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Oral follicular lymphoid hyperplasia: clinicopathologic of a case series

Hiperplasia linfoide folicular oral: clinicopatológico de uma série de casos

Mara Luana B. Severo; Glória Maria França; Clarissa F. Demeda; Roseane C. Vasconcelos; Antônio de Lisboa L. Costa; Leão P. Pinto; Éricka Janine D. Silveira; Pedro Paulo A. Santos

Universidade Federal do Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil.

ABSTRACT

Follicular lymphoid hyperplasia (FLH) is a reactive lymphoid proliferation that can simulates lymphomas, both clinically and histologically. The aim of the present study was to investigate the clinical, morphological and immunohistochemical characteristics of a series of FLH cases of the oral cavity, and discuss important diagnostic aspects and differential diagnosis concerning follicular lymphomas. A retrospective analysis of the records of a database comprising 38 years revealed nine cases diagnosed as FLH of the oral cavity. Patient age ranged from 8 to 44 years. Most lesions were located in the buccal mucosa and the presence of a painless nodule was the most common clinical finding. Histopathological analysis revealed the proliferation of lymphoid cells arranged in a follicular pattern, presenting primary and secondary follicles with a germinal center and mantle zone, with evidence of macrophages containing apoptotic bodies in their interior, as well as evidence of typical mitosis figures. Interfollicular region, lymphocytes, macrophages and epimioepithelial islands were observed. Immunohistochemical analysis revealed positivity of the lymphoid follicles for CD20, CD68, CD3 and B-cell lymphoma 2 (Bcl-2). The clinical presentation of FLH and histopathological evidence of lymphatic follicles presenting indistinct germinal centers with poorly defined mantle zone may represent a problem due to theresemblance to follicular lymphoma.

Key words: follicular lymphoid hyperplasia; immunohistochemistry; lymphoid tissue; lymphoid progenitor cells.

RESUMO

A hiperplasia linfoide folicular (HLF) é uma proliferação linfoide reativa que pode simular linfomas, tanto clínica quanto histologicamente. O objetivo deste estudo foi investigar as características clínicas, morfológicas e imuno-histoquímicas de uma série de casos de HLF da cavidade oral e discutir importantes aspectos diagnósticos e diagnósticos diferenciais em relação aos linfomas foliculares. Uma análise retrospectiva dos registros de um banco de dados de 38 anos revelou nove casos diagnosticados como HLF da cavidade oral. A idade dos pacientes variou de 8 a 44 anos. A maioria das lesões estava localizada na mucosa bucal, e a presença de nódulo indolor foi o achado clínico mais comum. A análise histopatológica revelou proliferação de células linfoides dispostas em padrão folicular, apresentando folículos primários e secundários com centro germinativo e zona de manto, com evidências de macrófagos contendo corpos apoptóticos em seu interior, além de evidências de figuras típicas de mitose. Observamos região interfolicular, linfócitos, macrófagos e ilhas epimioepiteliais. A análise imuno-histoquímica revelou positividade dos folículos linfoides para CD20, CD68, CD3 e linfoma de células B2 (Bcl-2). A apresentação clínica de HLF e as evidências histopatológicas de folículos linfáticos apresentando centros germinais indistintos com zona de manto mal definida podem representar um problema devido à semelhança com o linfoma folicular.

Unitermos: *hiperplasia linfoide follicular; imuno-histoquímica; tecido linfoide; células progenitoras linfoides.*

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RESUMEN

La hiperplasia folicular linfoide (HFL) es una proliferación linfoide reactiva que puede simular linfomas, tanto clínica como histológicamente. El objetivo de este estudio fue investigar las características clínicas, morfológicas e inmunohistoquímicas de una serie de casos de HFL en la cavidad oral y discutir importantes aspectos diagnósticos y diagnósticos diferenciales en relación con los linfomas foliculares. Un análisis retrospectivo de los registros de una base de datos de 38 años reveló nueve casos diagnosticados como HFL de la cavidad oral. La edad de los pacientes osciló entre 8 y 44 años. La mayoría de las lesiones se localizaron en la mucosa oral y la presencia de un nódulo indoloro fue el hallazgo clínico más común. El análisis histopatológico reveló proliferación de células linfoides dispuestas en patrón folicular, presentando folículos primarios y secundarios con centro germinal y zona del manto, con evidencia de macrófagos que contenían cuerpos apoptóticos en su interior, así como evidencia de figuras de mitosis típicas. Observamos el área interfolicular, los linfocitos, los macrófagos e las islas epimioepiteliales. El análisis inmunohistoquímico reveló positividad de folículos linfoides para CD20, CD68, CD3 y linfoma de células B2 (Bcl-2). La presentación clínica de HFL y las evidencias histopatológicas de folículos linfáticos que muestran centros germinales indistintos con una zona del manto mal definida pueden ser un problema debido a la similitud con el linfoma folicular.

Palabras clave: *hiperplasia follicular linfoide; inmunohistoquímica; tejido linfoide; células progenitoras linfoides.*

INTRODUCTION

Follicular lymphoid hyperplasia (FLH) is a benign lymphoproliferative process of unknown etiology, uncommon in the head and neck region. The condition mainly affects adult patients, ranging from 38 to 79 years old, with a male-to-female ratio of 3:1[1-4]. Chronic irritation and a response to an unknown antigen stimulus have been suggested as possible FLH etiologies[3,5].

Clinically, FLH manifests as a slow-growing, painless, ulcerated, and well-circumscribed hard nodule[1,3,4], having been described in the palate[1,3,4,6], tongue[7], and oral mucosa[8,9]. Morphological analyses have revealed a proliferation of lymphoid cells arranged in a follicular pattern and the presence of multiple germinal centers containing occasionally atypical B lymphocytes and macrophages. An interfollicular region and a mantle zone are also observed, in addition to small lymphocytes at the periphery of the germinal centers[1,4,10]. Surgical excision is the treatment of choice and local recurrence is observed only in a minority of patients. Spontaneous regression has also been reported[3].

The histopathological patterns of lymphoid hyperplasia can be divided into sinusoid, diffuse, follicular, and mixed. The mixed pattern is characterized by the presence of components of the sinusoid and follicular patterns. The follicular pattern is the most common in the head and neck region[11].

However, FLH can exhibit clinical and histopathological characteristics that resemble follicular lymphoma (FL), which may lead to erroneous diagnoses and consequent staging procedures of the lesion and incorrect treatment[3,5]. In this context, this study analyzed a series of FLH cases from the Oral Pathology Service of the Universidade Federal do Rio Grande do Norte (UFRN), Natal, Rio Grande do Norte, Brazil, and discusses histological and immunohistochemical criteria for the diagnosis of this rare oral cavity lesion by reviewing cases published in the literature.

CASE REPORT

Cases of patients with FLH diagnosed between 1980 and 2018 were retrieved from the archives of the UFRN Oral Pathology Service, approved by the UFRN Ethics Committee under no. 1.883.170. Data comprising patient age, gender, anatomical location, duration, and a history of swelling and painful symptoms were obtained from medical records stored along side the biopsies. Race was not considered, since the Brazilian population consists of a mixture of several ethnic groups. For the histopathological and immunohistochemical analyses, three previously trained independent examiners analyzed the following morphological lesion features in a descriptive manner: proliferation of lymphoid cells organized in a follicular pattern (primary and secondary follicles) and interfollicular area, in addition the identification of possible epimioepithelial islands and mitotic figures, through the observation of 5 µm thick slides stained with hematoxylin and eosin (HE). The immunohistochemical analysis of CD20, CD68, CD3, and B-cell lymphoma 2 (Bcl-2) antibodies was performed by observing 3 µm thick slides. The immunohistochemistry (IHC) results were descriptively analyzed by three examiners in a blind manner, using an Olympus CX41 microscope (Olympus Japan Co.,

Tokyo, Japan). Antibodies against CD20, CD68, CD3, and Bcl-2 were used (**Table 1**).

TABLE 1 – Specificity, manufacturer, dilution, antigen retrieval and incubation of antibodies used

Specificity	Manufacturer	Dilution	Antigen retrieval	Incubation
CD3	Dako	1:50	Citrate, pH 6.0, Pascal, 3 min	Overnight (18 h)
CD20	Dako	1:50	Citrate, pH 6.0, Pascal, 3 min	Overnight (18 h)
CD68	Dako	1:50	Citrate, pH 6.0, Pascal, 3 min	60 min
Bcl-2	Dako	1:50	Citrate, pH 6.0, Pascal, 3 min	Overnight (18 h)

Bcl-2: B-cell lymphoma 2.

Data were tabulated and analyzed by descriptive statistics using the Statistical Package for the Social Sciences – IBM SPSS® (version 20.0; IBM Corp., Armonk, NY, USA).

Among the 15,800 biopsies stored in the Oral Pathology Service archives for over 38 years, fifteen (0.09%) cases exhibited histopathological criteria for the diagnosis of FLH. Of these, twelve were observed in women and three in men (**Table 2**). The mean age at the time of diagnosis was 31.41 years old (range: 8-44 years).

The most commonly affected site in the fifteen cases was the cheek mucosa ($n = 6$) (**Figure 1A** and **1B**), followed by the posterior tongue ($n = 4$) (**Figure 1C**), hard palate ($n = 1$), soft palate ($n = 1$), submentonian region ($n = 1$), parotid region ($n = 1$) and submandibular gland ($n = 1$). FLH duration ranged from seven days to six years.

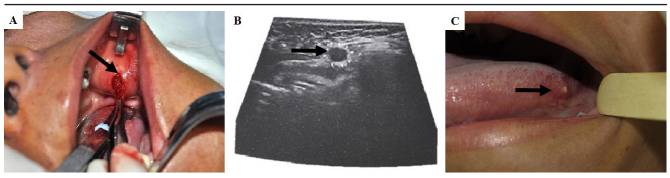

FIGURE 1 – *Clinic aspects of oral lymphoid hyperplasia*

A) surgical excision of nodular lesion on the left buccal mucosa; B) ultrasonography showed radiolucent image of a nodular solid, well-defined, hypoechoic with echogenic halo and texture, poorly vascularized with well-defined margins; C) clinical evidence of lymphoid hyperplasia on the left lateral border of the tongue, showing a lesion of small dimensions (0.8 cm), nodular and yellowish color.

Regarding clinical manifestations, swelling was observed in nine cases while ten patients displayed no painful symptoms. A firm/hard lesion consistency was observed in nine cases, and normal mucosa color, in five (Table 2).

An ultrasound (Figure 1B) was performed in one case, which revealed the presence of a well-defined, solid, poorly vascularized nodular lesion with an echogenic halo and hypoechogenic texture. Excisional biopsy was the treatment of choice in 80% of cases, although this information was not described in three cases (20%). No recurrence was observed during the follow-up period, which ranged from 8 months to 20 years.

Concerning the histopathological characteristics (**Table 3**), the presence of primary lymphoid follicles was observed in six lymphoid hyperplasia cases (40%) (**Figure 2A**), while the presence of secondary lymphoid follicles was noted in nine cases (60%) (**Figure 2B**).When the presence of primary lymphoid follicles was observed, predominantly diffuse lymphocytic inflammatory

TABLE 2 – Clinical characteristics of fifteen cases of oral follicular lymphoid hyperplasia

Age (years)	Gender	Duration	Location	Pain	Color	Consistency	Aspect	Diagnostic hypothesis	Imaging	Biopsy	Follow-up time
36	F	2 months	SR	Yes	NI	Rubber-like	NI	Hyperplastic lymph node/ lymphoid hyperplasia	NI	Excisional	10 years
15	F	1 year	Cheek mucosa	No	NI	NI	NI	NI	NI	Excisional	7 years
30	F	1 months	Cheek mucosa	No	Reddish	Firm	Hyperplastic	Lymph node swelling	Panoramic	Excisional	12 years
8	F	8 months	Parotid region	No	White	Firm	Nodular	Lymph node	US	Excisional	8 years
38	M	NI	Tongue	No	NM	Soft	Hyperplastic	Fibrous hyperplasia	NI	NI	17 years
44	F	7 days	Cheek mucosa	No	NM	Hard	NI	Neurofibroma/leiomyoma	US	NI	7 years
34	M	6 years	Cheek mucosa	No	NM	Firm	Nodular	Fibrolipoma/neurofibroma	NI	Excisional	6 years
41	F	1 year	Tongue	NI	NM	Hard	NI	Papillary hypertrophy	NI	Excisional	5 years
39	M	NI	SG	NI	NI	NI	NI	Submandibular gland alteration	NI	Excisional	5 years
NI	F	2 years	Hard Palate	No	Reddish	Firm	Nodular	Hemangioma/piogenic granuloma	NI	Excisional	20 years
NI	F	NI	Soft Palate	No	Blackened	Firm	Nodular	Fibrous hyperplasia /mucocele	NI	NI	13 years
43	F	5 months	Tongue	Yes	Reddish	Soft	Nodular	Fibrous hyperplasia	NI	Excisional	9 years
NI	F	8 days	Cheek mucosa	No	NM	Firm	Nodular	Neurofibroma/leiomyoma	NI	Excisional	6 years
10	F	4 months	Cheek mucosa	No	Purplish	Firm	Nodular	Rhabdomyoma	NI	Excisional	2 years
39	F	20 days	Tongue	NI	Yellowish	Soft	NI	Oral lymphoepithelial cyst	NI	Excisional	8 months

F: female; M: male; NI: not informated; SR: submentonian region; SG: submandibular gland; NM: normal mucosa; US: ultrasound.

TABLE 3 – Histopathological characteristics of the 15 cases of oral lymphoid hyperplasia

Histopathological characteristics	Number of cases	%
Primary lymphoid follicle	6	40
Secondary lymphoid follicle	9	60
Diffuse inflammatory infiltrate	10	66.6
Focal inflammatory infiltrate	5	33.3
Epimioepithelialis islands	4	26.6
Macrophages with apoptotic bodies	7	46.6
Mitotic figures	5	33.3

infiltrates were noted in the parafollicular region, displaying small lymphocytes in addition to plasma cells (**Figure 2C**). The presence of numerous blood vessels was also observed in this region, lined by bulky endothelial cells. Only two cases presented indistinct germinal centers, with poorly defined mantle areas and the absence of macrophages. Only five lymphocyte lesions displayed typical mitotic figures (**Figure 2D**). Macrophages were observed in high numbers in the germinative centers, and evidence of macrophages with apoptotic bodies was also noted (**Figure 2E**) in seven cases (46.6%). Epimioepithelial islands (**Figure 2F**) were found in 26.6% of the analysed cases.

IHC was performed in two cases and lymphoid follicles revealed immunopositivity to CD20, displaying greater immunoreactivity in the mantle zone in relation to the germinal center. Immunopositivity to CD68 was observed in macrophages located in both lymphoid follicles and parafollicular regions, as well as CD3, with evident immunolabeling in the mantle and interfollicular regions. Bcl-2 immunoreactivity was observed in the mantle zone of secondary follicles and presented moderate immunolabeling in the parafollicular regions. No immunoreactivity was observed for Bcl-2 within the germinal centers (**Figure 3A-D**).

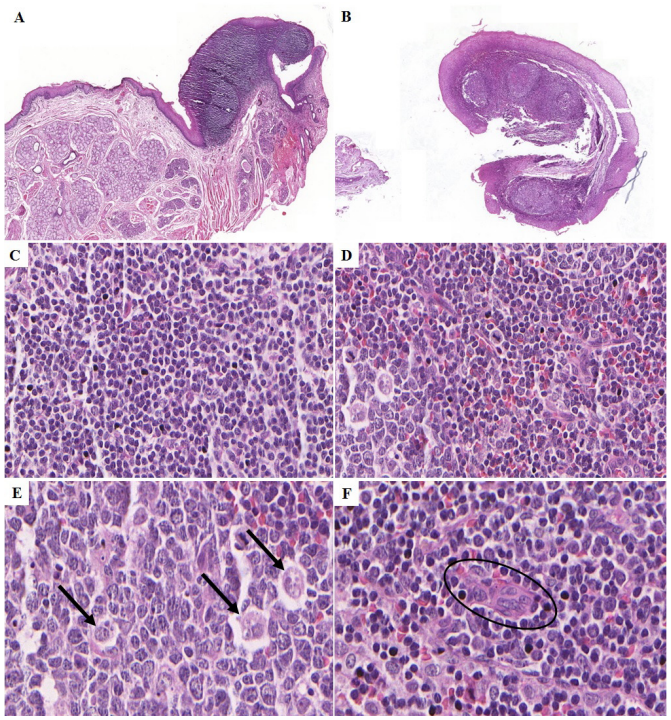

FIGURE 2 – *Histopathological characteristics of oral lymphoid hyperplasia*

A) presence of primary lymph nodes in close proximity to the oral mucosa lining epithelium; B) secondary lymph nodes with the formation of well-defined germinal centers (HE, pannoramic viewer – 1000 µm); C) interfollicular areas populated by small lymphocytes; D) lymphocyte with typical mitosis figure (black circle) in interfollicular region; E) presence of macrophages (black arrows) in the germinal centers of secondary lymphatic follicles; F) presence of epimioepithelial island (black circle) (HE, pannoramic viewer – 50 µm).

HE: hematoxylin and eosin.

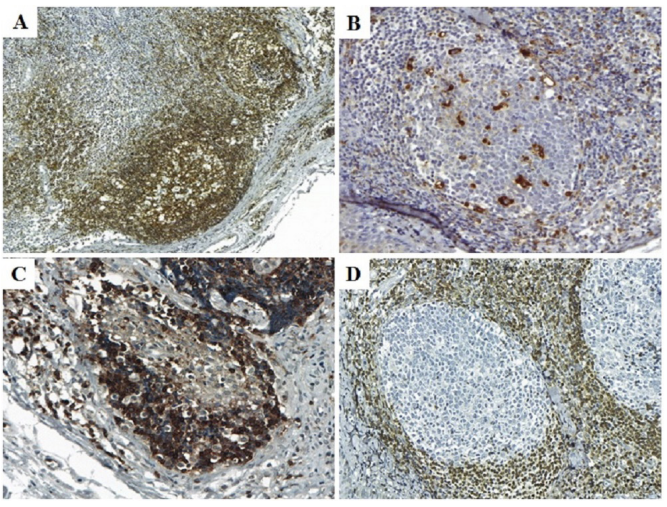

FIGURE 3 – *Immunohistochemical analysis of lymphoid hyperplasias*

A) immunopositivity in lymphoid follicles for CD20, exhibiting greater immunoreactivity in the mantle zone relative to the germinal center; B) immunoreactivity for CD68 in macrophages located in both lymphoid follicles and parafollicular regions; C) CD3 with evident immunolabeling in parafollicular regions; D) immunostaining for Bcl-2 in the mantle zone and parafollicular regions, abscence of positivity in the germinal center of follicles.

Bcl-2: B-cell lymphoma 2.

DISCUSSION

FLH, also called reactive lymphoid hyperplasia, is a benign lymphocyte proliferation, which can be either intra- or extranodular[2]. The condition was described for the first time by Adkins (1973)[12], who observed a strong clinical and morphological resemblance to malignant lesions such as FL in some cases. The author related the occurrence of FLH to the presence of persistent local irritations[5]. The rare occurrence of FLH in the oral mucosa and its histopathological resemblance to FL highlight the importance of establishing a correct diagnosis.

A limited number of publications regarding FLH of the oral mucosa are available in the literature. FLH etiology is still unknown, but it is believed to be the result of a humoral response to antigen stimulation or chronic irritation[2, 3]. The Epstein-Barr virus may be associated with an aggressive and persistent form of FLH. However, no association has been observed between the occurrence of FLH and smoking, alcohol consumption, medication use or systemic problems[5, 13]. In the present study, an association between a history of local trauma and FLH was observed in only two cases, whereas no probable cause in the remaining cases was noted.

In this study, FLH cases preferentially affected women, in accordance to previous literature findings[1, 3, 8, 13]. Patient age ranged from 8 to 44 years old, with a mean evolution of 16 months, dissimilar from the reports described in the literature that observed a change in age between 38 and 79 years old, with a mean evolution of nine months[1, 3, 5, 8, 13].

FLH is found mainly in the oropharynx, lateral border of the tongue, palate, and cheek mucosa[1, 5]. In contrast to the literature, in the present study most cases involved the cheek mucosa, while two cases involved the palate (one in the hard palate and another in the soft), a site commonly affected by this condition[5]. FLH clinically manifests as a slow-growing and non-ulcerated mass, which was observed in most of the assessed cases.

FLH cases are commonly asymptomatic[1, 3, 5, 6, 8, 13, 14]. This was observed in the present study for 66.6% of the cases. However, some lesions may be symptomatic[1, 4, 7], which was noted for two lymphoid hyperplasia cases herein, presenting painful symptomatology.

Histopathologically, FLH is characterized by follicular lymphoid proliferation mixed with fibrous connective tissue, forming interfollicular zones. The follicles may present germinal centers, circumscribed by the mantle zone, and in this case are called secondary lymphoid follicles[1,3-6, 8, 14, 15] while follicles with no germinal centers and no evidence of mantle zone are termed primary lymphoid follicles[7]. Atypical lymphocytes, eventual figures in typical mitoses and macrophages, can be observed[1,3-5, 10]. All these histopathological characteristics described were evidenced in the 15 cases analyzed in the present study. Eventual presence of epimioepithelial islands is noted[1, 4, 16], corroborating the results found herein, with evidence of these structures in only four FLH cases. Anjomshoaa *et al*. (2013)[1] observed abundant hyalinization areas within the germinal centers and interfollicular zone, as well as the presence of lymphoid tissue in the parenchyma of the minor salivary glands. This, however, was not observed in the present study. Microscopic findings do not always provide sufficient histological features for a diagnosis, and their interpretation, as well as differential diagnoses for lesions of a lymphoid origin, represent a challenge. Since reactive alterations in lymph nodes are diverse and complex, many may exhibit unusual features, which prevents the differentiation between benign and malignant alterations that can sometimes mimic a follicular lymphoma[16, 17].

FLH is one of the most common types of benign lymphoid hyperplasia, and it can be clinically and histologically confused with lymphoma[16]. A differential FLH diagnosis is mainly based on the histopathological findings and includes salivary gland tumors, palatal abscesses, benign lymphoepithelial lesions, and even mesenchymal tumors and tumor-like lesions, such as adenomatoid hyperplasia[13].

Lymphoma is the most relevant differential FLH diagnosis and the second most common malignant neoplasm of hematopoietic origin in the head and neck region. It normally affects the lymph nodes, spleen and other hematopoietic tissues. Lymphomas are generally classified into Hodgkin's and non-Hodgkin's lymphoma and can arise from B or T cells. Approximately 24% to 48% of these lymphomas arise at extranodal sites, and 3% to 5% of them occur in the oral cavity[18].

The differential diagnosis between FL and FLH frequently represents a problem. Custer (1952)[19] provided a detailed description of the histopathological characteristics that permit the distinction between reactive follicular hyperplasia and lymphoma for the first time. Nathwani *et al*. (1981)[15] defined four morphological criteria for differential diagnoses between FL and FLH. The most important histological feature to differentiate FLH from FL is the type of follicular pattern. A common finding in FL is the uniform distribution of the follicles, irrespective of their size or shape, and the presence of a narrow interfollicular zone. The second criterion is the number of follicles per area, with FL exhibiting numerous follicles in a small field. The third criterion is related to interfollicular tissue cell characteristics. In this respect, the presence of numerous follicular cells in the interfollicular region, which display features similar to those of intrafollicle cells, characterizes FL. The fourth criterion that allows for the differentiation of FLH from FL is the small number of benign histiocytes and the absence of phagocytic activity in FL. These histopathological parameters were detected in the fifteen cases assessed herein, which were thus diagnosed with FLH.

Another important finding is the lack of clear demarcation of the germinal centers in FL. Furthermore, in contrast to reactive lesions, FL does not contain numerous cell types. Nuclear atypia and atypical mitoses are observed. The internodular stroma of lymphomas is less vascularized and contains neoplastic cells[6, 20]. In case of prolonged antigen stimulation, FLH becomes florid,

with the observation of numerous follicles of variable shape and size, an event that represents a major difficulty in distinguish in this lesion from FL[16]. In these cases, the use of complementary diagnostic techniques, including polymerase chain reaction (PCR) for the analysis of heavy-chain immunoglobulins and immunohistochemistry, becomes important. These methods reveal the polyclonal phenotype characteristic of the benign lesion[3].

The immunohistochemical profile can be useful for a differential diagnosis, since FLH is generally positive for CD20, CD5, CD3, CD21/23, and Bcl-2[1, 16]. In the present study, intense immunostaining for CD20 was observed in the center of the follicles and little or no staining in the interfollicular areas. More intense CD3 staining was detected in the mantle zone and parafollicular areas. Focal staining was observed for CD68 and Bcl-2 in the mantle zone and parafollicular areas, but absent in the germinal centers.

Another lesion that should be included for differential diagnoses is lymphoma of the mucosa-associated lymphoid tissue (MALT) type[3, 20]. It is suggested that cases with involvement of multiple sites in the oral cavity are MALT lymphomas[5]. MALT lymphomas account for a significant proportion of extranodal lymphomas[21]. Extranodal marginal zone B-cell lymphomas are known to exhibit histological and clinical characteristics similar to those of benign lymphoid hyperplasias. Both lesions manifest as uni- or bilateral nodules that are firm or soft on palpation. MALT lymphomas contain cells with nuclear atypia and exhibit atypical mitoses, although mitosis rates rarely resemble those found in benign lesions[22].

Pathologists sometimes encounter benign reactive lymphoid lesions with characteristics that impair their differentiation from malignant lesions, such as FLH, which exhibits subtle differences compared to follicular lymphoma. Histopathological analyses combined with immunohistochemical and molecular methods are essential to establish a precise diagnosis and to implement appropriate patient management.

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CORRESPONDING AUTHOR

Pedro Paulo de Andrade Santos ID 0000-0002-5793-3886
e-mail: ppdasantos@gmail.com