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Clinicopathological features of granulomatous inflammatory lesions: a 69-year retrospective study

Thaís de Lima Araújo[1], Rubens Signoretti Oliveira Silva[1], Victor Zanetti Drumond[1], Ricardo Santiago Gomez[1], Vanessa de Fátima Bernardes[2*]

[1] Department of Oral Surgery, Pathology, and Clinical Dentistry, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

[2] Department of Pathology, Biological Sciences Institute, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

Corresponding author:
Vanessa F. Bernardes, DDs, MSc, PhD
Department of Pathology, Biological Sciences Institute, Universidade Federal de Minas Gerais.
Av. Presidente Antônio Carlos, 6627, third floor, block G, room 60,
Belo Horizonte, MG, Brazil. 31.270-901.
E-mail: bernardesvf@hotmail.com
Phone number: +55 (31) 99119-5646

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Aim: To evaluate the clinicopathological features of granulomatous inflammatory lesions through a retrospective analysis, emphasizing the importance of early and accurate diagnosis for timely treatment and improved prognosis. **Methods:** A retrospective cross-sectional study analyzed archived data (1953–2022) approved by the Research Ethics Committee (CAAE: 5.429.194). Samples with clinical and histological diagnoses of granulomatous lesions, nonspecific chronic inflammations, paracoccidioidomycosis, leishmaniasis, and tuberculosis were included. Initially, 88 cases were identified, and 28 cases met inclusion criteria after exclusions. **Results:** Granulomatous lesions predominantly presented as irregular ulcers (67.9%), located mainly on the tongue (32.1%), erythematous (46.4%), and symptomatic (50.0%). Histologically, lymphocytes and macrophages were present in all cases, while Langhans-type and foreign body-type giant cells appeared in 69%, and caseous necrosis was observed in 32%. **Conclusions:** Biopsy is essential for diagnosing oral lesions. Understanding the prevalence and clinicopathological features of granulomatous inflammatory lesions is critical for developing preventive measures and effective treatment strategies which directly influences the individual's prognosis, particularly considering the potential burden of these diseases.

Keywords: Granulomatous disease, chronic. Granuloma. Histology. Oral ulcers. Pathology.

Introduction

Granulomatous diseases arise from complex immunopathological processes in which the immune system aims to contain a persistent aggressor agent but fails to eliminate it. The common hallmark of these diseases is the development of granulomas. This complex mechanism is essentially characterized by overstimulation of the immune system, leading to a type IV hypersensitivity reaction[1,2]. Granulomatous responses can be classified into different types, such as necrotizing granulomas, non-necrotizing granulomas, and foreign body giant cell reactions[3]. Mycobacterial infections are typically associated with necrotizing granulomas, while sarcoidosis is a common cause of non-necrotizing granulomas[3]. A thorough, pattern-based diagnostic approach, incorporating clinical context, is essential for accurate identification of the underlying cause and optimal treatment planning[3].

In tropical regions, including areas such as Latin America and Africa, infectious diseases marked by granulomatous inflammation are highly prevalent. Tuberculosis (TB), one of the most common diseases, imposes a substantial burden on these populations. TB can manifest beyond the lungs, presenting as extrapulmonary tuberculosis (EPTB), which may involve the oral cavity among other sites[4]. Clinically, oral lesions of EPTB present as ulcers with a granulomatous center and a whitish halo, most commonly on the dorsum of the tongue[5]. Tongue manifestations may appear as ulcers, nodules, fissures, or granulomas, with ulcers being irregular, hardened, and often painful[6]. Histological findings include lesions known as tubercles, described as characteristic granulomatous inflammatory reactions against *Mycobacterium tuberculosis* (MTB) bacilli mediated by host immune cells[7]. The granulomas, whether caseous or not, contain bacilli within macrophages, alveolar exsudate rich in fibrin, lymphocytes, and multinucleated giant cells near the fibroblastic border[7].

In a similar fashion, mucocutaneous leishmaniasis has a widespread global distribution, affecting regions across Americas, Asia, and Africa with a notably higher incidence of lesions affecting the oral mucosa[8]. They are characterized by vegetative and ulcerative lesions, accompanied by coarse granulations, with painful symptoms that can sometimes cause dysphagia and odynophagia due to nasal involvement, leading to malnutrition and prolonged healing time due to reduced food intake[9]. The main histopathological pattern of this disease is typically described as a histioplasmacytic infiltrate (cellular exsudative pattern), associated with a granulomatous reaction, which may or may not include necrotic centers[10]. Furthermore, among the reaction patterns presented, one closely resembles those found in tuberculosis, as organized granulomas with epithelioid cells, Langhans-type giant cells, and an outer lymphocytic crown, termed the exsudative and tuberculoid reaction, can be observed[10].

In cases of granulomatosis with polyangiitis (Wegener's granulomatosis), the most characteristic initial lesion presents as hyperplastic gingiva, with swollen areas of red-purple coloration and interdental papillae covered by diffuse petechiae. Moreover, due to the granular appearance of the gingival surface lesions, the term "strawberry gingiva" is used to refer to the affected gingiva[11]. However, in most cases, histopathological findings are less specific, demonstrating acute or chronic inflammation, as well as pseudoepitheliomatous hyperplasia[11].

A correct and early diagnosis of any disease is crucial for promptly initiating treatment, which directly impacts the individual's prognosis, particularly given the potential burden of these diseases. Therefore, this study aimed to evaluate the clinicopathological characteristics of granulomatous inflammatory lesions through of a retrospective survey analysis.

Material and Methods

Ethical issues and reporting guideline

This study was approved by the Ethics and Research Committee (COEP) of Universidade Federal de Minas Gerais (UFMG) under protocol number: 5.429.194. The research was conducted at the Oral and Maxillofacial Pathology Laboratory of the School of Dentistry at Universidade Federal de Minas Gerais (FAO-UFMG).

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional committee and the 1964 Helsinki Declaration[12], including its amendments. Informed consent was obtained from all participants, and their anonymity was maintained.

The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[13].

Study design and sample setting

This is a cross-sectional and retrospective study of archived data in an anatomopathological diagnostic center. The selected samples were obtained from individuals undergoing soft tissue biopsies and were archived in the Oral and Maxillofacial Pathology Laboratory of FAO-UFMG. The material used was fixed in formalin and embedded in paraffin.

Among the samples, those with clinical diagnostic hypotheses and histological diagnoses of lesions with similar characteristics were selected, including granulomatous inflammations, nonspecific chronic inflammations, paracoccidioidomycosis, leishmaniasis, tuberculosis, among others. The period evaluated was from 1953 to 2022. The following exclusion criteria were applied: samples with insufficient material for analysis, intraosseous biopsies, and samples that did not present histological characteristics of chronic granulomatous lesions.

Data gathering and diagnostic procedure

Through information stored in the digital system of the Oral and Maxillofacial Pathology Laboratory of the Department of Oral Surgery, Pathology and Clinical Dentistry of FAO-UFMG, the following information was collected from the selected patients: code, name, age, gender, type of material, disease duration, type of lesion, staining, symptomatology, size (in mm), material collection method, manifestation, radiographic findings, location, other observations, clinical diagnosis, macroscopic picture, microscopy, diagnosis and date. Subsequently, searches were made for formalin-fixed paraffin-embedded (FFPE) samples, Hematoxylin and Eosin (H&E) stained histological slides, and filled-out forms for histological analysis.

All H&E stained slides were reviewed by experienced oral pathologists, considering the following histopathological criteria: presence of areas with granuloma formation, presence or absence of caseous necrosis areas, and inflammatory infiltrate composed of macrophages, lymphocytes, and multinucleated giant cells.

Results

Sample characteristics

Eighty-eight cases of Granulomatous Inflammatory Lesions (GIL) were selected, with 46 males and 42 females. Of these, 10 were excluded due to insufficient material for analysis, 6 were excluded as they were intraosseous biopsies or biopsies from extra-oral regions, and 44 were excluded for not presenting compatible histological characteristics. Thus, 28 cases were selected. Considering that the twenty-eight selected cases revealed a diverse array of clinical and histological diagnoses, the complexity of analyzing granulomatous inflammatory and infectious conditions is underscored. Table 1 and Table 2 showcases a minutely description of descriptive statistics of demographic and clinical features.

Table 1. Frequency data of selected samples

Variable	N	(%)
Age		
Under 20 years old	06	(21.4)
21 to 60 years old	15	(53.6)
Over 60 years old	07	(25.0)
Gender		
Female	09	(32.1)
Male	19	(67.9)
Lesion Type		
Ulcer	19	(67.9)
Nodule	01	(03.6)
Cistic	02	(07.1)
Tumor	03	(10.7)
Vesicular-bullous	01	(03.6)
Plaque	01	(03.6)
Not informed	01	(03.6)
Lesion Color		
Erythematous	13	(46.4)
Similar to oral mucosa	04	(14.3)
Purple	01	(03.6)
White	01	(03.6)
Brown	01	(03.6)
Not informed	08	(28.6)

Continua

Continuação		
Symptomatology		
Symptomatic	14	(50.0)
Asymptomatic	05	(17.9)
Not informed	09	(32.1)
Biopsy Type		
Incisional biopsy	21	(75.0)
Excisional biopsy	03	(10.7)
Curettage	01	(03.6)
Not informed	03	(10.7)
Presentation		
Primary	22	(78.6)
Recurrent	02	(07.1)
Not informed	04	(14.3)
Localization		
Tongue	09	(32.1)
Buccal Mucosa	03	(10.7)
Palate	05	(17.9)
Lip	04	(14.3)
Inferior alveolar ridge	03	(10.7)
Superior alveolar ridge	02	(07.1)
Submandibular region	02	(07.1)
Size (mm)		
Under 10mm	02	(07.1)
10 to 30 mm	13	(46.4)
Over 30 mm	02	(07.1)
Multiple	01	(03.6)
Not informed	10	(35.7)
Evolution Time (Months)		
Less than 6 months	12	(42.9)
6 to 12 months	08	(28.6)
Over 12 months	01	(03.6)
Indeterminate	05	(17.9)
Not informed	02	(07.1)

Table 2. Means and standard deviation of ages, progression time, and lesion size.

Variable	Mean (SD)	Min - Max	Included	
			n	%
Age (years)	44.4 (22.0)	02 – 94	28/28	(100%)
Progression Time (Months)[a]	06.4 (5.9)	0.3 – 24.0	21/28	(75.0%)
Size (mm)[b]	22.4 (15.3)	5 – 60	17/28	(60.7%)

Notes: Max, Maximum; Min, Minimum; mm, millimeter; SD, Standard Deviation; [a]missing data from 7 cases of this group;
[b]missing data from 11 cases of this group.

The most encountered cases included clinical diagnosis of tuberculosis and paracoccidioidomycosis, both of which, while frequently hypothesized, necessitate confirmation through complementary tests for accurate diagnosis. The lesions characterized as chronic inflammatory, whether with or without granuloma formation, highlight the need for further investigations, such as histopathological analysis and specific laboratory tests, to exclude other infectious diseases, including leishmaniasis and syphilis. Additionally, differential diagnoses include systemic disorders such as sarcoidosis, granulomatosis with polyangiitis, Crohn's disease, histiocytosis, as well as squamous cell carcinoma. This diversity of diagnoses emphasizes the importance of clinical and microscopic correlation, reinforcing the necessity for a comprehensive approach to the effective management of these conditions. Supplementary File 1 provides all relevant data.

Histological findings

Histological slides stained with H&E of granulomatous inflammatory lesions exhibit distinct and complex morphological characteristics. A prominent finding is the formation of granulomas, which are nodular structures composed of a central core of activated macrophages, often transformed into epithelioid cells with abundant cytoplasm and elongated nuclei (Figure 1A and Figure 1B). These granulomas are intermingled with multinucleated giant cells, formed by the fusion of multiple macrophages, which may display nuclei arranged in a semicircle (Langhans-type giant cells) or dispersed randomly (multinucleated giant cells foreign-body-type), and often exhibit areas of caseous necrosis characterized by the loss of cellular structure and the presence of debris from dead cells, a hallmark of granulomatous inflammation typically seen in response to certain infections or chronic inflammatory conditions. (Figure 2A and Figure 2B). Granulomas of the foreign body type are characterized by the presence of non-biological materials, such as sutures or splinters, which are not directly phagocytosed by macrophages, autoimmune reactions or frequently caused by low-virulence and highly resistant (immunogenic) aggressors, in which epithelioid cells do not form typical palisades (Figure 2B). These circumstances induce a granulomatous response with a distinct histological pattern, often featuring multinucleated giant cells that attempt to enclose the lesion to mitigate its progression. Additionally, there is peripheral infiltration of lymphocytes and plasma cells, with lymphocytes showing small nuclei and scant cytoplasm, and plasma cells having an eccentric nucleus and basophilic cytoplasm due to rough endoplasmic reticulum (not demonstrated). Fibroblasts may also be present, contributing to the formation of fibrous tissue around the granulomas, signaling a chronic response and an attempt to isolate the irritant. The GIL samples revealed varied morphological components: epithelioid cells were observed in 23% of cases, histiocytes in 38%, Langhans-type giant cells and foreign bodies were found in 69% of the cases, and caseous necrosis in 32%. Additionally, lymphocytes and macrophages were present in all analyzed samples. Table 3 shows all histological characteristics of granulomatous inflammatory lesions found in the samples.

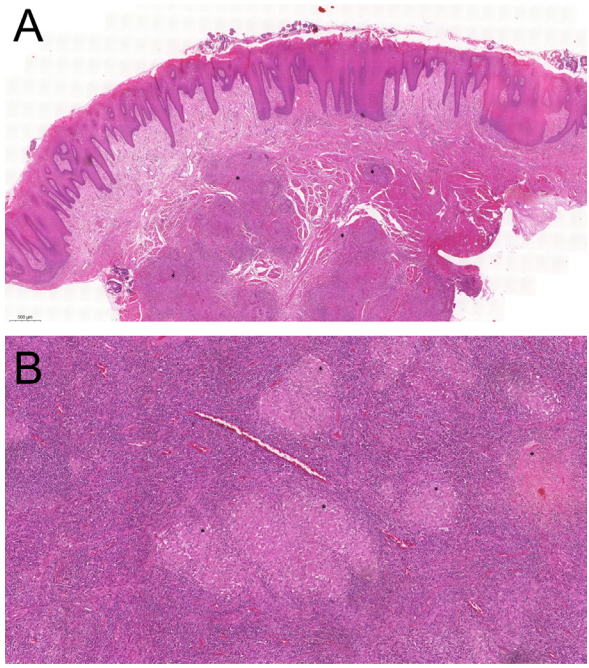

Figure 1. Histological features of granulomatous inflammatory lesion exhibiting areas of granuloma formation (A) H&E, x20. (B) Higher magnification showing detailed granuloma structure, H&E, x100.

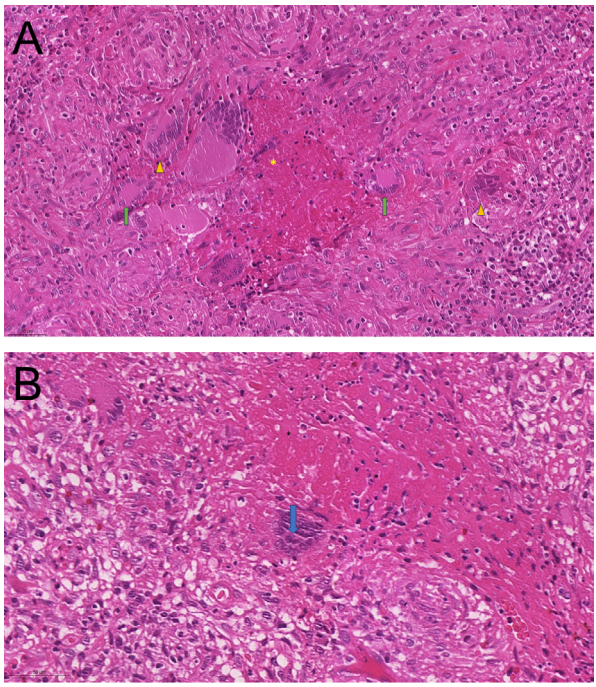

Figure 2. Histological features of caseous necrosis. (A) Area of caseous necrosis marked with an asterisk, multinucleated giant cells of foreign-body type indicated by the arrowhead, and Langhans-type giant cell at the arrow (H&E, 400x). (B) Area of caseous necrosis marked with an asterisk, multinucleated giant cells of foreign body type at the arrow (H&E, 400x).

Table 3. Histological characteristics of granulomatous inflammatory lesions

Sample	Histological Characteristics					
	Granuloma-forming cells			Presence/ absence of giant cells	Type of giant cells (Langhans and Foreign Body)	Necrosis (caseous, non-caseous and absent)
	Epithelioid cells	Lymphocytes	Macrophages			
1	+	+	+	+	Lg	CN
2	+	+	+	+	Lg	-
3	-	+	+	-	-	-
4	+	+	+	+	Lg / FB	CN
5	+	+	+	+	Lg / FB	CN
6	+	+	+	+	Lg / FB	-
7	+	+	+	+	Lg / FB	-
8	-	+	+	+	Lg /FB	-
9	-	+	+	-	-	-
10	-	+	+	-	-	-
11	+	+	+	+	Lg / FB	CN
12	-	+	+	-	-	-
13	+	+	+	-	-	CN
14	+	+	+	+	Lg / FB	CN
15	-	+	+	+	FB	-
16	+	+	+	+	Lg / FB	-
17	-	+	+	+	FB	-
18	-	+	+	+	FB	-
19	-	+	+	+	FB	-
20	+	+	+	+	Lg	CN
21	+	+	+	+	Lg / FB	CN
22	+	+	+	+	Lg / FB	CN
23	-	+	+	+	FB	-
24	-	+	+	+	Lg / FB	-
25	-	+	+	+	FB	-
26	-	+	+	-	FB	-
27	-	+	+	-	-	-
28	+	+	+	-	FB	-

Notes: Analysis of presence and absence of specific cells found in granulomas with or without caseous necrosis from biopsies of nonspecific granulomatous inflammatory lesions using H&E staining (+): presence; (-): absence; Abbreviations: FB: Foreign body type giant cells; Lg: Langhans type giant cells; CN: Caseous necrosis.

Discussion

The present identified that the most prevalent features in oral lesions in GIL included irregular ulcers (67.9%), erythematous appearance (46.4%), symptomatic presentation (50.0%) with the most frequent location being the dorsum of the tongue (32.1%). Kohli and colleagues[14] also observed consistent histopathological features in GIL cases, nothing the presence of epithelioid cells, lymphocytes, multinucleated giant

cells, including both Langhans and foreign body types, across all analyzed samples. In alignment with Kohli's findings, this study found epithelioid cells in 23% of cases, histocytes in 38%, and Langhans-type giant cells along with foreign body cells in 69%. Additionally, lymphocytes and macrophages were present in all instances examined, further reinforcing the characteristic cellular profile associated with GIL.

Biological sex is a significant factor in health outcomes, with men being more affected by certain conditions due to genetic, hormonal, and lifestyle differences. However, these disparities are also shaped by social determinants, including limited healthcare access, socioeconomic challenges, and lower adherence to preventive practices, which are more prominent in men due to societal roles and expectations[15]. In this study, 67.9% of the sample belonged to the male sex, converging with literature data. Regarding age, in this study, the highest rate of involvement was in individuals in the fifth decade of life, with an average age of 44.4 years. Several hypotheses merit consideration, particularly tuberculosis, as its social profile predominantly affects men in economically productive age groups, likely due to factors such as increased exposure and socioeconomic challenges that hinder access to healthcare and preventive measures[15].

To understand the epidemiological profile of the individuals mays plays a pivotal role in the understanding of the dynamics of some entities approached in this study, especially TB, paracoccidioidomycosis, and leishmaniasis. These entities share a common epidemiological profile, they are common in tropical regions, especially Africa and Latin America, and sometimes affects and acts as a burden in most unprivileged individuals[16-18]. A concise understanding of the clinical features and also the histopathological features of these diseases is crucial to the treatment and prognosis. A concise and briefly stablished diagnosis can be effective to manage the disease in initial phase and prevent sequels or even death, particularly in cases of TB, that accounts about 1.3 million of death in 2013[18]. A cross-sectional assessment compiling clinical and pathological findings, along with demographic characteristics, has a significant impact, drawing the attention of oral medicine providers and pathology practitioners to better understand this disease.

In this context, TB may present in the oral cavity as ulcerated lesions on the palate, lips, or tongue, often accompanied by persistent cervical lymphadenopathy[19]. Primary oral tuberculosis, resulting from direct inoculation, is rare; more commonly, it arises secondarily through hematogenous or lymphatic spread, or by direct extension from adjacent structure[7,19]. Autoinoculation can also occur in patients with pulmonary tuberculosis, where infected secretions come into contact with injured oral mucosa[7]. Histopathologically, oral tuberculosis is characterized by the presence of caseous granulomas, composed of activated macrophages, epithelioid cells, and lymphocytes, often with central caseous necrosis. These granulomas are typically encased in fibrous tissue, and multinucleated Langhans giant cells are commonly observed[7]. Syphilis presents infrequently with oral manifestations during its primary stage, typically as a painless, self-limiting ulcer, often on the tongue. However, oral lesions during the secondary stage can complicate differential diagnosis, as they present with ulcers characterized by whitish or reddish borders, sometimes covered by a fibrinous pseudomembrane[20]. While histopathol-

ogy is rarely necessary for diagnosis, tissue samples may reveal a dense infiltrate of plasma cells and lymphocytes in the superficial lamina propria, occasionally extending into the deeper stroma. Additional features include epithelial hyperplasia, obliterative endarteritis, and ulceration with fibrinopurulent exudate or abscess formation[21].

Leishmaniasis, a parasitic infection caused by protozoa, can also affect the oral cavity, typically in its mucocutaneous form, which involves both oral and nasal mucosa. The tongue is the most commonly affected site[22,23]. Lesions are often ulcerative and granulomatous in appearance. Histologically, non-necrotizing granulomatous inflammation is observed in the subepithelial region, with macrophages containing amastigotes—the intracellular form of the parasite. Additionally, the epithelium may exhibit pseudoepitheliomatous hyperplasia, a thickening and hyperplasia of the epithelial layer that can resemble malignant processes[22]. Paracoccidioidomycosis, a fungal infection, may manifest as moriform stomatitis, with ulcerated lesions having an erythematous, granular base and hemorrhagic points[24]. These lesions can appear anywhere in the oral cavity[24]. Histopathologically, the lesions show pseudoepitheliomatous hyperplasia and an inflammatory infiltrate of both mononuclear and polymorphonuclear cells in the lamina propria. Granulomatous reactions with yeast forms of *Paracoccidioides brasiliensis* are often present, appearing as ovoid cells with a double refractive membrane[23,24].

These infectious and granulomatous conditions share certain histopathological features, such as the presence of granulomatous inflammation and multinucleated giant cells in tuberculosis and paracoccidioidomycosis. However, key differences—such as the caseous necrosis in tuberculosis, intracellular amastigotes in leishmaniasis, and the fungal yeast forms in paracoccidioidomycosis—are crucial for accurate diagnosis. Clinical evaluation, serological testing, and histopathological examination remain essential for differentiating these diseases and ensuring appropriate management.

In a comparable manner a thorough understanding of the epidemiological profiles of individuals affected by autoimmune granulomatous diseases, such as granulomatosis with polyangiitis (GPA), sarcoidosis, Crohn's disease, and histiocytosis, is essential for grasping the broader implications of these conditions on public health. These conditions, while distinct in their pathophysiology, share several key epidemiological traits, including the formation of granulomas as a hallmark feature. Additionally, they predominantly affect young adults, with a predominance in men, particularly in GPA and Crohn's disease, suggesting the potential role of sex-related factors in disease development and progression[25]. The gender disparity observed in these diseases, where men are more commonly affected, may be linked to factors such as hormonal influences, genetic predisposition, and environmental exposures[25]. Moreover, early identification of clinical manifestations and histopathological changes is critical for the timely and effective management of these diseases. In Crohn's disease, for example, early recognition of intestinal obstruction—a common complication—can significantly reduce the risk of intestinal perforation or the need for surgical intervention[26].

In light of the foregoing, granulomatosis with polyangiitis (GPA) is a rare systemic disorder of unknown etiology, characterized by necrotizing granulomatous inflammation of the respiratory tract, glomerulonephritis, and vasculitis[27]. Oral manifestations include nonspecific erosive or ulcerative lesions, as well as hyperplastic gingivitis, often referred to as "strawberry gingivitis"[27]. The diagnosis is confirmed when necrotizing granulomas and granulomatous vasculitis are observed in gingival biopsies[28]. Sarcoidosis may affect the oral cavity, gums, tongue, lips, palate, bone structures, and salivary glands. Clinical presentation varies according to the lesion site. Gingival involvement often mimics drug-induced gingivitis, while nodules resembling abscesses or tumors may develop on the palate, lips, and mucosa[29]. Sarcoid granulomas are composed of epithelioid cells, T lymphocytes, plasma cells, and fibroblasts with areas of fibrinoid necrosis and hyalinosis[30]. In Crohn's disease, oral lesions may present as deep linear ulcers, gingival hyperplasia, and "cobblestoning" of the mucosa, with associated lymphadenopathy[31]. Histological examination reveals non-caseating granulomas, deep fissures in the mucosa, and Langhans-type giant cells[31]. Langerhans cell histiocytosis (LCH) is an acquired clonal disorder with variable clinical presentation. Oral manifestations include gingival hyperplasia and paresthesia[32]. Predominantly affecting males and children aged 2–18 years, LCH is histologically characterized by lymphocytic infiltrates and Langerhans cells[32].

Another condition that should be included in the differential diagnosis, given its similar clinical presentation and epidemiological profile, and its high prevalence in the oral cavity, is squamous cell carcinoma (SCC), which is the most common malignant tumor of the oral mucosa. Epidemiologically, SCC predominantly affects older adults, with a notably higher incidence in men compared to women[33]. This disparity is largely attributed to the greater prevalence of risk factors associated with male behavior, particularly the higher rates of tobacco use and alcohol consumption in this group. Studies indicate that smoking is one of the most significant risk factors for the development of SCC, as it contributes to carcinogenesis in the oral cavity through the induction of genetic mutations and the promotion of inflammatory processes[33]. Similarly, alcohol consumption, especially in combination with smoking, significantly amplifies the risk of SCC due to its synergistic effect on epithelial cell damage and tumor promotion[33]. Oral squamous cell carcinoma often starts asymptomatically, becoming painful as it advances. It commonly affects the tongue, lips, and floor of the mouth, typically presents as an ulcer, lump, or a red/white lesion, and may also manifest as a non-healing sore that should raise suspicion if lasting over two weeks[34]. Oral squamous cell carcinoma develops from the epithelial lining of the oral cavity, pharynx, and larynx. Histopathologically, it is distinguished by varying levels of cellular atypia and squamous differentiation, which are key factors in determining its diagnosis and prognosis[35].

Effective management strategies, guided by a thorough understanding of the clinical and pathological features of these diseases, can prevent serious long-term complications and improve the overall prognosis for affected individuals. By considering individual risk factors, healthcare providers, including physicians and pathologists, can refine diagnostic approaches, optimize treatment strategies, and ultimately improve patient outcomes. The significance of biopsy in oral lesions is underscored, as his-

topathology is a commonly used technique for investigating lesions and establishing a diagnosis. This study has certain limitations, including the analysis of historical slides and the lack of complete data in patient records, which may have been lost or inadequately documented. These gaps compromise the detailed analysis of cases. Furthermore, dentists face challenges in diagnosing granulomatous inflammatory lesions, as these lesions can be associated with various pathological conditions. In many instances, histological analysis using H&E staining, along with clinical findings, appears insufficient for a definitive diagnosis. For more accurate diagnosis, it is often necessary to utilize complementary tests, such as immunohistochemistry or other molecular tests, which can provide essential additional information for understanding the lesions and offer a better insight into each patient's individual condition.

Due to the mentioned facts, the importance of biopsy in oral lesions is reinforced, as histopathology is a widely employed method to investigate lesions and reach a diagnosis, so that the correct course of action, as well as treatment selection, can be appropriately determined. Furthermore, observing the prevalence and epidemiological profile are necessary so that new preventive measures and treatment for rare diseases with possible oral manifestations can be considered and implemented. Through this research, it was possible to understand the clinical and histopathological characteristics of patients diagnosed with granulomatous inflammatory lesions treated at the School of Dentistry of the Federal University of Minas Gerais between the years 1953 and 2022.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Data availability

Datasets related to this article will be available to the corresponding author upon request.

Author Contribution

Thaís de Lima Araújo: Data Collection, Writing the manuscript, Data Analysis, Review, and Editing. **Rubens Signoretti Oliveira Silva:** Data Collection, Data Analysis, Review,

and Editing. **Victor Zanetti Drumond:** Data Analysis, Interpretation and Statistics, Review. **Ricardo Santiago Gomez:** Conception and design of the study, Review. **Vanessa Fátima Bernardes:** Conception and design of the study, Review, and Editing. All authors actively participated, at least, in two distinct criteria about the authorship 1. the manuscript's findings, and 2. have revised and approved the final version of the manuscript.

References

1. James DG. A clinicopathological classification of granulomatous disorders. Postgrad Med J. 2000 Aug;76(898):457-65. doi: 10.1136/pmj.76.898.457.
2. Alamoudi WA, Abdelsayed RA, Sollecito TP, Alhassan GA, Kulkarni R, Bindakhil MA. Causes of oral granulomatous disorders: an update and narrative review of the literature. Head Neck Pathol. 2024 Aug;18(1):72. doi: 10.1007/s12105-024-01678-7.
3. Shah KK, Pritt BS, Alexander MP. Histopathologic review of granulomatous inflammation. J Clin Tuberc Other Mycobact Dis. 2017 Feb 10;7:1-12. doi: 10.1016/j.jctube.2017.02.001.
4. Woodman M, Haeusler IL, Grandjean L. Tuberculosis genetic epidemiology: a Latin American perspective. Genes (Basel). 2019 Jan;10(1):53. doi: 10.3390/genes10010053.
5. de Souza BC, de Lemos VM, Munerato MC. Oral manifestation of tuberculosis: a case-report. Braz J Infect Dis. 2016 Mar-Apr;20(2):210-3. doi: 10.1016/j.bjid.2015.12.001. Epub 2015 Dec 31.
6. Kim SY, Byun JS, Choi JK, Jung JK. A case report of a tongue ulcer presented as the first sign of occult tuberculosis. BMC Oral Health. 2019 Apr;19(1):67. doi: 10.1186/s12903-019-0764-y.
7. Natarajan A, Beena PM, Devnikar AV, Mali S. A systemic review on tuberculosis. Indian J Tuberc. 2020 Jul;67(3):295-311. doi: 10.1016/j.ijtb.2020.02.005.
8. Pigott DM, Bhatt S, Golding N, Duda KA, Battle KE, Brady OJ, et al. Global distribution maps of the leishmaniases. Elife. 2014 Jun;3:e02851. doi: 10.7554/eLife.02851.
9. Oliveira AG, Brito PD, Schubach AO, Oliveira RV, Saheki MN, Lyra MR, et al. Influence of the nutritional status in the clinical and therapeutical evolution in adults and elderly with American Tegumentary Leishmaniasis. Acta Trop. 2013 Oct;128(1):36-40. doi: 10.1016/j.actatropica.2013.06.005.
10. de Magalhães AV, Moraes MA, Raick AN, Llanos-Cuentas A, Costa JM, Cuba CC, et al. [Histopathology of cutaneous leishmaniasis by Leishmania braziliensis braziliensis. 1. Histopathological patterns and study of the course of the lesions]. Rev Inst Med Trop Sao Paulo. 1986 Jul-Aug;28(4):253-62. Portuguese. doi: 10.1590/s0036-46651986000400008.
11. Stewart C, Cohen D, Bhattacharyya I, Scheitler L, Riley S, Calamia K, et al. Oral manifestations of Wegener's granulomatosis: a report of three cases and a literature review. J Am Dent Assoc. 2007 Mar;138(3):338-48; quiz 396, 398. doi: 10.14219/jada.archive.2007.0166.
12. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov;310(20):2191-4. doi: 10.1001/jama.2013.281053.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007 Oct;370(9596):1453-7. doi: 10.1016/S0140-6736(07)61602-X.
14. Kohli R, Punia RS, Kaushik R, Kundu R, Mohan H. Relative value of immunohistochemistry in detection of mycobacterial antigen in suspected cases of tuberculosis in tissue sections. Indian J Pathol Microbiol. 2014 Oct-Dec;57(4):574-8. doi: 10.4103/0377-4929.142667.

15. Humayun M, Chirenda J, Ye W, Mukeredzi I, Mujuru HA, Yang Z. Effect of gender on clinical presentation of tuberculosis (TB) and age-specific risk of TB, and TB-Human immunodeficiency virus coinfection. Open Forum Infect Dis. 2022 Oct;9(10):ofac512. doi: 10.1093/ofid/ofac512.

16. Hahn RC, Hagen F, Mendes RP, Burger E, Nery AF, Siqueira NP, et al. Paracoccidioidomycosis: current status and future trends. Clin Microbiol Rev. 2022 Dec;35(4):e0023321. doi: 10.1128/cmr.00233-21.

17. Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. PLoS One. 2012;7(5):e35671. doi: 10.1371/journal.pone.0035671.

18. Dheda K, Gumbo T, Maartens G, Dooley KE, McNerney R, Murray M, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. Lancet Respir Med. 2017 Mar 15:S2213-2600(17)30079-6. doi: 10.1016/S2213-2600(17)30079-6.

19. Ito FA, de Andrade CR, Vargas PA, Jorge J, Lopes MA. Primary tuberculosis of the oral cavity. Oral Dis. 2005 Jan;11(1):50-3. doi: 10.1111/j.1601-0825.2004.01055.x.

20. Leão JC, Gueiros LA, Porter SR. Oral manifestations of syphilis. Clinics (Sao Paulo). 2006 Apr;61(2):161-6. doi: 10.1590/s1807-59322006000200012.

21. Smith MH, Vargo RJ, Bilodeau EA, Anderson KM, Trzcinska A, Canterbury CR, et al. Oral manifestations of syphilis: a review of the clinical and histopathologic characteristics of a reemerging entity with report of 19 new cases. Head Neck Pathol. 2021 Sep;15(3):787-95. doi: 10.1007/s12105-020-01283-4.

22. Mignogna MD, Celentano A, Leuci S, Cascone M, Adamo D, Ruoppo E, et al. Mucosal leishmaniasis with primary oral involvement: a case series and a review of the literature. Oral Dis. 2015 Jan;21(1):e70-8. doi: 10.1111/odi.12268. Epub 2014 Jul 12.

23. Palmeiro MR, Rosalino CM, Quintella LP, Morgado FN, da Costa Martins AC, Moreira J, et al. Gingival leishmaniasis in an HIV-negative patient. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 Dec;104(6):e12-6. doi: 10.1016/j.tripleo.2007.07.008.

24. Almeida OP, Jacks J Jr, Scully C. Paracoccidioidomycosis of the mouth: an emerging deep mycosis. Crit Rev Oral Biol Med. 2003;14(5):377-83. doi: 10.1177/154411130301400508.

25. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol. 2013 Oct;17(5):603-6. doi: 10.1007/s10157-013-0869-6.

26. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009 Nov;361(21):2066-78. doi: 10.1056/NEJMra0804647.

27. Hanisch M, Fröhlich LF, Kleinheinz J. Gingival hyperplasia as first sign of recurrence of granulomatosis with polyangiitis (Wegener's granulomatosis): case report and review of the literature. BMC Oral Health. 2016 Aug;17(1):33. doi: 10.1186/s12903-016-0262-4.

28. Labrador AJP, Valdez LHM, Marin NRG, Ibazetta KAR, Chacón JAL, Fernandez AJV, et al. Oral granulomatosis with polyangiitis a systematic review. Clin Exp Dent Res. 2023 Feb;9(1):100-11. doi: 10.1002/cre2.706.

29. Blinder D, Yahatom R, Taicher S. Oral manifestations of sarcoidosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997 Apr;83(4):458-61. doi: 10.1016/s1079-2104(97)90145-1.

30. van Maarsseveen AC, van der Waal I, Stam J, Veldhuizen RW, van der Kwast WA. Oral involvement in sarcoidosis. Int J Oral Surg. 1982 Feb;11(1):21-9. doi: 10.1016/s0300-9785(82)80044-6.

31. Padmavathi B, Sharma S, Astekar M, Rajan Y, Sowmya G. Oral Crohn's disease. J Oral Maxillofac Pathol. 2014 Sep;18(Suppl 1):S139-42. doi: 10.4103/0973-029X.141369.

32. Capodiferro S, Tempesta A, Limongelli L, Ingravallo G, Maiorano E, Sfasciotti GL, et al. Primary oro-facial manifestations of langerhans cell histiocytosis in pediatric age: a bi-institutional retrospective study on 45 cases. Children (Basel). 2020 Aug;7(9):104. doi: 10.3390/children7090104.

33. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009 Apr-May;45(4-5):309-16. doi: 10.1016/j.oraloncology.2008.06.002. Epub 2008 Sep 18.

34. Markopoulos AK. Current aspects on oral squamous cell carcinoma. Open Dent J. 2012;6:126-30. doi: 10.2174/1874210601206010126.

35. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020 Nov;6(1):92. doi: 10.1038/s41572-020-00224-3. Erratum in: Nat Rev Dis Primers. 2023 Jan;9(1):4. doi: 10.1038/s41572-023-00418-5.