

## Benign Lymphoid Hyperplasia of the Tongue Masquerading as Carcinoma: Case Report and Literature Review

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### Abstract

Lymphoid hyperplasia of the tongue is a very rare benign lymphoproliferative lesion that closely resembles carcinoma or lymphoma, clinically or histopathologically. A case of benign lymphoid hyperplasia (BLH) of the tongue is reported. Clinically this lesion presented as a painless ulcer, which mimicked carcinoma of the tongue. Microscopy showed typical histologic features of multiple germinal centers with a rim of small mature lymphocytes together with a mixed, mainly mononuclear infiltrate which clinched the diagnosis of benign lymphoid hyperplasia. This diagnosis averted extensive investigations and major surgery. The etiology of these lesions is unknown. Their distinction from carcinoma and lymphoma is discussed.

**Keywords:** Benign lymphoid hyperplasia, lymphoma, tongue, immunohistochemistry

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## Introduction

Benign lymphoid hyperplasia (BLH) of the oral cavity and especially of the tongue is an uncommon, poorly understood entity which may be confused clinically and histologically with malignant lymphoma.<sup>1,2</sup> A limited number of publications addressing this subject are available in the literature and little is known about the etiology, natural history, and distinctive histologic features of these lesions. The posterior hard palate is the most common site to be affected.<sup>3</sup> It frequently occurs in elderly women; typically presents as an asymptomatic, slow growing, soft to firm non-ulcerated mass; and is occasionally bilateral. Some patients may present with multicentric oral lesions and/or associated lymphadenopathy. Clinical and laboratory investigations are usually normal. The lesion behaves in a benign manner and spontaneous regression has been reported. 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 a malignant process after long-term follow-up.<sup>2,3</sup>

Morphologically, BLH is characterized by a dense lymphoid infiltrate within the lamina propria and submucosa. The squamous epithelium is normal or slightly hyperplastic. The lymphoid infiltrate may show the classical features of a benign reactive follicular hyperplasia, causing no difficulties in diagnosis. However, not uncommonly, a lymphoid follicular lesion may be present showing indistinct germinal centers, ill-defined mantles, and a lack of tingible-body macrophages imparting an impression of monotony to the lymphoid cell population. This constellation of features may lead to an erroneous diagnosis of follicular lymphoma, with consequent staging procedures and unnecessary treatment.

Though one of the most common clinical differential diagnoses of an ulcer on the lateral border of the tongue is carcinoma, confirmation can be done only by histopathology, which will avoid further investigations and disfiguring treatment. The clinical and histologic similarities to carcinoma and lymphoma have been emphasized in this article. To date, only two articles are available on BLH of the tongue.<sup>1,2</sup> This case adds an additional example of this rare entity and we include a review of the available literature.

## Case Report

A 36-year old female presented with a progressive, painless ulcer on the left side of the tongue of nine months duration. The lesion bled during mastication and interfered with speech. There was no history of dental trauma, cough with expectoration, fever, or weight loss. Also, there were no other systemic symptoms like arthritis, xerostomia, or any other swellings over the body. The patient had been a tobacco chewer for twelve years.

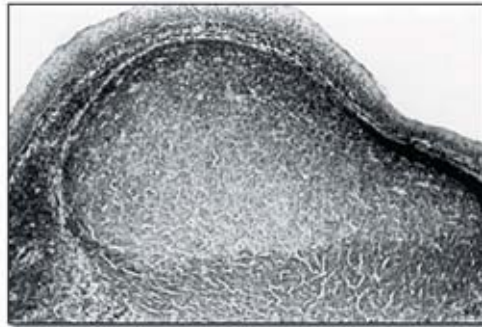
On examination her general condition and vital signs were normal. There was no cervical lymphadenopathy. Systemic review was unremarkable. Local examination revealed an ulcer of about 4 x 3 cm on the left lateral border of the tongue with slight everted edges (Figure 1). It was non-tender, firm, and bled to touch. The teeth had brownish stains but the rest of the oral cavity was normal.

Investigations revealed a normal hemogram and the ESR was 12 mm/h. Serological studies (ELISA for HIV and VDRL) were non-reactive. A chest x-ray was normal. A provisional diagnosis of malignancy of the left lateral border of the tongue was made and a wedge biopsy of the lesion was performed. Histopathological examination showed an ulcerated keratinized stratified squamous epithelium with focal areas of hyperplasia. The subepithelial tissue contained lymphoid follicles in various sizes and shapes; the germinal centers showed polymorphic lymphoid cell population in different stages of transformation with few mitotic figures, tingible-body macrophages with well-defined mantle zone composed of small lymphocytes with one area of squamous metaplasia. At certain areas, the mantle zone appeared slightly diffused. The interfollicular regions showed numerous vascular channels with occasional large lymphocytes and plasma cells (Figures 2 and 3). Hence, a diagnosis of benign lymphoid hyperplasia was made.

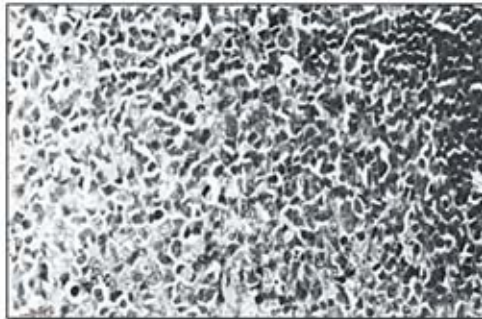
The lesion was subjected to surgical excision. There was no gross evidence of infiltration into the underlying lingual musculature. Histologic examination of excised tissue showed appearances essentially similar to those seen in the biopsy. The patient has been kept under close follow-up for the past four years, and there have been no signs of local recurrence.



**Figure 1.** Clinical photograph showing the lesion.



**Figure 2.** Photomicrograph showing dense lymphoid infiltrate containing germinal center and lymphoid follicle (H & E stain, Original magnification x 100).



**Figure 3.** Photomicrograph showing reactive germinal centers with tingible body macrophages and frequent mitosis (H & E stain, Original magnification x 400).

### Discussion

BLH, the so-called 'pseudolymphoma,' has been alternatively termed benign lymphoid polyp, lymphoid pseudotumor, or lymphocytic pseudotumor.<sup>4</sup> The term 'pseudolymphoma' is an unfortunate one because of its possible confusion for the unwary with malignant

lymphoma. Nevertheless it has gained acceptance where, by convention, it is reserved for benign lymphoproliferative lesions that are reactive in nature.<sup>2</sup> It has been described in many locations of the body, notably skin, gastrointestinal tract, lungs, nasopharynx, larynx, and breasts.<sup>5</sup> In the context of lymph nodes pseudolymphomatous atypical reactive hyperplasia has been reported in patients receiving a number of drugs, including long-term treatment with the anti-convulsant drug diphenylhydantoin. Cutaneous lesions of pseudolymphoma have been variously termed as Spiegler-Fendt sarcoid.<sup>2</sup> The plethora of diagnostic labels reflect the uncertainty of the etiology and pathogenesis of these lesions.

Adkins<sup>6</sup> initially reported the clinicopathological features of BLH in the oral mucosa in 1973. Since then a number of reports have appeared, and it seems the hard palate is the most common site affected.<sup>3,5,7</sup> Occasionally the lesions may be multifocal and bilateral. BLH of skin or mucosa typically presents as an asymptomatic, non-ulcerated mass, but our patient presented with a painless ulcer on the left lateral border of the tongue, which is the most common site for malignancy, especially in a patient who has been a chronic tobacco chewer for twelve years. The size may vary from 10 mm to 40 mm in diameter. At palpation, the lesion is soft; rarely does a cervical or generalized lymphadenopathy exist.<sup>7</sup> It is generally recognized the clinical presentation of these benign lesions may be quite similar to that of a carcinoma or lymphoma in the same location, so histologic examination of a tissue sample of adequate size is essential for their differentiation. The diagnosis of BLH is favored over that of carcinoma or lymphoma when there is a mixed infiltrate of small, round lymphocytes; large lymphoid cells; plasma cells; eosinophils; macrophages; and neutrophils rather than a uniform infiltrate of one lymphoid cell type. The presence of germinal centers aids greatly in the diagnosis of a benign lesion, although it is recognized germinal centers may not be present in all areas of a benign lesion. A majority of these histological features was found in our patient. Endothelial cell hyperplasia within the lymphoid infiltrate is more commonly seen in benign lesions. Involvement of regional lymph

nodes is considered to favor the diagnosis of a carcinoma or lymphoma.<sup>7,8</sup> However, the differentiation between BLH and lymphoma can be very difficult at times and some authors question the existence of 'pseudolymphoma' as a truly benign, distinct entity. Some authors suggest criteria based on architectural, cytological, and immunologic features to assign lymphoid lesions to one of three categories: definitely benign, definitely malignant, and those of uncertain prognosis. The features thought most useful in predicting benign behavior are (1) the presence of well-formed germinal centers predominantly composed of small and large sized lymphocytes with tingible-body macrophages, (2) sharply defined mantle zones of small regular lymphocytes, and (3) the polyclonal nature of the infiltrate, as in our patient.

Immunohistochemical staining of cell surfaces or cytoplasmic immunoglobulins in lymphocytic infiltrates has been used to aid in the histologic differentiation between reactive lymphoid infiltrates and malignant lymphoma. It is generally recognized lymphomas are monoclonal, as shown by a single light-chain type among the lymphocytes, while reactive lymphocytic infiltrates are polyclonal. It was thought immunocytochemical staining is much more likely to provide useful information when fresh tissue is available.<sup>9</sup> Recently, several families of antileucocyte monoclonal antibodies have been described for use in routinely fixed and processed specimens, foregoing the need for fresh tissue. These antibodies not only allow the classification of lesions into B - or T - cell categories, they also allow immunologic profiles to be established; when used as a part of standardized protocol, these antibodies can aid in distinguishing benign from malignant proliferation. A reticular pattern of positive staining with  $\kappa$  and  $\lambda$  light chains is usually seen in reactive germinal centers. Such a pattern is not seen in follicles of non-Hodgkin's lymphomas. The polyclonal nature of the lesion suggests a reactive lymphoid infiltrate rather than a malignant one. The staining reactions in the extramantle zones confirm the polyclonal and pleomorphocellular nature of the proliferation of lymphocytes in the lesion. In our case, as the histological features were typical of BLH, the diagnosis was fairly straightforward and, thus, immunophenotyping was not considered.

The etiology of BLH has not been clarified. A detailed literature review has not revealed any source of persistent chronic irritation such as an ill-fitted denture, association with Sjogren's syndrome, or an infectious etiology. An association with HIV has not been documented. There has been one case of a widely disseminated, persistent lymphoid hyperplasia with some histological features of Castleman's disease described. This case also included involvement of the cervical nodes, the lacrimal and parotid glands, orbits, mediastinum, and hard palate. Epstein-Barr virus (EBV) DNA was detected in one of the specimens. Clonal rearrangements of the immunoglobulin heavy chain and the T - cell receptor were detected in a further specimen, and these authors suggested EBV may be associated with a form of aggressive and persistent lymphoid hyperplasia that contains clonal rearrangements of DNA.<sup>10</sup>

The clinical differential diagnoses included carcinoma of the tongue (most common in this part of the globe), tuberculosis, syphilis, and rarely minor salivary gland tumors. The treatment of choice for BLH of the tongue is local excision of the lesion; this was executed in our patient. In a very low proportion of patients radiotherapy (RT) alone or a combination of surgery and RT has been tried. Treatment with steroids has not been reported. Some patients have experienced multicentric recurrences following treatment.<sup>3,5,7</sup>

The length of follow-up necessary to provide an unequivocal distinction between BLH and lymphoma is not known. It has been suggested some cases with multiple sites of BHL in the oral cavity eventually turn into MALT type (Mucosa Associated Lymphoid Tissue) lymphoma. But follow-up reported in various case reports in the literature with involvement of more than one site reveal no recurrence or transformation to a lymphoma, giving little strength to this hypothesis.<sup>5</sup> In a report of long-term cutaneous lymphoid hyperplasia a patient's disease was considered benign if there was no evidence of lymphoma or leukemia after (minimum) five years from the original biopsy.<sup>11</sup> Some authorities, however, advocate that at least five recurrence-free years following biopsy in the absence of definitive treatment are required to indicate a diagnosis of BLH.<sup>2</sup>



## Conclusion

In conclusion follicular hyperplasia of the tongue is a benign condition, which can be adequately treated by surgical excision. Awareness of this entity combined with the use of

immunohistochemistry (when diagnosis is doubtful) allows a correct diagnosis to be made avoiding extensive investigation and aggressive treatment to the patient.

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