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Case Report

Intra-oral Sarcoidosis: A Presentation that Deceived, Possible Search into Existing Literature

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Abstract

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. A 40 year old male patient with lesions in tongue and the palate was examined. Clinical signs were recorded and incisional biopsies from the tongue were taken. The diagnosis of sarcoidosis was established by the histopathological evidence of typical non-caseating granulomas from tissue biopsy, supported by an elevated serum Angiotensin Converting Enzyme (S-ACE) value of 62.4U/L and a 24hr. urine calcium of 538mg.

1.Introduction

Although sarcoidosis has been identified as a specific disease entity for more than one century, the specific cause of sarcoidosis is unknown. In addition, the diagnostic criteria, treatment algorithms, method of follow-up and natural course of the disease have not been clearly elucidated.[1] Sarcoid granulomas are thought to result from the interaction of an antigen with the immune system.[2] It has been conjectured that granulomatous inflammation in sarcoidosis is necessary to clear the antigen.[3] If this theory is correct, it is plausible that effective anti-sarcoidosis therapy may resolve granulomatous inflammation that may result in failure of clearance of the putative sarcoidosis antigen(s).

In this scenario, when treatment is withdrawn, the antigen may still be present and could lead to recurrent granulomatous inflammation and, therefore, relapse.[4] This schema is supported by data that suggest that a relapse of sarcoidosis is more common in patients previously treated for sarcoidosis[5], or with higher doses of corticosteroids.[6] In addition, this concept is consistent with the premise that anti-sarcoidosis treatment improves granulomatous inflammation but does not alter the natural course of the disease.[3][6]-[12]

Therefore, the granulomatous inflammation of sarcoidosis may be beneficial and should probably be left unsuppressed, provided that it does not result in significant patient symptoms or organ dysfunction. When treatment is indicated for sarcoidosis, corticosteroids are considered the drug of choice because they appear to have the greatest likelihood of efficacy and work most rapidly.[13]

Although corticosteroids are currently entrenched as the drug of choice for most forms of sarcoidosis, alternative agents are often used because of the frequency of the development of corticosteroid side effects. The diagnosis of sarcoidosis remains a challenging issue principally because there is no specific reliable diagnostic test available. Various algorithms and criteria have been established as diagnostic guidelines that may be useful while the development of a gold standard diagnostic test yet needs to be worked-out. Oral involvement in sarcoidosis is extremely rare. The first oral lesion of sarcoidosis was reported in 1942 by Schroff. To our knowledge, there are only 7 cases of Sarcoidosis of tongue reported till date.[14]

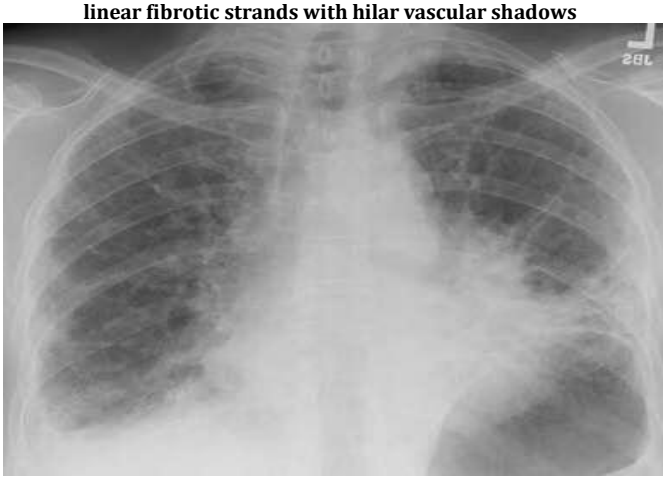
2. Case Report

A 40 year old male patient reported to the Department of Oral Medicine and Radiology with the chief complaint of missing teeth. The past medical history of the patient revealed that the patient had some severe breathing problem few years ago for which he was kept on long treatment and a follow-up for quite some time. He was also subjected to repeated chest radiography during same time.

Intra-oral examination of the patient revealed a multi-lobulated growth in relation to the dorsal aspect of the tongue which presented with irregular margins and mimicked the clinical picture of that of median rhomboid glossitis. (Figure 1) Incisional biopsies were taken from the tongue from two different areas which revealed non-caseating epithelioid granulomas infiltrated with "Langerhans cell type of multinucleated giant cells". Since the histopathological findings were compatible with sarcoidosis, in order to confirm the diagnosis, serum Angiotensin Converting Enzyme (S-ACE) and 24 hr. urine calcium were advised which revealed an elevated serum Angiotensin Converting Enzyme (S-ACE) value of 62.4U/L (normal value: 18-55 U/L) and a 24hr. urine calcium of 538mg (normal value <180 mg). Chest radiography revealed bilateral linear fibrotic strands with hilar vascular shadows. (Figure 2) Acid-fast bacilli were not found in smears from specimens of the tongue and culture for isolation of Mycobacteria sp. in Löwenstein-Jensen medium was negative. The radiograph of the maxillofacial region did not show any abnormality. Based on the above laboratory findings, the diagnosis of sarcoidosis was established. The patient was then referred to the higher centre for further investigation, opinion and needful.

Figure 1: revealing a multi-lobulated growth in relation to the dorsal aspect of the tongue presenting with irregular margins and mimicking median rhomboid glossitis

Figure 2: revealing a chest radiograph presenting with bilateral linear fibrotic strands with hilar vascular shadows



3. 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.[15] 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.[16] Moreover, both tumor necrosis factor (TNF) and TNF receptors are increased in this disease. 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.[17] Active sarcoidosis has also been associated with plasmatic hypergammaglobulinemia.[18]

The exact cause of the disease though is still not known; however, both genetic and environmental factors seem to play important roles.[19] 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 intention 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[20][21] to elevated serum angiotensin-converting enzyme (ACE)[22] and alkaline phosphatase[23] 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.[6]-[10] For patients with advanced pulmonary fibrosis from sarcoidosis, lung transplantation remains the only course for long-term survival.[24] Alternative therapies include methotrexate (MTX)[25], anti-malarials, chloroquine and hydroxychloroquine[26][27], cyclophosphamide[28][29] which has been used as a steroid-sparing treatment in patients with refractory sarcoidosis, azathioprine[30], chlorambucil[31] which may be beneficial in patients with progressive disease unresponsive to corticosteroids and in case, they are contraindicated, cyclosporine[32] which may be of benefit in progressive sarcoidosis resistant to conventional therapy and pentoxifylline[33], Leflunomide[34] and thalidomide[35][36] 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.[37] In some cases, oral involvement is the first, or only, manifestation of the disease.[38] Most of the lesions are seen to spontaneously resolve with time with the start of systemic therapy while some authors also suggest surgical excision for treatment of the oral soft tissue or jaws lesions.[39][40]

4. Conclusion

Although very rare, oral lesions of sarcoidosis may be the first or, the only presenting manifestations of this complex disease process. 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.

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