

Oral sarcoid granuloma associated with discoid lupus erythematosus: Case report

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Abstract:

Sarcoidosis is a chronic systemic disorder characterized by the formation of non-caseous granulomas. Oral manifestations are less frequent and may present as submucosal nodules. Because of its heterogeneity and similarity to other diseases, the diagnosis becomes challenging. **Objective:** To report a case of oral sarcoid granuloma in a patient with discoid lupus erythematosus. **Case report:** A female patient, complaining of a three-month swelling of the lower lip. Previous nasal lesion with a diagnosis of granulomatous dermatitis was also reported. The labial biopsy was performed, showing sarcoid granulomas. Other complementary exams were requested to verify systemic involvement by sarcoidosis. The lesion spontaneously regressed, and an 18-month follow-up showed no recurrence. Due to the absence of a probable etiological factor associated with the lesion triggering, the histological and clinical evidences, a probable coexistence of discoid lupus erythematosus and sarcoid reaction or early-stage sarcoidosis was suggested. **Conclusion:** This rare case highlights the possibility of association between lupus and sarcoid granulomas, emphasizing the need for the dental surgeon to contemplate the differential diagnosis of sarcoidosis or sarcoid reaction in patients with lupus who present oral lesions similar to those of the present case, since the oral lesions of lupus are polymorphic and have a varying presentation.

Keywords: Lupus Erythematosus, Discoid; Granuloma; Pathology, Oral; Sarcoidosis.

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INTRODUCTION

Sarcoidosis is a chronic systemic disorder, characterized by non-caseous granulomas formation. Jonathan Hutchinson reported the first case of sarcoidosis in 1879, but the term was introduced only in 1899¹. The lungs are the most affected organs, with approximately 90% of the patients presenting alterations in chest radiographs during the disease. Cutaneous, cardiac, ophthalmologic, hepatic and joint manifestations can be observed², in addition to sites rarely involved, such as the oral mucosa. Sarcoidosis is, therefore, a heterogeneous disorder, both in terms of clinical presentation and severity. Despite of significant advances in characterization of this disease, its etiology remains uncertain. It is suggested that genetic, environmental and infectious factors may corroborate to its triggering, and more evidence is conferred to genetic ones³⁻⁵.

Due to its heterogeneity, there are increasingly difficulties in establishing diagnostic criteria for sarcoidosis, since its clinical presentation may resemble other diseases. The main differential diagnosis is tuberculosis. However, other conditions may present lesions with clinical features like those of sarcoidosis, such as leishmaniosis, deep fungal infection and sarcoid reaction, and their occurrence should be considered. Currently, the association between clinical, radiographic and histological findings, after eliminating differential diagnosis, has been the basis for the diagnostic conclusion⁶.

The differentiation between sarcoidosis as an autonomic disease and the sarcoid reaction is a challenge. Sarcoid reaction associated with infectious or non-infectious antigens consists on a non-specific clinical manifestation of an existing disease. Nevertheless, no biomarker allows a precise distinction between these disorders⁷, since sarcoidosis can coexist and mimic other pathologies, such as Sjogren's syndrome, rheumatoid arthritis, discoid lupus erythematosus (DLE) and systemic lupus erythematosus (SLE)^{8,9}.

Diagnosis difficulties due to clinical similarities between sarcoidosis and DLE cutaneous lesions have been reported since 1966, and the histopathological examination is mandatory for establishing this diagnosis. Thus, this article aims to report a case of oral sarcoid granuloma associated with DLE.

CASE REPORT

A 54-year-old female patient was referred to the Stomatology Department of the Federal University

of Ceará for clinical evaluation of lesion located in the lower lip. At the extraoral clinical examination, there was slight lip asymmetry, as well as a desquamated whitish plaque and a scalp alopecia, with atrophic center and erythematous borders (Figure 1).



Figure 1. Clinical appearance of alopecia lesions on the scalp, evidencing atrophic center and erythematous borders.

The patient reported having a previous similar lesion on the left ear and a lesion on the nose. Nodular growths were observed in the nasal and lower lip regions, which emerged simultaneously. The labial lesions presented an evolution of three months of duration. The nasal lesion was previously biopsied at the Dermatology Department of the Walter Cantídio University Hospital of the Federal University of Ceará, Brazil, diagnosed as a chronic non-caseating granulomatous dermatitis. In the lower lip region, nodular, painless, normochromic, sessile, and firm palpation increases were observed, measuring approximately 2 to 3 cm. (Figure 2).

A 15-year diagnosis of discoid lupus erythematosus (DLE), which was not under treatment, was emphasized on medical history. Furthermore, the patient underwent a total hysterectomy, performing, therefore, hormone replacement therapy. After DLE diagnosis, chloroquine treatment was performed for 11 years.

Several dose adjustments due to joint and ophthalmological symptoms were performed. However, due to persistent symptoms, the medication was

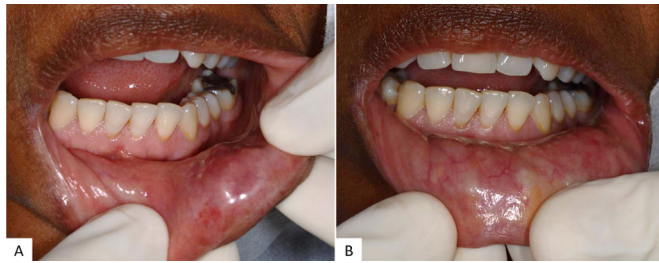


Figure 2. Multiple normochromic nodules in the lower lip, firm to palpation, measuring approximately 2 x 3 cm (A and B).

discontinued. Another therapeutic alternative was initiated with thalidomide. Nevertheless, the patient presented adverse reactions to the medication, such as tremors, palpitations and dizziness, resulting in its suspension and follow-up of the dermatological lesions.

Clinical features of the lower lip lesions, associated with a histopathological report of chronic granulomatous dermatitis of the nasal one, suggested the clinical diagnosis of a possible granulomatous lesion. However, a meticulous investigation was required, since granulomatous lesions may be associated with several other causes, like genetic or environmental factors, infectious or idiopathic organisms. Thus, differential diagnosis including infectious (tuberculosis, leishmaniosis and deep fungal infection) and non-infectious (foreign body reaction and sarcoidosis) diseases with granulomatous lesions, associated with DLE, were considered.

Examinations were requested, including complete blood count, Montenegro's intradermal reaction, electrolyte dosage, hepatic enzymes (alkaline phosphatase, TGO, TGP), urine tests (creatinine and calcium), immunoglobulin and angiotensin converting enzyme (ACE) tests. Other examinations, such as echocardiogram, chest computed tomography and x-ray were also requested.

The patient presented mild anemia [erythrocytes in millions 4.07 / mm³, reference value (RV): 4.3 to 5.9 / mm³; hemoglobin 11.8 g / dL, RV: 13.7 to 17.7 g; hematocrit 35,3%, RV: 41,0 to 54,0%]; high concentrations of ACE (241,0 U/L; RV: 15,8 to 122,3 U/L) and immunoglobulins (IgG 2.866,0 mg/dL; RV: 700,00 to 1600,00 mg/dL). No other changes were observed in other exams. Medical history, associated with histopathological findings, high concentrations of ACE and immunoglobulins suggest the diagnosis of sarcoid granuloma associated with LED.

An incisional biopsy was performed in one of the lower lip lesions (Figure 3), showing fibrous connective tissue containing non-caseous, compact, approximately rounded and uniform granulomas, without lymphocyte

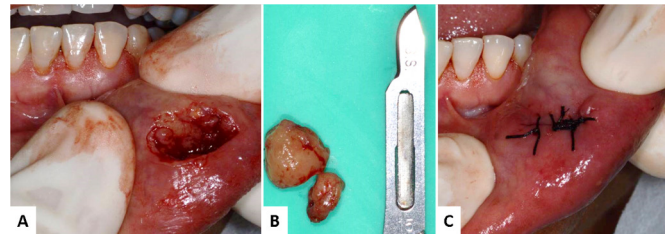


Figure 3. Clinical aspect of the lower lip region during biopsy (A), fragments of tissue sent for histopathological examination (B) and clinical aspect of the region after biopsy (C).

halo, separated by thin fibrous tissue. These granulomas invaded and dissociated areas of skeletal striated muscle, but preserved nerve bundles (Figure 4).

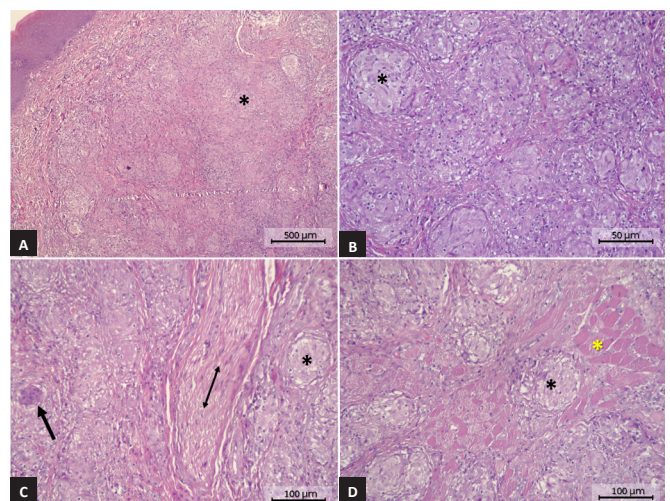


Figure 4. Photomicrographs of incisional biopsy, showing: (A) keratinized oral epithelium, supported by a fibrous lamina propria, where there are multiple granulomatous formations (black asterisks) in the depths, approximately rounded and uniform, separated by thin trunks of compact fibrous tissue (HE, 100x). (B) compact granulomatous formations, formed by epithelioid histiocytes, permeated and surrounded by rare lymphocytes (naked granulomas) and collagen bundles (HE, 400x). (C) granulomatous formations preserving nerve bundles (double arrow), evidencing multinucleated giant cell (black arrow) (H & E, 200x). (D) Granulomatous formations invading and dissociating areas of skeletal muscle (yellow asterisks) (H & E, 200x).

Wade-Fite and Grocott stains revealed, respectively, negative reaction to acid-alcohol resistant bacillus and fungi in the periphery and in the interior of the granulomas. In addition, an immunohistochemical assay was performed to detect *Leishmania braziliensis*, which was also negative. No changes were observed in imaging tests.

Due to the lack of well-established research protocols that distinguish sarcoid reaction from true sarcoidosis, as well as the clinical difficulty in performing the differential diagnosis of these two conditions, we cannot rule out the hypothesis of early-stage sarcoidosis associated with DLE.

The hypothesis of a sarcoid reaction associated with DLE was considered as a possible diagnosis, since the patient did not present clinical signs [pulmonary symptoms of cough, dyspnea and chest pain, as well as clinical findings on skin (plaque eruptions), eyes (alterations in vision, iridocyclitis) and joints (arthritis)] suggestive of sarcoidosis. Radiological or laboratory signs of involvement of other organs (kidney, liver, heart and lung) by sarcoidosis were not evidenced either.

During follow-up, the labial lesions regressed spontaneously. The same tests previously requested were repeated, and no abnormality was observed, mainly in relation to ACE levels and immunoglobulins, which returned to normal levels.

No evidence of lesion recurrence was observed in the eighteenth month of follow-up (Figure 5). The patient continues to be accompanied by a multidisciplinary team, including Dentistry, Rheumatology, Dermatology and Ophthalmology.



Figure 5. Clinical aspect of the lower lip region, showing absence of volume changes (18 months).

DISCUSSION

The DLE presents as erythematous plaques, which tend to regress spontaneously, causing scars. The main affected areas are face, scalp, ear and neck. Lesions on the oral mucosa may also occur, typically manifesting as chronic plaques or oral lichen-plane-like lesions, cheilitis and plaque-like palatal lesions. In patients with oral lesions, 56% also have cutaneous lesions. These lesions can often persist for months to even years, causing discomfort in most cases¹⁰.

In the present case, the synchronous occurrence of lower lip and nose lesions, the latter previously diagnosed as a granulomatous lesion, did not demonstrate clinical or histopathological similarities with typical lesions of DLE.

In view of the absence of etiological factor associated with the occurrence of lip lesions and the histological evidence of a sarcoid granuloma, a probable coexistence of LED and sarcoidosis cannot be ruled out, since both diseases can occur simultaneously or mimic one another¹².

For decades, it was believed that infectious agents were responsible for the occurrence of sarcoidosis. However, epidemiological and genetic studies have shown a genetic predisposition associated with environmental factors^{13,14}. Besides, it is suggested that similarities between exogenous and endogenous agents may induce an autoimmune process (molecular mimicry), leading to the formation of specific granulomas in the affected organs⁸.

Previous genetic studies have established that variants in class I and II locus of human leukocyte antigens (HLAs) play roles in the susceptibility of developing sarcoidosis, as well as other autoimmune diseases, including lupus⁹. Additionally, evidence suggests that, given the similarities in the immunophenotyping profiles of patients with DLE and SLE, the pathogenesis of these two disorders also present resemblance between themselves¹⁵.

The first clinical association between SLE and sarcoidosis was described in 1945, in which two patients with SLE presented non-caseous granulomas in the lungs, lymph nodes and blood vessels at the autopsy, thus suggesting the relationship between both diseases¹⁶. Since then, there have been reports of more than 20 cases in the literature that propose this simultaneous occurrence¹⁷.

However, there are no pathognomonic clinical features of sarcoidosis. Furthermore, it is known that multiple organs can be affected. Respiratory tract manifestations are the most common, and symptoms may consist of dyspnea, cough, and chest pain. Other symptoms may be seen in the skin (eruptive and / or plaque-like lesions), joints (arthritis), eyes (iritocyclitis), heart (arrhythmias), and many other sites.

Upon clinical examination of the head and neck region, there may be an increase in the volume of parotid and/or submandibular glands. Some patients may also present hepatomegaly and/or splenomegaly, which also contributes to the various hematological alterations. Oral involvement of sarcoidosis is uncommon¹⁸, although there is no precise data on the incidence that it occurs. The lesions are usually asymptomatic, affecting buccal mucosa, followed by gingiva, lips, floor of mouth, tongue and palate. Clinical features include submucosal nodules, firm on palpation, with overlying mucosa unchanged or

with granular macules. Ulceration may occasionally occur, making them secondarily infected and symptomatic^{19,20}.

The histopathological findings of sarcoidosis are independent of the involved organ or the clinical presentation of the lesion. The epidermis is normally unchanged, whereas the dermis exhibits a superficial and deep infiltrate of granulomatous formations, composed of epithelioid cells and discreetly surrounded by sparsely arranged lymphocytes (hence also called naked granulomas). Such microscopic characteristics were also evidenced in this case. However, histopathological findings alone do not allow the precise differentiation between a sarcoid reaction and true sarcoidosis²¹.

Because it is a diagnosis of exclusion, there are no well-established criteria for a diagnostic conclusion of sarcoidosis. Despite the various clinical manifestations inherent to this disease, histological confirmation is indispensable for the definitive diagnosis. Heinle and Chang⁶ proposed, in 2014, major (presence of non-caseous granulomas and absence of acid-alcohol resistant bacillus on biopsy) and minor (erythema nodosum, hypercalciuria, anemia, pancytopenia, cardiac arrhythmia, hilar adenopathy on chest radiography, uveitis, spondyloarthritis, elevated immunoglobulins and liver enzymes and bronchoalveolar lavage findings) criteria, in order to guide clinical evidence to a more accurate diagnosis⁶. Additionally, ACE levels are elevated in most of the patients⁵. The patient of the present case presented two major criteria and two minor criteria, in addition to elevated levels of ACE, which may perhaps suggest a sarcoidosis associated with DLE.

However, pulmonary manifestations are the most commonly found and corroborate for the diagnosis of sarcoidosis^{5,22}. These findings were not observed in the present case, in which chest X-ray and computed tomography revealed no evident pulmonary alterations. Additionally, there were no signs of cardiac, renal and hepatic involvement by the disease.

The clinical course of sarcoidosis is variable and may present as asymptomatic or symptomatic. Spontaneous resolution of the condition often occurs, even in the absence of treatment, as was observed in the patient of this case. Due to its clinical heterogeneity, there are no well-established therapeutic protocols for the disease, and corticotherapy is mostly indicated for cases of severe ocular involvement, pulmonary involvement in stages 2 and 3, neurological, renal, cardiac and cutaneous manifestations, as well as splenomegaly. After the diagnostic hypothesis, a 3 to 12 months follow-up

is recommended to determine the clinical course of the disease^{1,19}. In the present case, after 18 months of follow-up, no recurrence of the lesions was observed.

About 60% of the cases of oral lesions microscopically diagnosed as sarcoid granulomas resulted in a subsequent diagnosis of sarcoidosis¹⁹. However, the differentiation between a sarcoid reaction and sarcoidosis itself is still unclear. Some authors recommend the characterization of the genetic risk for sarcoidosis, as well as the elaboration of a genetic mapping for a better understanding of the two conditions²³. However, these procedures are not used in the diagnostic routine.

The importance of the dental surgeon in the early diagnosis of oral sarcoid granulomas, likewise their follow up, is emphasized. This rare case highlights the possibility of association between lupus and sarcoid granulomas, focusing in the need for the dental surgeon to contemplate the differential diagnosis of sarcoidosis or sarcoid reaction in patients with lupus who present oral lesions similar to those of the present case, since the oral lesions of lupus are polymorphic and have a varying presentation. Besides, further researches in order to discover tools that assist in the differentiation between sarcoidosis and sarcoid reaction are necessary.

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