoxyphylline and thalidomide have also shown promise in the treatment of sarcoidosis, but more controlled clinical trials are necessary to show their effectiveness (Moller, 2003).

Oral sarcoidosis

Oral involvement in sarcoidosis is uncommon. Schroff (1942) reported the first suspected case of sarcoid granulomas in the oral mucosa, but Poe (1943) reported the first confirmed case of sarcoidosis affecting the oral cavity in the mandible. Since then, to our knowledge, there have been only 68 well-documented cases of oral sarcoidosis reported in English literature (Table 4).

Most of the oral sarcoidosis cases reported in the English literature exist as single or multiple case reports. Only the cases from the English literature with confirmed histopathology from the oral lesions were included in this review. Cases without confirmed histopathology from the oral lesions and the cases involving the parotid glands and lymph nodes of the head and neck area were excluded. Cases showing sarcoid granulomas from lip or palatal biopsies from otherwise normal looking oral mucosa with no clinical manifestations in the oral cavity were also excluded.

Of the data available for the 68 cases reported in the literature, 39 cases were female, 25 were male (female to male ratio of 1.5/1), and no data was available for four cases. There was slight racial predilection to Caucasians (26 whites, 23 blacks, three Asian, one Hispanic and 15 no data available). The ages ranged from 5 to 72 years (median = 37 years).

The soft tissues of the oral cavity were affected in 47 cases and the jaw bones in 21 cases (Table 2). In the soft tissues of the oral cavity buccal mucosa was the commonest site affected with 13 cases followed by gingiva (10), lips (6), floor of the mouth/sublingual gland (5), tongue (5), palate (3), submandibular gland (2) and multiple oral site involvement (3) (Table 4). The common clinical presentations were mainly due to the lytic and permeative lesions in the bone and included loose teeth (7 cases), pain radiating to the ears (6 cases), nasal obstruction (1 case), swelling of...
the mandible (one case), maxillary bone loss (one case), and non-healing socket (one case). Three other cases did not report the symptoms (Table 3). Oral lesions were the first manifestation of the systemic sarcoidosis in 24 cases.

Parotid gland involvement occurs in 6% of patients with sarcoidosis. The gland involvement is usually bilateral and is slightly more common in women (James and Sharma, 2000). Submandibular and sublingual glands involvement is less common than parotid gland involvement (Narang and Dixon, 1975; Mandel and Kaynar, 1994). Clinical presentation of sarcoidosis in major salivary glands is usually as painless firm swellings, and fluctuation in the size does not occur during the meal time. Xerostomia may also be present (Mandel and Kaynar, 1994). Other rare but pathognomonic presentation of glandular involvement is Heerfordt syndrome. This syndrome is defined as systemic sarcoidosis characterized by parotitis (usually bilateral), uveitis, and facial nerve paralysis (James and Sharma, 2000).

The involvement of the minor salivary glands in the oral cavity in sarcoidosis may be much higher than previously reported. When palatal or labial salivary glands from clinically normal mucosa in sarcoidosis patients were biopsied, the rate of involvement ranged from 19% (Giotaki et al, 1986) to 58% (Nessan and Jacoway, 1979). It is possible that some of the swellings seen on the mucosa of patients with sarcoidosis, are actually expansions of localized minor salivary glands. The exact number of minor salivary gland involvement is not known, but it is possible that if it is extensive, it may contribute to xerostomia. In the presence of xerostomia, in a patient with sarcoidosis, minor salivary gland biopsy may be useful in differentiating sarcoidosis from Sjögren’s syndrome (Drosos et al, 1989).

The differential diagnosis for oral sarcoidosis found on biopsy in the oral cavity is orofacial granulomatosis (OFG) which encompasses a group of related conditions affecting the oral and maxillofacial region, characterized by the presence of non-specific granulomatous inflammation (Wiesenfeld et al, 1985; Sciubba and Said-Al-Naief, 2003). Orofacial granulomatosis includes bacterial infections (tuberculosis, syphilis, cat-scratch disease and leprosy), fungal infections (histoplasmosis, coccidiomycosis), foreign body granulomas and Crohn’s disease (Sciubba and Said-Al-Naief, 2003). Clinical history, additional haematological and biochemical tests in combination with specific histochemical stains will help in a precise diagnosis. Medical history has to be evaluated and the patient has to be referred to a physician for possible a systemic involvement.

In a literature search for treatment of oral sarcoidosis, we found data for only 49 of the patients (Tables 3 and 4). Multiple methods were employed in the treatment of oral sarcoidosis ranging from no treatment (Cohen et al, 1981; Hayter and Robertson, 1988) to radiation therapy (Hoggins and Allan, 1969). Surgical excision and curettage (Narang and Dixon, 1975; Betten and Kop pang, 1976; Hillerup, 1976; Schwartz, 1981) was the most commonly employed treatment, followed by steroids (MacLeod et al, 1985; Nagata et al, 1999). Oxygen therapy (Orlean and O’Brien, 1966) was also reported. Corticosteroids and other drugs were needed in only 18 of the patients. From the review, we conclude that sarcoidosis presenting in oral cavity as localized swellings may be treated with simple surgical excisions. Presentations as gingival hyperplasia and gingivitis may be controlled by scaling, polishing and strict good oral hygiene. Jaw lesions should be curretted and the mobile tooth splinted. Corticosteroids should only be considered in the painful and progressive lesions in consultation with the patient’s physician.

### Table 3 Intraosseous jaw sarcoidosis

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Age</th>
<th>Race/sex</th>
<th>Chief complaint</th>
<th>Location</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poe (1943)</td>
<td>41</td>
<td>B/F</td>
<td>Pain of left ear</td>
<td>Posterior mandible</td>
<td>NA</td>
</tr>
<tr>
<td>Kalman and Mallett (1954)</td>
<td>54</td>
<td>W/F</td>
<td>Pain/lump</td>
<td>Anterior maxilla</td>
<td>Curettage</td>
</tr>
<tr>
<td>MacDonald et al (1985)</td>
<td>45</td>
<td>W/F</td>
<td>Pain</td>
<td>Anterior mandible</td>
<td>Exploration</td>
</tr>
<tr>
<td>Van Swol (1973)</td>
<td>22</td>
<td>B/F</td>
<td>Loose teeth</td>
<td>Maxilla/mandible</td>
<td>N/A</td>
</tr>
<tr>
<td>Thomas et al (1976)</td>
<td>30</td>
<td>B/M</td>
<td>Pain of TMJ</td>
<td>Right TMJ</td>
<td>Steroids</td>
</tr>
<tr>
<td>Hillerup (1976)</td>
<td>22</td>
<td>W/M</td>
<td>Mandibular lesion</td>
<td>Posterior mandible</td>
<td>Curettage</td>
</tr>
<tr>
<td>Betten and Kop pang, 1976</td>
<td>49</td>
<td>W/M</td>
<td>None</td>
<td>Posterior mandible</td>
<td>Curettage</td>
</tr>
<tr>
<td>Schwartz (1981)</td>
<td>29</td>
<td>W/F</td>
<td>Pain of TMJ</td>
<td>Mandible condyle</td>
<td>Condylectomy</td>
</tr>
<tr>
<td>Cohen and Reinhardt (1982)</td>
<td>59</td>
<td>W/F</td>
<td>Non-healing socket</td>
<td>Posterior mandible</td>
<td>Curettage</td>
</tr>
<tr>
<td>Makris and Stoller (1983)</td>
<td>27</td>
<td>B/F</td>
<td>None</td>
<td>Maxilla/mandible</td>
<td>N/A</td>
</tr>
<tr>
<td>Verheijen-Breemhaar et al (1987)</td>
<td>28</td>
<td>N/A/F</td>
<td>Loose teeth</td>
<td>Anterior maxilla</td>
<td>Extraction</td>
</tr>
<tr>
<td>Hildebrand et al (1990)</td>
<td>41</td>
<td>B/M</td>
<td>Nasal obstruction</td>
<td>Anterior maxilla</td>
<td>Steroids</td>
</tr>
<tr>
<td>Rubin et al (1991)</td>
<td>25</td>
<td>B/F</td>
<td>None</td>
<td>Anterior maxilla</td>
<td>NA</td>
</tr>
<tr>
<td>Kesper et al (1994)</td>
<td>16</td>
<td>W/F</td>
<td>Loose teeth</td>
<td>Anterior maxilla</td>
<td>Steroids</td>
</tr>
<tr>
<td>Hong and Farish (2000)</td>
<td>40</td>
<td>B/M</td>
<td>Loose teeth</td>
<td>Anterior maxilla</td>
<td>Steroids</td>
</tr>
<tr>
<td>White and Crocker (2000)</td>
<td>37</td>
<td>W/M</td>
<td>Maxillary bone loss</td>
<td>Posterior maxilla</td>
<td>Remission</td>
</tr>
</tbody>
</table>

NA, not available; B, black; W, white; F, female; M, male.
Conclusion

Sarcoïdosis is a relatively common disease but its oral manifestations are relatively uncommon. Oral lesions may be the initial manifestation of the disease. Suspected cases of oral sarcoïdosis should be biopsied and also be referred to a physician to rule out other systemic involvement.
Oral Diseases
L Suresh and L Radfar

References


