

# Oral lymphangiomas – clinical and histopathological relations: An immunohistochemically analyzed case series of varied clinical presentations

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## Abstract

Lymphangiomas are benign malformations that represent hamartoma of malformed lymphatics and are composed of cystically dilated lymphatic channels which do not communicate or drain into other lymphatic channels or veins leading to accumulation of lymph. They are congenital malformations with rare occurrence in oral cavity within which tongue dorsum is the most affected site. Venous malformations are often difficult to differentiate from lymphatic malformations leading to the development of several lymphatic markers like D2-40 which seems to be useful for distinguishing vascular from lymphatic vessels. The most effective treatment is surgery having good prognosis for most of the patients but depending on their location (neck/tongue) and size (large size) they may cause airway obstruction causing death. Herewith, we present the rare cases of oral lymphangiomas of tongue, palate and buccal mucosa with varied and characteristic clinical presentations.

**Keywords:** D2-40, hamartoma, lymphangioma, lymphatic markers, vascular malformation

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## INTRODUCTION

Lymphomas are the hamartomas which arise from malformed lymphatics which fails to drain into other lymphatics or veins and hence accumulate lymph and enlarge forming cystically dilated lymphatics.<sup>[1,2]</sup> These slow-growing, painless soft-tissue mass was first described in 1828 by Redenbacher and then in 1854 Virchow first described lymphangiomas of the tongue.<sup>[2]</sup> They are benign developmental malformations rather than true neoplasms characterized by abnormal proliferation of lymphatic channels.<sup>[2-4]</sup> According to the another school of thought, they may originate endothelial fibrillar membranes which

bulges from the cystic wall and penetrates the surrounding tissue which canalize and form more cyst.<sup>[4]</sup> They have marked predilection for head and neck region which accounts for 50%–75% of cases out of which 50% of the lesions are present since birth and 90% of lesions arises within 2 years of age.<sup>[2,3,5,6]</sup>

Lymphangiomas have been classified into 3 types: (1) Lymphangioma simplex or capillary lymphangioma consisting of small, thin-walled capillary-sized lymphatic vessels; (2) cavernous lymphangioma, comprising large, dilated lymphatic vessels; and (3) cystic lymphangioma

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or cystic hygroma exhibiting large macroscopic cystic spaces.<sup>[3,7,8]</sup>

In the oral cavity, tongue dorsum is the most common site and that too the anterior two-third part followed by lips, buccal mucosa, soft-palate and floor of the mouth.<sup>[2,3]</sup> Surgical excision is the preferred treatment when vital structures are not involved.<sup>[2,5]</sup> Other procedures such as laser therapy, sclerotherapy, radiation therapy, electrocautery, cryotherapy, ligation, embolization and steroid administration have also been suggested.<sup>[2,9]</sup> This report presents four cases of oral lymphangiomas with varied clinical presentation.

## CASE REPORTS

### Case 1

A 6-year-old boy reported with painless palatal lesion which was gradually increasing in size. His mother gave a history that she noticed the lesion at the age of 4 months and due to static and asymptomatic nature; she assumed some kind of mole over there and ignored it. Since the past few months, she noticed that the lesion was gradually increasing and attained the present size and for the same, she sought treatment and reported us. The boy was with a good health, and no systemic illness or other contributory findings were noticed. Intraoral examination revealed that there was bluish-opaque appearing lesion and mucosal surface appeared pebbly with few reddish to bluish black patchy papules; at the middle third of the plate extending from at the level of mesial surface of 54 to the anterior border of soft plate; size approximately 3 cm × 2.5 cm. Surrounding mucosa appeared wrinkled, nontender on palpation and did not bleed on provocation. Provisional diagnosis as lymphangioma of palate was made [Figure 1a]. An incisional biopsy was performed and sent for histopathology. Histopathology revealed numerous single endothelial lined vessels of variable sizes from subepithelial region till the depth of submitted tissue. Few large cavernous spaces too were seen, mostly filled with lymph [Figure 1b]. Immunostaining with lymphatic marker

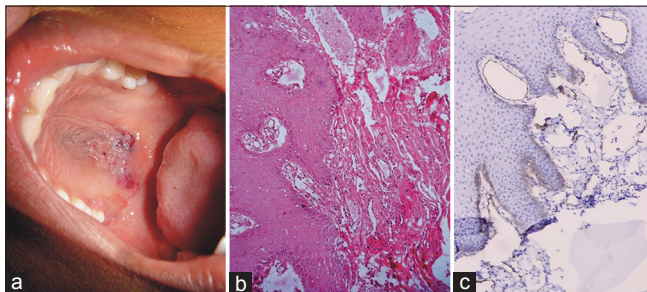
D2-40 yield positive results [Figure 1c] and a diagnosis of lymphangioma (simplex) was confirmed.

### Case 2

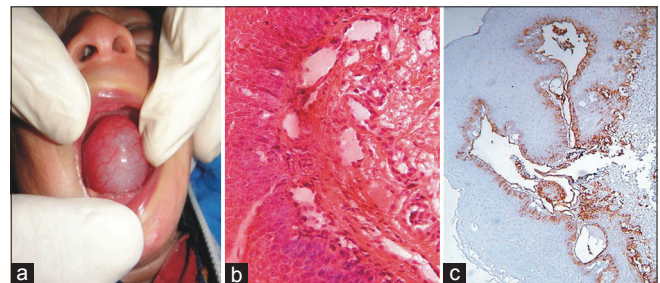
A 13-day-old baby boy was referred to us by child specialist with tongue swelling since birth; causing difficulty in feeding. The baby was with good health. Hematological examinations were within normal limit. Intraoral examination revealed that there was a large fluctuating, tense swelling over ventral surface of tongue pushing entire tongue toward palate. The swelling was extending from tip of the tongue to the base as well as extending bilaterally up to the lateral borders; covering the entire ventral surface of the tongue. The swelling was translucent in color with many fine, prominent radiating blood vessels [Figure 2a]. Aspiration of the lesion showed colorless mucoïd fluid and a provisional diagnosis as mucocele was given. An incisional biopsy was taken for histopathology. Histopathology revealed parakeratotic stratified squamous epithelium with almost flattened rete ridges. Stroma showed many small dilated endothelium-lined vessels containing homogeneous eosinophilic material suggestive of lymph vessel [Figure 2b]. The findings were suggestive of cavernous lymphangioma. Further positive staining with D2-40 marker confirmed the diagnosis [Figure 2c].

### Case 3

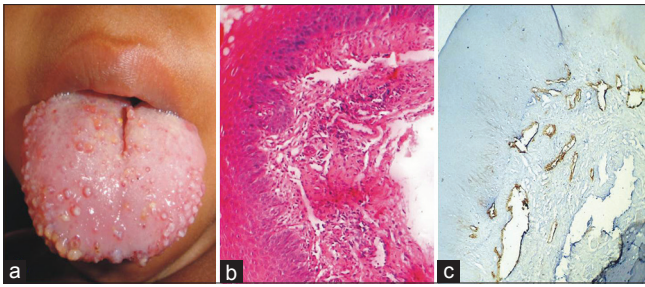
A 2-year-old child reported with tongue lesion for the past 6–7 days and there was difficulty in closing mouth. History revealed that he previously had red eruptions over tongue 4 months back, that disappeared completely on medications. After 2½ months, these red lesions reappeared and for the past 6–7 days, we observed protruded enlarged tongue with difficulty in closing mouth and many small elevated nodules with pink or yellowish [Figure 3a]. All the routine examinations were in normal range. Provisional diagnosis as lymphangioma of tongue with macroglossia was made. Incisional biopsy was taken and sends for histopathology. Multiple bits of H and E stained sections under microscopic examination showed globular areas filled with RBCs and degenerated tissue, whereas at the periphery,



**Figure 1:** (a) Clinical picture; (b) Photomicrograph (H&E, ×10); (c) Photomicrograph (D2-40 stain, ×10)



**Figure 2:** (a) Clinical picture; (b) Photomicrograph (H&E, ×10); (c) Photomicrograph (D2-40 stain, ×10)



**Figure 3:** (a) Clinical picture; (b) Photomicrograph (H&E,  $\times 10$ ); (c) Photomicrograph (D2-40 stain,  $\times 10$ )

it showed necrotic slough. Underlying connective tissue stroma was loose fibro-cellular and showed numerous single endothelial lined vessels of variable sizes [Figure 3b]. Immunostaining with D2-40 marker was carried out, and the positive finding [Figure 3c] confirmed the diagnosis of capillary lymphangioma.

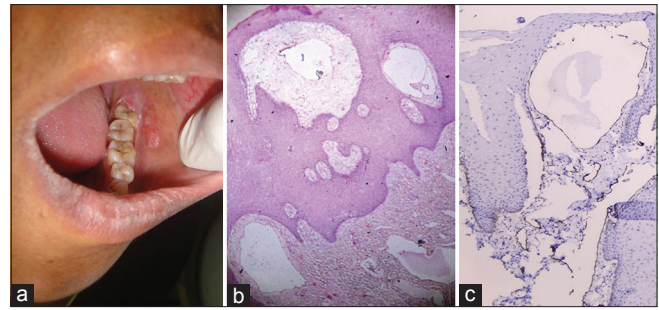
#### Case 4

A 32-year-old female reported with an intraoral lesion in the left buccal mucosa. Initially, swelling was smaller and gradually increased to present size, measuring 2 cm  $\times$  1 cm (approx.) and shows erythematous area with transparent vesicles giving granular appearance. It was soft, compressible and nontender on palpation. Hematological examinations were within normal limit. Provisional diagnosis as lymphangioma of the left buccal mucosa was made [Figure 4a]. An incisional biopsy was performed and sent for histopathology. Histopathology revealed stratified squamous epithelium overlying fibro-cellular connective tissue stroma. Epithelium is hyperplastic. Stroma revealed dilated endothelial lined vessels of variable sizes [Figure 4b]. These findings were suggestive of cavernous lymphangioma which was confirmed by positive staining by D2-40 marker [Figure 4c].

#### DISCUSSION

Three theories were proposed for explaining the origin of lymphangiomas, first suggests the cessation of normal growth of primitive lymph channels during embryogenesis, the second was the inability of primitive lymphatic sac to reach the venous system and the third suggested the development of lymphatic tissue in the wrong area during embryogenesis.<sup>[10]</sup> Clinically, they are classified into macrocystic ( $>2 \text{ cm}^3$ ), microcystic ( $<2 \text{ cm}^3$ ) and mixed (combination of both).<sup>[11]</sup>

Oral lymphangiomas may manifest as a translucent plaque made from small thin-walled vesicles appearing like frog eggs [Figures 1a and 4a].<sup>[2]</sup> Oral lesions frequently appear on tongue showing irregular nodularity demonstrating pebbly



**Figure 4:** (a) Clinical picture; (b) Photomicrograph (H&E,  $\times 10$ ); (c) Photomicrograph (D2-40 stain,  $\times 10$ )

appearance and translucent hue owing to its superficial location and having gray, pink or yellowish color with macroglossia, which is also a pathognomonic feature of lymphangioma of tongue [Figure 3a].<sup>[2,7,11,12]</sup> Nodular masses of red or blue color may also appear clinically which can be due to rupture of blood capillary into the inner lymphatic space [Figure 1a].<sup>[7]</sup> Deeper lesions were presented as masses of soft and diffuse growth with normal color [Figure 2a].<sup>[2,11]</sup>

Although history and physical examination can suggest the diagnosis of lymphangiomas but at times it is necessary to confirm the diagnosis and differentiate them from other entities and therefore differential diagnosis includes hemangioma, dermoid cyst, teratoma, amyloidosis, thyroglossal duct cyst, neurofibromatosis, granular cell tumor, mongolism, congenital hypothyroidism, primary muscular hypertrophy, lipomas, neurofibroma, salivary gland and thyroid tumors, heterotopy of gastric mucosal cyst and meningoencephalocele.<sup>[2,11,13]</sup>

Radiographic evaluation such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) may be required. US can be used routinely to evaluate the size and extension of the lesion.<sup>[10]</sup> Both CT and US are useful to evaluate solid or cystic nature of the lesion whereas MRI has been suggested to be most useful in evaluating the extension of the lesion.<sup>[13]</sup>

Histopathologically, lymphangioma consists of lymphatic vessels which are lined by thin endothelial lining with marked dilatations and this lymphatic space may appear empty or consist of proteinaceous material and occasional lymphocytes, macrophages and neutrophils.<sup>[2,12]</sup>

Conventionally, there are three different histological groups of lymphangioma: simplex (capillary), cavernous and cystic. It has been suggested that when lymphangiomas are present in fairly dense tissue such as tongue or floor of the mouth, they presents as cavernous type whereas when confined

to very loose fascia like fascia of the neck they presents as cystic type or cystic hygromas.<sup>[10]</sup>

Although all three types may be found together depending on the severity.<sup>[10]</sup> In this series, deeper lesion of the tongue (Case 2) and lesion of buccal mucosa present as cavernous lymphangioma whereas superficial tongue lesion (Case 3) and palatal lesion (Case 1) present as simplex type. It has been concluded that histological differences are attributed to different anatomical location and thus histological classification is of little clinical benefit.<sup>[12]</sup>

Differentiating lymphatics and blood vessels by light microscopy has long been a problem.

Pan-endothelial markers such as CD105, CD31, and CD34 are generally used for identification of microvessels, but none of these are specific for lymphatic vessels. Recently, numerous relatively specific antibodies for lymphatic vessels have been identified such as podoplanin, vascular endothelial growth factor receptor 3, lymphatic vessel endothelial HA receptor-1, D2-40 and Prox 1.<sup>[12,14]</sup>

D2-40 is a monoclonal antibody which was used to identify an oncofetal glycoprotein (M2A antigen) expressed by testicular germ cell neoplasm. This M2A was found in lymphatic endothelial cells but not in blood endothelial cells therefore D2-40 can be used as a reliable marker to detect lymphatic endothelial cells.<sup>[12,14]</sup> In our series, all cases showed positive staining with D2-40 marker.

Lymphangiomas treatment depends on their size, location and infiltration to the surrounding tissues.<sup>[11]</sup> Surgical excision is the treatment of choice with the inclusion of a surrounding border of normal tissue. Recurrence rate is around 39% because of its infiltrative nature and surgeons often worry in achieving complete resection.<sup>[2,13]</sup> Therefore nonsurgical therapy like sclerosing therapy and that too with OK-432 has also been suggested for recurrent and unresectable cases as it has main advantage of the absence of perilesional fibrosis as compared to other sclerosing agent.<sup>[10]</sup>

Classical cases with varied clinical presentation have been presented and discussed in relation with histopathology and location, and overall finding were confirmed by D2-40 staining. Depending on their location complication may arise such as tongue's extrusion, obstruction of upper airways, difficulties in mastication and speech. Due to such

complications, as well as difficulties in achieving complete resection, early diagnosis and intervention is necessary to allow proper treatment and prevents complications.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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