

## Intra-Oral Sarcoidosis: A Specific Disease Entity Known For More Than A Century, But Still A Dilemma

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**Abstracts:** Sarcoidosis is a multisystem inflammatory disease of unknown etiology that predominantly affects the lungs and intra-thoracic lymph nodes. Sarcoidosis is manifested by the presence of non-caseating granulomas in affected organs and tissues. Although the condition has been identified as a specific disease entity for more than a century, the exact etiology of it is still unknown. The present review tries to provide an insight into the possible etio-pathogenesis that seems convincing with an overview of the contemporary treatment modalities recommended and adopted for this complex disease process. [Nayyar A NJIRM 2015; 6(3):98-104]

**Key Words:** Sarcoidosis, chronic granulomatous conditions.

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**Introduction:** Although sarcoidosis has been known as a specific disease entity for more than a century, the exact etiology of it has still not been clearly elucidated. In addition, the diagnostic criteria, treatment algorithms, method of follow-up and natural course of the disease have not been clearly stated.<sup>1</sup> Sarcoid granulomas are thought to arise from the interaction of the causative antigen with the host's immune system.<sup>2</sup> It is but obvious that inflammation in any situation is an important part of the host defense mechanisms.<sup>3</sup> As per this hypothesis and as has already been clearly said in the literature, inflammation is always beneficial in clearing the antigen and anti-inflammatory therapy including immunosuppressive therapy done with corticosteroids leaves a scope for an infection or, condition which arises as a result of the pathogen or, any other inciting stimulus to be unresolved thereby leading to recurrences and relapses with eventual failure of the primary treatment.<sup>4-6</sup> In addition, this concept is consistent with the fact that anti-sarcoidosis treatment, which is especially done with the help of immunosuppression achieved with corticosteroids, the mainstay of treatment in sarcoidosis patients, resolves granulomatous inflammation but does not alter the natural course of the disease process and should be used with caution provided it does not lead to the onset of symptoms in seemingly asymptomatic patients or, further worsening of the patients' condition.<sup>3,6-12</sup> When treatment is indicated for sarcoidosis patients, corticosteroids are considered to be the first line of therapy because of their proven efficacy and early action in terms of symptom relief.<sup>13</sup> Despite corticosteroids being

considered and used as the first line of therapy for sarcoidosis patients, they are inherently bound to have been associated with certain unavoidable side effects that probes for a search of suitable alternatives especially in patients who have some other forms of co-morbidities where treatment of the faced condition leads to a further worsening of the pre-existing disease(s) and/or, disorder(s). To conclude, the diagnosis of sarcoidosis still remains a challenge in absence of specific and reliable diagnostic tests. Various algorithms and criteria have been established as diagnostic guidelines although a gold standard diagnostic test yet needs to be worked-out. Oral involvement in sarcoidosis is very rare. The first suspected case of oral sarcoidosis presenting with sarcoid granulomas in the oral mucosa was reported in 1942 by Schroff<sup>14</sup> while Poe<sup>15</sup> in 1943 reported the first confirmed case of oral sarcoidosis that involved the mandible. In the soft tissues of the oral cavity to be affected by sarcoidosis, buccal mucosa is the most commonly affected site followed by gingival, lips, floor of the mouth, tongue, palate and submandibular glands. The common clinical presentations include localized swellings or nodules to ulcers, swelling with multiple ulcers, gingivitis, gingival hyperplasia and gingival recession. The jaw bone involvement has been although seen to show no specific jaw predilection with almost equal involvement of maxilla and mandible and sometimes, involvement of both the maxilla and mandible simultaneously. In maxilla, however, anterior maxilla has been seen to be affected more commonly as compared to posterior maxilla while in mandible, posterior mandible is

seen to have a predilection than the anterior body of the mandible. The clinical presentations in these cases included mainly lytic and permeative lesions in the bone affected eventually leading to loosening of the teeth in the affected areas, pain that radiated to the ear region, symptoms of nasal obstruction to unhealed sockets post-extractions and/or, minor surgical procedures apart from resorptive lesions that were seen to lead to extensive bone loss.<sup>16</sup> Parotid gland involvement occurs in 6% of the patients with sarcoidosis and the clinical presentation is usually seen in the form of bilateral parotid gland enlargement, slightly more common in females,<sup>17</sup> and either presenting with varying grades of xerostomia<sup>18</sup> or, as a part of the well-known entity of recent times, Heerfordt Syndrome defined as systemic sarcoidosis characterized with parotitis which is usually bilateral, uveitis and facial nerve paralysis.<sup>17</sup> The possible differential diagnoses of oral sarcoidosis include the varied causes for orofacial granulomatosis including bacterial (tuberculosis, syphilis, cat-scratch disease and leprosy) to fungal (deep fungal infections including histoplasmosis and coccidioidomycosis) foreign body granulomas and Crohn's Disease and Ulcerative Colitis.<sup>19,20</sup> Clinical history, appropriate hematological and biochemical evaluations alongwith histopathological examination of the affected tissue when required help to arrive-at a specific diagnosis. Medical history, in addition, has to be evaluated carefully and the patient has to be referred to physician for possible systemic involvement. Oral involvement in sarcoidosis is relative uncommon. To our knowledge there are only 7 cases of sarcoidosis of tongue reported to date.<sup>21</sup>

**Discussion:** Sarcoidosis is a multisystem inflammatory disease of unknown etiology that predominantly affects the lungs and intra-thoracic lymph nodes. Sarcoidosis is manifested by the presence of non-caseating granulomas in affected organs and tissues. It is characterized by a seemingly exaggerated immune response against a difficult-to-discern antigen.<sup>22</sup> T cells play a central role in the development of sarcoidosis as they likely propagate an excessive cellular immune reaction. There has been seen an active accumulation of CD4 cells at the sites of disease activity accompanied by the release of interleukin

(IL)-2. This may manifest clinically by an inverted CD4/CD8 ratio.<sup>23</sup> Moreover, both tumor necrosis factor (TNF) and TNF receptors are increased in this disease. The importance of TNF in propagating inflammation in sarcoidosis has been demonstrated by the efficacy of anti-TNF agents, infliximab,<sup>24,25</sup> in treating this disease. Over the past decade, several studies have shown a benefit of tumor necrosis factor alpha (TNF- $\alpha$ ) antagonists for the treatment of sarcoidosis.<sup>24, 26-28</sup> There is a sound rationale for this therapy because TNF- $\alpha$  is released by macrophages recovered from sarcoidosis patients<sup>29</sup> and TNF- $\alpha$  is thought to be integrally involved in the development of the granulomatous inflammation.<sup>30,31</sup> Infliximab appears to be a particularly effective for lupus pernio (disfiguring facial sarcoidosis),<sup>27</sup> neurosarcoidosis,<sup>28</sup> and pulmonary sarcoidosis.<sup>32</sup> Adalimumab may be effective for sarcoidosis<sup>33,34</sup> although, extrapolating from clinical reports, the optimal dose may need to be higher than that routinely used in rheumatoid arthritis.<sup>35</sup> Furthermore, all TNF- $\alpha$  antagonist agents have been occasionally associated with relapse, worsening, or development of sarcoidosis.<sup>36-40</sup> These occurrences are most commonly reported with etanercept and are postulated to be the result of TNF- $\alpha$  antagonist-induced stimulation of interferon-gamma production leading to granulomatous inflammation.<sup>36</sup>

In addition to T cells, there is evidence of B cell hyperreactivity with immunoglobulin production. The levels of these immunoglobulins tend to be significantly higher in active than in inactive stages of the disease process and correlate with serum angiotensin-converting enzyme (ACE) levels which are significantly elevated during the active phases of the disease process.<sup>41</sup> Active sarcoidosis has also been associated with plasmatic hypergammaglobulinemia.<sup>42</sup> B-cell accumulation has been shown in pulmonary lesions, and a beneficial effect with anti-CD20 monoclonal antibody therapy has been reported in select patients. Rituximab is a monoclonal antibody directed at the C20 cell surface antigen of B-lymphocytes. Although the granulomatous inflammation of sarcoidosis is thought to primarily develop through an interaction with T-lymphocytes, there is often abnormal B-lymphocyte activity, as demonstrated by the

frequent development of a polyclonal gammopathy in active sarcoidosis.<sup>43</sup> Several case reports and open-label case series have shown the potential efficacy of rituximab in the treatment of sarcoidosis.<sup>44-47</sup>

The exact cause of the disease though is still not known; however, both genetic and environmental factors seem to play important roles.<sup>48-50</sup> Sarcoidosis is neither a malignant nor an autoimmune disease. The clinical presentation in sarcoidosis varies with the extent and severity of the disease from being asymptomatic in approximately 5% of the cases to vague, systemic complaints in the form of fever and anorexia in around 45% of cases, pulmonary complaints of dyspnea, cough, chest pain and hemoptysis, though rare, in approximately 50% of cases, Löfgren syndrome with clinical manifestations in the form of fever, bilateral hilar lymphadenopathy and polyarthralgias and variable dermatological and ocular manifestations depending on the extent of involvement of the affected viscera and disease severity. Ocular involvement, although rare, may lead to blindness if left untreated. Other possible manifestations might also include gross osseous involvement, heart failure due to cardiomyopathy, heart block and sudden death, lymphocytic meningitis and cranial nerve palsies and hypothalamic/pituitary dysfunction, again though seen rarely, may mandate immediate attention and are a cause of dreaded prognosis with high mortality and morbidity. Clinically, sarcoidosis may present in an acute, sub-acute or chronic fashion. Distinct presentations of sarcoidosis are associated with different clinical courses with approximately 50% of the patients undergoing remission usually within 2-3 years. The other 50% of the patients have persistent, generally progressive disease requiring treatment to mitigate the consequences of unremitting inflammation and subsequent fibrosis in the specific visceral organs affected, most commonly, lungs.

The diagnosis requires histologic evidence of granulomatous inflammation, exclusion of alternative causes, and evidence of systemic disease. Because there is no available diagnostic test for sarcoidosis, the diagnosis is never completely secure. Routine laboratory investigations are often unrevealing but possible

abnormalities include hypercalcemia in about 10-13% of patients and hypercalciuria in about a third of patients<sup>51,52</sup> to elevated serum angiotensin-converting enzyme (ACE)<sup>53</sup> and alkaline phosphatase<sup>54</sup> levels that are consistently raised during the active phases of the disease process. Hypercalcemia or hypercalciuria may occur due to non-caseating granulomas that secrete active form of vitamin D. An elevated alkaline phosphatase level could suggest hepatic involvement. Elevated serum ACE levels may be explained on the basis of the hypothesis that non-caseating granulomas secrete ACE which may function as a cytokine. Infact, serum ACE levels may correlate with total body granuloma load. Serum ACE levels are elevated in 60% of patients at the time of diagnosis. Levels may be increased in fluid from bronchoalveolar lavage or in cerebrospinal fluid however, there is no clear prognostic value.

A chest radiograph is central to evaluation. The ultimate diagnosis however requires histologic evidence of granulomatous inflammation with possible exclusion of alternative etiologies and added evidence of systemic disease. The central histologic finding is the presence of non-caseating granulomas with special stains negative for fungus and mycobacteria.

Most patients require only symptomatic therapy with NSAIDs although approximately 10% of the patients need treatment for extra-pulmonary disease and 15% of patients require treatment for persistent pulmonary disease. Corticosteroids are the mainstay of therapy while some data suggest that corticosteroid use may be associated with increased relapse rates in addition to the well-known adverse effect profiles. Although corticosteroids are used for symptom relief and remain the mainstay of treatment, their efficacy in this disease is still unclear.<sup>6-10</sup> For patients with advanced pulmonary fibrosis from sarcoidosis, lung transplantation remains the only course for long-term survival.<sup>55</sup> Alternative therapies include methotrexate (MTX)<sup>56</sup>, anti-malarials, chloroquine and hydroxychloroquine<sup>57,58</sup>, cyclophosphamide<sup>59,60</sup> which has been used as a steroid-sparing treatment in patients with refractory sarcoidosis, azathioprine<sup>61</sup>, chlorambucil<sup>62</sup> which may be beneficial in patients with progressive disease unresponsive to corticosteroids and in case, they

are contraindicated, cyclosporine<sup>63</sup> which may be of benefit in progressive sarcoidosis resistant to conventional therapy and pentoxifylline<sup>64</sup>, Leflunomide<sup>65</sup> and thalidomide<sup>66,67</sup> which have been used for refractory sarcoidosis, particularly for cutaneous disease, as well as for the long-term management of extra-pulmonary sarcoidosis.

The oral lesions may be solitary or, multiple and are seen as a part of the generalized disease process.<sup>16</sup> In some cases, oral involvement is the first, or only, manifestation of the disease.<sup>68</sup>

Multiple methods were employed in the treatment of oral sarcoidosis ranging from no treatment<sup>69-71</sup> to radiation therapy<sup>72</sup>. Surgical excision and curettage<sup>73-76</sup> was the most commonly employed treatment, followed by steroids<sup>77-79</sup>. Oxygen therapy was also reported.<sup>80</sup> 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 curettage, gingivectomy and maintenance of strict oral hygiene protocols. Jaw lesions should be curretted and the mobile teeth splinted. Most of the lesions are seen to spontaneously resolve with time with the start of systemic therapy while some authors are strongly of the opinion that surgical excision is a must for treatment of the oral soft tissue or jaws lesions.<sup>81,82</sup>

**Conclusion:** Although very rare, oral lesions of sarcoidosis may be the first or, the only presenting manifestations of this complex disease process. Also, this multisystem disorder can never be completely cured, so, a periodic follow-up of the patients becomes almost mandatory in the evaluation of this disease process during the course taken by it for its effective management and to avoid any subsequent complications, ruling-out their possibility at the earliest. Oral involvement in sarcoidosis is relative uncommon but when it is seen, a proper medical history has to be evaluated carefully and the patient has to be referred to physician for possible systemic involvement.

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