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Parotid follicular lymphoid hyperplasia – a rare entity: the challenges in differential diagnosis

Hiperplasia linfoide folicular em parótida – uma rara entidade: os desafios no diagnóstico diferencial

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ABSTRACT

A 61-year-old female patient presented a nodular lesion located in the right buccal mucosa with a 3-month evolution. Clinical hypotheses of salivary duct cyst and mucocele were proposed, and the patient underwent excisional biopsy. Microscopically, a well-circumscribed and encapsulated lymphoid aggregate fragment was observed, characterized by layers of well-differentiated small lymphocytes and collections of reactive lymphoblasts. These findings, associated with immunohistochemistry, established the diagnosis of follicular lymphoid hyperplasia. Currently, the patient is well, under follow-up after six months.

Key words: lymphoid tissue; pseudolymphoma; diagnosis differential; lymphoma; oral medicine.

RESUMO

Paciente do sexo feminino, 61 anos de idade, exibiu lesão nodular localizada em mucosa jugal direita com evolução há três meses. As hipóteses clínicas de cisto do ducto salivar e mucocele foram estabelecidas, e a paciente foi submetida à biópsia excisional. Microscopicamente, foi observado fragmento de agregado linfoide bem circunscrito e encapsulado, caracterizado por camadas de pequenos linfócitos bem diferenciados e coleções de linfoblastos reativos. Esses achados, associados ao estudo imuno-histoquímico, estabeleceram o diagnóstico de hiperplasia linfoide folicular. Atualmente, a paciente encontra-se bem, sob proservação após seis meses.

Unitermos: *tecido linfoide; pseudolinfoma; diagnóstico diferencial; linfoma; medicina bucal.*

RESUMEN

Paciente del sexo femenino de 61 años de edad exhibió lesión nodular localizada en mucosa yugal derecha con tiempo de evolución de tres meses. Se establecieron las hipótesis clínicas de quiste del ducto salival y mucocele, y la paciente se sometió a una biopsia excisional. Microscópicamente, se observó un fragmento de agregado linfoide bien circunscrito y encapsulado, caracterizado por capas de linfocitos pequeños bien diferenciados y colecciones de linfoblastos reactivos. Esos hallazgos, asociados al estudio inmunohistoquímico, basaron el diagnóstico de hiperplasia folicular linfoide. Al presente, la paciente se encuentra bien, bajo seguimiento seis meses después.

Palabras clave: *tejido linfoide; seudolinfoma; diagnóstico diferencial; linfoma; medicina oral.*

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INTRODUCTION

The diagnosis of oral lesions can be hampered by their anatomical particularities and the wide spectrum of lesions[1]. Follicular lymphoid hyperplasia (FLH) is an uncommon and poorly understood entity[2]; it is a reactive proliferation of lymphocytes to unknown antigenic stimuli. Clinically and histologically, it resembles a follicular lymphoma[3].

This condition has been described in several sites of the body, mostly skin, gastrointestinal tract, lung, nasopharynx, larynx, and breasts; in rare situations, it affects the oral cavity[2]. It has a predilection for elderly women. Clinically, it presents as a painless, slow growing and not-ulcerated swelling[4], which is frequently described on the palate and at the base of the tongue[3].

Morphologically, the lesion is characterized by a dense lymphoid infiltrate within the lamina propria and the submucosa. This infiltrate can show the classical features of a benign reactive follicular hyperplasia, without causing difficulties for diagnosis. Nevertheless, the presence of ill-defined germinal centers is not uncommon, and the lack of macrophages gives the lesion a monotonous aspect of lymphoid cells. Those features can mimic a follicular lymphoma[3, 5, 6]. Local excision has been the treatment of choice, although a small portion of patients have suffered recurrence after the procedure; however, there is no evidence of malignant transformation over time[3].

The objective of this work was to describe a case of FLH in buccal mucosa, as well as to elucidate the main histologic and immunohistochemical characteristics for differential diagnosis of a follicular-type lymphoma.

CASE REPORT

A 61-year-old female patient was admitted at an oral medicine service due to a lesion in the right buccal mucosa. During anamnesis, the chief complaint was the evolution, of approximately three months, of a soft-tissue lesion. Relevant local or systemic alterations were not detected.

At physical examination, the patient had a symmetrical face, mouth opening, cervicofacial lymph node chains without alteration and oral mucosa normal in color. Clinically, the lesion was not observed, but palpation of the region revealed a nodular lesion of firm consistence, smooth surface and normal color (**Figure 1A**). The main diagnostic hypothesis was salivary duct cyst or mucocele. Ultrasonography was ordered; its result suggested a cystic lesion, with heterogeneous content, measuring 0.6 × 0.5 × 0.5 cm (**Figure 1B**). Excisional biopsy was performed as a diagnostic and treatment method.

Histology revealed a well-circumscribed encapsulated lesion and the presence of lymphocytes with monomorphic aspect; interspersed, some cells of clearer cytoplasm, the reactive lymphoblasts (**Figure 2A**, **B**, **C**). Macrophages and congested blood vessels were also observed, suggesting the presence of some antigen (**Figure 2D**).

Immunohistochemistry was used for the differential diagnosis of follicular lymphoma. Bcl-2 expression is used for identification of antiapoptotic protein; as it is present in malignant neoplasms and reactive lesions, it demonstrates positivity in both lymphoma and FLH. In this report, positivity for the CD3 and CD20 markers was identified, meaning that the lesion presented, respectively, T and B lymphocytes. However, the CD10 marker indicated the presence of germinal cells, namely, progenitor lymphocytes, which were positive in the lymphoma and negative in the FLH; its immunohistochemical expression was essential for the differential diagnosis between both lesions (**Figure 3**).

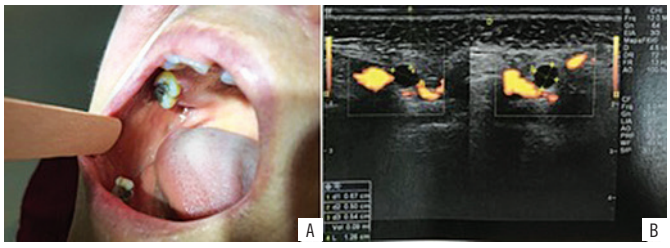

FIGURE 1 – *Initial image of the patient*
A) intraoral clinical aspect; B) ultrasonography presenting cyst with heterogeneous content measuring 0.6 × 0.5 × 0.5 cm, at a distance of 1.2 cm from the skin.

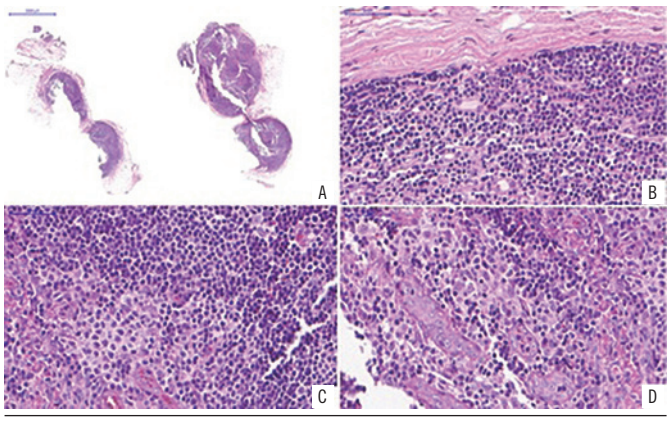

FIGURE 2 – *Histopathological aspects of FLH (HE)*
A) microscopic aspect of the surgical specimen showing a well-circumscribed encapsulated lymphoid lesion; B) capsule of dense fibrous connective tissue and lymphocytes with monotonous morphology; C) double population of lymphocytes (small well-differentiated lymphocytes, and collections of reactive lymphoblasts); D) sprouting of small vessels and endothelial cells.

FLH: follicular lymphoid hyperplasia; HE: hematoxylin and eosin.

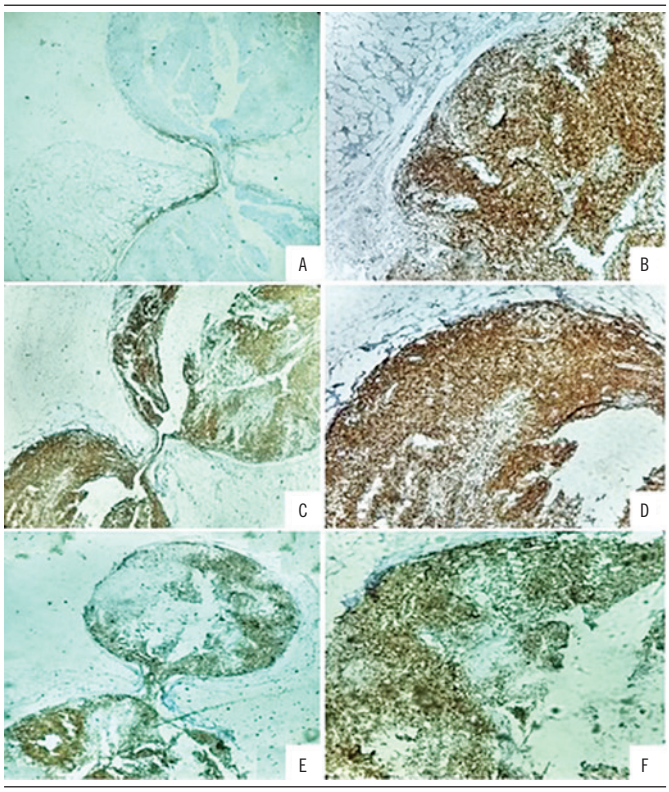

FIGURE 3 – *Immunohistochemistry to exclude a diagnosis of follicular lymphoma A) CD10 (-) identifies lymphoid progenitor cells, germinal cells in lymphoid tissues, and immature B cells; B) Bcl-2 (+) is an antiapoptotic marker and is highly expressed in follicular lymphomas; C and D) CD3 (+) is a T-cell surface glycoprotein; E and F) CD20 (+) quantitatively identifies B lymphocytes.*

DISCUSSION

The lymphoid tissue plays an important role in the host immune response; it is normally found in the oral cavity and in the oropharynx. Aggregates of lymphoid tissue can be observed bilaterally in the posterolateral surfaces of the tongue and are considered variations of the normal anatomical structure[7]. FLH is a rare benign proliferative process. It was given a varied nomenclature, such as benign lymphoid hyperplasia, reactive lymphoid hyperplasia, and pseudolymphoma[8]. The etiology of FLH is still unknown; however, this lesion can be a reactive lymphoid proliferation induced by a non-specified antigenic stimulus[3]. It can also be associated with a source of persistent chronic irritation, as an ill-fitting prosthesis, as well as to Sjögren syndrome or an infectious etiology[4, 8, 9].

Patients' ages range from 38 to 79 years, with an average of 61 years[1, 4]. Females are more affected than males, at a proportion of 3.2:1. This condition generally presents as a unilateral, slow-growing, non-ulcerated mass[8, 10, 11]. The most affected site is the hard palate, followed by the base of the tongue[3]. Size varies from 10 mm to 40 mm[9].

The clinical case in question is in agreement with the literature, as the patient is 61 years old and is a woman. However, the lesion was smaller than average dimensions and occurred in the buccal mucosa, a quite uncommon site for this type of disease.

Differential diagnosis includes, malignant or benign salivary gland tumors, mesenchymal tumors, adenomatous hyperplasia and lymphomas. If the surface is ulcerated, squamous cell carcinoma must be considered[5, 10, 12]. In this clinical case, salivary duct cyst and mucocele were considered in the differential diagnosis due to location and the clinical aspect of the lesion.

The histological relationship between the lymphoid tissue and the glandular epithelium is evident in several non-neoplastic lesions of the parotid gland, which include FLH and cystic lesion; the latter is characterized as a multicystic proliferation with reactive germinal centers, infection by the human immunodeficiency virus (HIV) and lymphoepithelial sialadenitis (LESA) of Sjögren syndrome, involving infiltration of the ductal epithelium by lymphocytes of marginal zone or the monocytoid B-cell type, forming lymphoepithelial lesions. Microscopically, the parotid gland shows epithelial cysts and epimyoepithelial islands in a hyperplastic lymphoid stroma. Although most cases described in the literature involve HIV-infected men, numerous cases of histologically similar multicystic lymphoepithelial lesions of the parotid gland were found in HIV-negative patients. Cystic alterations in the LESA of Sjögren syndrome, despite being uncommon, are occasionally found, and lymphoepithelial cysts of the parotid are known to occur without any predisposing systemic condition[13]. The histopathological features of FLH can suffer variations composed of lymphoid follicles and germinal centers surrounded by a well-defined mantle zone[3]. Our case presented a cystic aspect at ultrasonography, being histopathologically characterized as lymphoid follicles and by the mantle zone.

Immunohistochemical analysis is essential for differentiation of lymphoma. Germinal centers are usually positive for antibodies Bcl-6, CD10, CD20, CD21, CD23, CD79a and Ki-67, while they do not express Bcl-2, CD2, CD3, CD5 and CD138. The mantle and interfollicular zones are normally positive for Bcl-2, CD2, CD3, CD5, CD20 and CD138. The present case was composed of areas corresponding to the mantle and interfollicular zones, therefore, morphological and immunohistochemical analyses are fundamental for differential diagnosis[4].

The treatment of choice for FLH is surgical excision. Although recurrences are rare, some patients do relapse after treatment. Prolonged follow-up did not show evidence of malignant transformation[2]. Glucocorticoids have several physiological and pharmacological effects on the body; the anti-inflammatory effect is one of the most important, for this reason, they can be employed

in this type of lesion[12]. The prognosis of a reactive inflammatory lesion is completely distinct from that of malignant neoplasias. FLH presents slow growth and a recurrence rate of 16.7%[3]. In this clinical case, the patient was treated with surgical excision, presenting good prognosis. She has been under follow-up and with no recurrence up to the present day.

CONCLUSION

FLH plays an important role in foreign antigen recognition and processing and, when present, differentiation from a follicular lymphoma can be difficult. Immunohistochemistry is fundamental for correct diagnosis.

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