

Follicular Lymphoid Hyperplasia in Palate: A Case Report with Immunohistochemical Analysis and Review

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Abstract

Follicular lymphoid hyperplasia of the hard palate is a reactive lymphoid proliferation which closely simulates the palatal lymphomas, both clinically and histologically. It is therefore imperative that the pathologist be familiar with the features that separate these two conditions. It reported a case of FLH in a 70-year-old white woman, showing a nodular lesion in right posterior soft palate, reddish, soft, asymptomatic. Histopathological analysis revealed lymphoid aggregates with discrete lobular appearance in the lamina propria of connective tissue showing numerous lymphocytes in the periphery with scanty cytoplasm and homogeneously basophilic nuclei and central areas of germinal centers showing tingible-body macrophages and occasional mitotic figures. In order to distinguish Follicular Lymphoma (FL) from Follicular Hyperplasia (FH), immunohistochemical staining method for bcl-2 was used showing positivity in the mantle zone and absence of immunostaining in the cellular elements within the follicle centres.

Keywords: Benign lymphoid hyperplasia; Lymphoid proliferation; Oral mucosa; Palate; Immunohistochemistry

Introduction

Follicular Lymphoid Hyperplasia (FLH) of the palate is a poorly understood and very rare non-neoplastic lymphoproliferative disease in the oral mucosa, which may be confused clinically and histologically with malignant lymphoma [1-7]. FLH has a benign biological behavior, however recurrent or persistent; spontaneous regression has been reported and their clinical course requires a long-term follow-up. The condition most commonly affects elderly women [1-4,8].

It has been described in many locations of the body, notably skin, gastrointestinal tract, lungs, nasopharynx, etc. Rarely, the oral cavity may be involved, usually occurs as a painless, slow growing non-ulcerated mass in the posterior hard palate. It is often unilateral but occasionally it may be bilateral or involve a large area of the hard palate [8].

Morphologically, FLH is characterized by a dense lymphoid infiltrate within the lamina propria and submucosa, replacing the palatal mucous glands. Residual salivary gland ducts with periductal hyalinization may be seen within the infiltrate. The squamous epithelium is normal or slightly hyperplastic. The lymphoid infiltrate may show the classical features of a benign reactive follicular hyperplasia, with reactive germinal centres which vary in size and shape with prominent tingible-body macrophages and a polymorphic lymphoid cell population. However, the large number of variables features of the FLH may lead to an erroneous diagnosis of follicular lymphoma, with consequent staging procedures and unnecessary treatment [8].

Local excision is the treatment of choice. A small number of patients have developed recurrences after local excision but have not shown any evidence of malignization after long-term follow-up [8].

Review of the Literature

From 1980 to 2009, 21 cases of intra-oral FLH located in the palate have been published (Table 1). The epidemiological analysis of these cases, including the case reported here, showed that there is predilection for females, with 17 cases (77.3%) and 5 (22.7%) in males,

with a ratio female: male of 3.4:1; ages ranged from 38 to 79 years, averaging 61.6 years.

The size of lesions ranged from 0.1cm to 4.0cm, with a mean of 2.5 cm, and in 7 cases this data was not reported. Most cases had no information regarding the presence or absence of symptoms; only 8 (36.3%) cases were reported as asymptomatic lesions.

The length of time of the lesions was recorded in 13 (59.1%) cases, ranging from 1 to 36 months, with an average of 8.9 months.

Of the cases examined, 19 (86.3%) had information on the clinical follow up, which ranged from 3 months to 16 years, with an average of 63.8 months (approximately 5.4 years). It was found that one patient (4.5%) survived with evidence of injury, but with a reduction in the initial size, one (4.5%) survived with evidence of injury, but with a small increase in size, another one (4.5%) survived with injuries, 15 (68.1%) survived free of injury and 4 (18.1%) had no information about the evolution of the pathology. There were no reported deaths associated with the presence of intra-oral FLH. Four patients (18.1%) developed multicentric recurrence [8].

Seven cases (31.8%) of FLH occurred in patients with other diseases, while three patients (13.6%) had associated lymphadenopathy, one had undergone a total thyroidectomy, one had rheumatoid arthritis and serologic changes consistent with autoimmune disease systemic disorder, one had non-Hodgkin's lymphoma and one had associated hypertension and osteoporosis, accounting for 4.5%, respectively.

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AUTHOR	AGE/SEX	LOCATION	SIZE	CLINICAL FEATURES	OTHER PATHOLOGIES	DURATION	TREATMENT	FOLLOW-UP / STATUS
Harsany et al. [2]	60 F	Hard palate (L)	40 mm	NS	None	2 months	Surgical excision, low-dose radiotherapy	144 months / Reduced in size
Harsany et al. [2]	47 M	Bilateral hard palate, right side of the soft palate	NS	NS	Nodular lymphocytic lymphoma	NS	Surgical excision	48 months / DF
Harsany et al. [2]	72 F	Palate - multifocal	15mm	NS	None	3 years	Surgical excision	108 months / NS
Harsany et al. [2]	70 F	Palate (L)	18 mm	NS	Cervical lymphadenopathy	NS	Radiotherapy	84 months / DF
Wright, Drinsworth [3]	72 F	Posterior palate	30 mm	NS	None	NS	Surgical excision	24 months / DF
Bradley et al. [4]	76 F	Posterior palate (L)	NS	Normal overlying mucosa, asymptomatic	None	NS	Incisional biopsy	36 months / DF
Bradley et al. [4]	73 F	Posterior palate (L)	NS	Normal overlying mucosa, asymptomatic	None	NS	Incisional biopsy	96 months / DF
Bradley et al. [4]	62 F	Posterior palate (L)	35 mm	Normal overlying mucosa, asymptomatic	None	4 months	Incision biopsy	41 months / DF
Bradley et al. [4]	41 F	Palate (L)	NS	Normal overlying mucosa, asymptomatic	None	3 months	Surgical excision	39 months / DF
Bradley et al. [4]	51 M	Posterior palate (L)	NS	Normal overlying mucosa, asymptomatic	None	NS	Surgical excision (recurred after 2 years in contralateral palate excised)	60 months / DF
Bradley et al. [4]	60 F	Posterior palate – bilateral	“Large”	Normal overlying mucosa, asymptomatic	Rheumatoid arthritis, serologic changes consistent with autoimmune disease systemic	NS	Incisional biopsy	120 months / Small residual swelling
Davila, Thompson [5]	49 F	Junction of the hard and soft palate (L)	30 mm	NS	Generalized lymphadenopathy	1 year	Surgical excision	84 months / DF
Napier, Newlands [6]	38 F	Junction of the hard and soft palate	10 mm	Slightly raised, non-tender, purplish-red mass	None	9 months	Surgical excision	NS
Napier, Newlands [6]	79 F	Junction of the hard and soft palate	“several cm”	Firm, slightly lobulated, diffuse swelling, purplish-red mass	None	NS	Surgical excision	NS
Mopsik et al. [7]	63 M	Posterior palate	30 mm	Soft mass, normal overlying mucosa, asymptomatic	None	1 year	Surgical excision	NS
Menasce et al. [8]	51 M	Junction of the hard and soft palate	20 mm	Slightly raised lesion	None	4 months	Surgical excision	48 months / DF
Menasce et al. [8]	75 M	Hard palate – posterior midline	10 mm	Swelling, raised non-ulcerated lesion	None	1 year	Surgical excision	24 months / DF
Menasce et al. [8]	61 F	Multifocal	20 mm	Swelling at the base of the tongue	Total thyroidectomy	NS	Surgical excision	192 months / DF
Kolokotronis et al. [10]	74 F	Hard palate (R)	25 mm	Painless, firm swelling	None	1 year	Surgical excision	18 months / DF
Jham et al. [15]	55 F	Posterior hard palate (L)	4 cm	Normal-coloured, smooth-surfaced swelling	Non-Hodgkin lymphoma	NS	No treatment (negative aspiration)	3 months / DF
*Gordón-Núñez et al	70 F	Soft palate (R)	2 cm	Normal overlying mucosa, soft consistence, reddish, sessile mass	Hypertension and osteoporosis	7 months	Surgical excision	8 months / DF

Abbreviations: M - male; F - Female; DF - Disease Free; NS - Not Stated, * Our case.

Table 1: Clinical and pathological features of the oral FLH cases previously reported.

Case Report

A 70 year old white woman, showing a nodular lesion in right posterior soft palate, reddish, soft, asymptomatic, slow-growing, sessile, measuring approximately 2 cm, with 7 month, without radiographic evidence of bone involvement and no regional lymphadenopathy (Figure 1). The patient had hypertension and osteoporosis. Fibroma and glandular lesion were the clinical hypotheses. An excisional biopsy was performed and the specimen was sent to the Laboratory of Pathological Anatomical, Oral Pathology Discipline, Rio Grande do Norte Federal University, Natal/Brazil. Histopathological analysis revealed lymphoid aggregates in the lamina propria of connective tissue, arranged in structures with discrete lobular appearance (Figures 2A, B and C), showing numerous lymphocytes in the periphery with scanty cytoplasm and homogeneously basophilic nuclei, forming the mantle zone. In central areas of these lymphocytic formations, germinal centers showed up, showing cells with large and dimly stained nuclei, sometimes revealing conspicuous nucleoli and scanty cytoplasm, tingible-body macrophages and occasional mitotic figures (Figure 2D). Permeating the interfollicular region, it was noted blood vessels of various sizes. The epithelial lining of the oral mucosa was composed of hyperplastic stratified squamous epithelium. Immunostaining for bcl-2 protein showed positivity in the mantle zone and absence of immunostaining in the cellular elements within the follicle centres (Figures 3A, B, C and D). Based on histopathological and immunohistochemical data, the diagnosis of oral follicular lymphoid hyperplasia was made. The patient is on follow up, and approximately 22 months after surgery, there was no evidence of disease.

Discussion

Follicular lymphoid hyperplasia of the hard palate is an uncommon, poorly understood entity which may be confused clinically and histologically with malignant lymphoma. The clinicopathological features of lymphoid hyperplasia in the oral mucosa were initially reported by Adkins in 1973 [1]. Although the number of patients seen by the author was not clearly stated in this report, he quoted the hard palate as the most common site affected [1].

The cases examined indicate that the FLH occurs more frequently in elderly female, aged 38 to 79 years, averaging 62 years. This case agrees with the literature both in the predilection for sex and in age, it is a female patient of 70 years.

Clinically, the usual manifestation is a firm, painless, non-ulcerated, non-fluctuant, slow growing mass or swelling on the one side of the

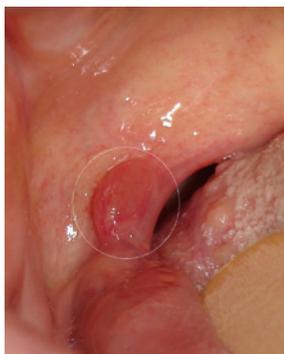


Figure 1: Clinical aspect of the nodular reddish lesion in the right posterior soft palate.

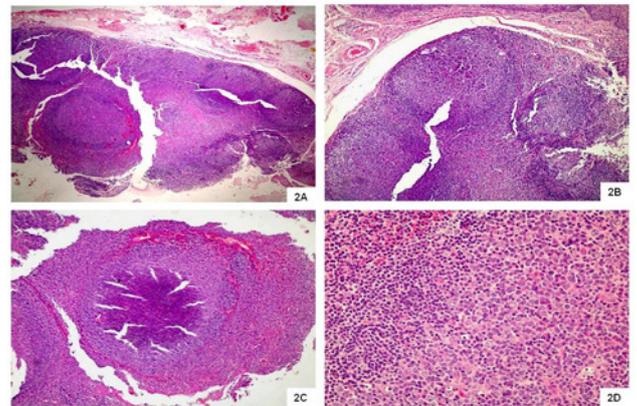


Figure 2: **A)** Lamina propria of connective tissue showing dense lymphoid infiltrate containing germinal centres and multiple lymphoid follicles of variable size and shape with discrete mantle zones (hematoxylin-eosin, X40). **B)** Follicular lymphoid infiltrate showing germinal centres and well-defined mantle zones (hematoxylin-eosin, X100). **C)** Germinal centers: cells with large and dimly stained nuclei, cells with conspicuous nucleoli and scanty cytoplasm, tingible-body macrophages Germinal centres and mantle zones (hematoxylin-eosin, X200). **D)** A relatively large number of residual centrocytes, centroblasts and immunoblasts, small mantle zone lymphocytes. Some centroblasts resembling L&H Reed-Sternberg cells (circle) (hematoxylin-eosin, X400).

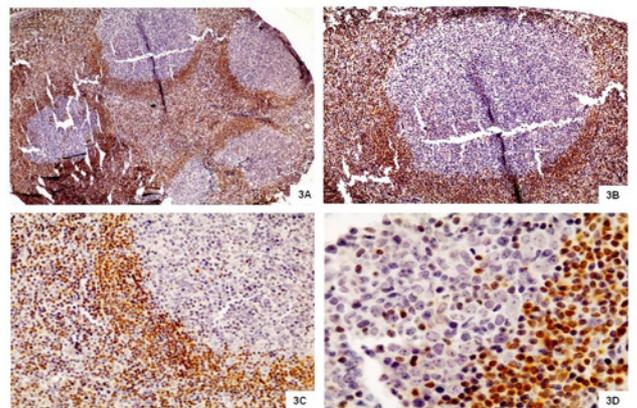


Figure 3: **A)** Immunostaining for bcl-2 protein is strongly positive in the mantle zone and negative within the follicle centre (Bcl-2, Immunoperoxidase stain with hematoxylin counterstain, X100). **B)** Germinal centre showing cells non-reactive for bcl-2 and positivity for this protein in cells of the mantle zone (Bcl-2, Immunoperoxidase stain with hematoxylin counterstain, X200). **C)** Strong immunoreactivity for bcl-2 protein in the mantle zone and negativity within the follicle centre (Bcl-2, Immunoperoxidase stain with hematoxylin counterstain, X400). **D)** Details of the immunostaining for bcl-2 protein in the mantle zone and negativity in the follicle centre (Bcl-2, Immunoperoxidase stain with hematoxylin counterstain, X1000).

palate. Occasionally, the lesions may be multifocal, and the patients may have bilateral involvement [1,2,4,8]. Lymphoid hyperplasia may affect the lymph nodes, the lymphoid tissue of Waldeyer's ring, and the aggregates of lymphoid tissue that are scattered throughout the oral cavity, particularly in the oropharynx, the soft palate, the tongue, and the floor of the mouth [9]. The size of the sessile mass varies from 10 mm to 40 mm in diameter [1-8], with an average of 2.6cm. At palpation, the lesion is soft and the tissues are non-colored [4,7], or colored (usually reddish-blue or blue-black) [1,4,5]. The length of time varies from 1 to 36 months, with an average of 9 months. The case reported here

showed soft consistence, with changing color (reddish lesions), surface intact and radiolucent radiographic appearance. The size and duration of the injury were below average (2cm and 8 months, respectively).

The clinical differential diagnoses include lymphomas of the palate, minor salivary gland tumors, palatal abscesses, and other rarer entities like benign lymphoepithelial lesion of the palate, mesenchymal tumors, and “tumor-like” lesions such as adenomatoid hyperplasia [10]. Glandular lesion and fibroma were the clinical diagnoses cited in this case. It should be emphasize the importance of a correct differential diagnosis of FLH, since they can be confuse with a malignant lymphoma, an aggressive lesion, being primary the histological and immunohistochemical analysis for definitive diagnosis [11,12].

Djavanmardi et al. [13], reported that the consideration of major importance for FLHs is their similarity to oral lymphomas, especially considering that non-Hodgkin lymphoma occurs with variable clinical signs and symptoms. Further, 25% of non-Hodgkin lymphomas are extra nodal, with 3-4% of all cases being located in the head and neck [14].

As previously mentioned, only 7 cases (33.3%) reported information about the symptoms of the lesion, all of which were asymptomatic, which is consistent with the case reported here.

Radiographically, there is no osseous abnormalities [3], and others laboratory investigations are usually normal [7,8]. The absence of radiographic change in the case reported here confirms the information reported in the literature.

The diagnosis of FLH of hard palate is based on the histological findings. Morphologically, multiple germinal centers are present and may have a rim of well-differentiated B lymphocytes, together with a mixed, mainly mononuclear infiltrate with many plasmacytic lymphocytes. Immunohistochemistry confirms that the lesion is reactive rather than neoplastic due to the polyclonal light chain restriction in the germinal centres and mature and immature B cells in the mantle zone with both B and T lymphocytes in the extramantle zone [1-8,11].

In some cases, as shown by Kolokotronis et al. [10] and Menasce et al. [8], the histological features are typical of lymphoid hyperplasia, causing no difficulties in diagnosis and without the need for further investigation. However, in other cases, the differential diagnosis between lymphoid hyperplasia and a lymphoma can be very difficult. Occasionally, a lymphoid follicular lesion may be present which shows indistinct germinal centres, ill-defined mantles and a lack of tingible-body macrophages imparting an impression of monotony to the lymphoid cell population. In such cases, the diagnosis is uncertain and the patient undergoes extensive clinical and laboratory investigation as part of the staging process for lymphoma [1,4,5,7,8].

In the case reported by Jham et al. [15], there was a vaguely nodular lymphoid proliferation with indistinct germinal centres, highly suggestive of follicular lymphoma and multiple immunostaining were performed to confirm the reactive nature of the lesion (positivity in lymphoid follicles for CD20, CD79a, CD10, BCL6 and CD21 and negativity for Bcl-2. The parafollicular areas showed positivity for CD3, CD5, CD30 and CD15. Both areas were positive for CD45 positive). In the same study, the authors emphasize the importance of the detection of IgH at the DNA level by use of PCR to assess monoclonality has become a routine technique in the initial diagnosis

of lymphoproliferative disorders. In this case, IgH analysis revealed that the tumour was polyclonal and further excluded a neoplastic process.

The treatment of choice for FLH is surgery, with the lesions responding well to excision [1]. According to Harsany et al. [2], radiotherapy has also been employed as treatment. Prolonged follow-up has not shown any evidence of malignant transformation [4]. In the case reported by Jham et al. [15], no further treatment was instituted due to the large size of the lesion (4cm) and to its asymptomatic character, and the patient will be kept under follow-up for 3 months. In our case, was planned and performed a surgical excision of the lesion and the patient is free of disease after 22 months years of follow-up.

A small number of patients have developed recurrences after local excision, others had experience of multicentric recurrences after treatment [2,4,8]. The duration of required follow-up to provide a clear distinction between the FLH and a lymphoma is not known. It has been suggested that some cases with involvement of multiple sites in the mouth over time may represent evolution into a MALT-type lymphoma (“Mucosa Associated Lymphoid Tissue”) [16]. However, information on clinical follow up in several reported cases with multifocal involvement; show that there was no recurrence or transformation into lymphoma [8]. Nevertheless, some authors advocate the need for at least five years of follow-up free of recurrence, after the biopsy, with absence of definitive treatment, to indicate a diagnosis of FLH [16].

The literature data shows that in regard to their malignant potential, the FLH effectively it is a non-neoplastic lymphoproliferative disorder in the oral mucosa, as it was not found reports of malignancy [10,11], similar the case reported here, where the patient not presented any abnormality in physical examination of the palatine region affected by the lesion after surgery.

At the present time, the etiology and the pathogenesis of this uncommon lesion is unknown. Wright and Dunsworth [3] believe that this follicular lymphoid hyperplasia of the palate represents a primary reactive lymphoid proliferation to some unknown antigenic stimulation. Mopsik and colleagues [7] reported that chronic irritation from a removable prosthesis cannot be excluded. However, the small number of patients who wear such prostheses makes this causal relationship unlikely [7,8]. The occurrence of lesions does not seem to correlate with the use of tobacco, or alcohol, or any medications [4]. An association with Sjögren syndrome, HIV-infection, or any other infection disease has not been documented [8]. Some authors suggest that Epstein-Barr virus may be associated with an unusual, aggressive and persistent form of lymphoid hyperplasia [17].

In conclusion, it has been reported here one more case of oral follicular lymphoid hyperplasia in the palate and proves it the unknown etiology of the lesion, as it has not been identified any causal factor involved in this case. In spite of its rarity in the oral tissues, due the clinical and histopathological characteristics similar to other entities such as follicular lymphomas, the diagnosis of this lesion requires a professional’s keen sense of clinical suspicion and definitive diagnosis requires a thorough histopathological analysis, aided, typically, by immunohistochemistry and/or, more recently, molecular studies in order to establish an appropriate treatment.

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