



## LYMPHANGIOMA OF TONGUE IN PAEDIATRIC PATIENTS: A REVIEW

### Pedodontics

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### ABSTRACT

Lymphangioma is a rare benign tumor resulting from a congenital malformation of the lymphatic system, usually diagnosed in infancy and early childhood. Intraoral lymphangiomas occur more frequently on the dorsum of tongue, followed by the palate, buccal mucosa, gingiva, and lips. Lymphangioma of the tongue is a common cause of macroglossia in children associated with difficulty in swallowing and mastication, speech disturbances, airway obstruction, mandibular prognathism, open bite, and other possible deformities of maxillofacial structures. The most effective treatment depends on their size and location.

### KEYWORDS

Lymphangioma, Tongue, Macroglossia

#### INTRODUCTION:

Lymphangioma is a rare, benign, congenital hamartomatous malformation of unknown etiology originating from the lymph vessels. About 50% of the lesions are usually noted at birth and around 90% develop by the age of two [1]. It commonly affects the head and neck region accounting for 75% of all cases, involving the anterior triangle, the upper middle third of the clavicle in the posterior triangle of the neck, anterior edge of the trapezius muscle, posterior border of the sternocleidomastoid, the submandibular and parotid regions. Apart from the head and neck region, lymphangioma of proximal extremities, buttocks, and trunk have also been reported, only 1% of the lesions occurs at the intestinal, pancreatic, and mesenteric level of the gastrointestinal tract [1,2]. In the oral cavity, the anterior two-thirds of the tongue is the most commonly involved. Other sites include cheeks, lips, the floor of the mouth, palate, gingiva and alveolar ridge of the mandible have also been reported. Occasionally, oral lymphangioma is associated with various syndromes like Turner's syndrome, Noonan's syndrome, Trisomies, Cardiac anomalies, Foetal hydrops, Foetal alcohol syndrome, and Familial pterygium colli [3,4]. However, this paper highlights the aetiopathogenesis, clinical signs and symptoms, classification, histopathological features, markers of lymphangioma, differential diagnosis, investigations, diagnosis, management, and complications of lymphangioma of tongue in pediatric patients.

In the oral cavity, lymphangioma commonly occurs during the first decade of life and mostly on the dorsal surface and lateral border of the tongue [5]. In 1854, Virchow first described lymphangioma. Despite the fact that lymphangioma is a rare lesion, it contributes to 4% of all vascular tumors and 25% of vascular tumors in children. There is no evidence of racial predilection and equal gender incidence is reported in most of the studies [3]. It has been reported that the incidence of lymphangioma ranges from 1.2 to 2.8 per 1000 newborns [6]. It is hypothesized that they develop from congenital obstruction or sequestration of the primitive lymphatic cells that present proliferative capacity and are commonly capable of accumulating fluids, which give them a cystic appearance. Because these cells do not anastomose efficiently with bigger lymphatic vessels, they provoke areas of lymphatic blockage [2]. Lymphangiomas usually manifest as papillary lesions with the same color as the adjacent mucosa. The clinical presentation depends on the size and extent of the lesion. Deep lesions present as soft masses with a similar color to the normal tissue. Tongue lymphangiomas are usually superficial with a pebbly surface resembling a cluster of translucent vesicles. The anterior two-thirds of the tongue is the most commonly affected site leading to swelling and enlargement of the tongue. Patients with tongue lymphangioma usually suffer from speech disturbances, poor oral hygiene, and bleeding from the tongue when exposed to trauma [3]. Small lymphangiomas < 1cm in dimension occur on the alveolar ridge in

about 4% of black neonates. These lesions occur bilaterally on the alveolar ridge [6].

#### Aetiopathogenesis:

The etiology of lymphangioma remains unclear, but two different theories have been proposed to analyze the origin. One of the major theories suggests that the lymphatic system originates from five poorly developed sacs arising from the venous system which include paired jugular sacs, paired posterior sacs, and a single retroperitoneal sac. In the maxillofacial region, an endothelial outpouching from the jugular sac spread centrifugally to form the lymphatic system. Another hypothesis states that the lymphatic system originates from mesenchymal clefts in the venous plexus reticulum and spread centripetally toward the jugular sac [5,7]. But according to some studies, three theories have been proposed to explain its origin. The first suggests that a blockage or arrest of normal growth of the primitive lymph channels occurs during embryogenesis, the second is that the primitive lymphatic sac does not reach the venous system, and the third hypothesizes that the lymphatic tissue lays in the wrong area during embryogenesis [6].

#### Clinical features:

Clinically, lymphangioma manifests as a small, slow-growing, painless, pink or yellow soft tissue mass studded with transparent cystic vesicles [8]. Even though lymphangioma is evident at birth but remains unnoticed until the eruption of teeth or even after puberty with an incidental trauma or an upper respiratory tract disorder at the site. With each episode of upper respiratory tract infection, the tongue enlarges and while protruding through the lip margin, it is frequently exposed to trauma. These repeated episodes of infection and trauma lead to fibrous tissue being laid down. This leads to further dilatation of lymphatic channels and permanent enlargement of the tongue [9]. However, most of the lesions are recognized early based on their size and the associated symptoms of respiratory obstruction and problems with feeding, which are the most common presenting symptoms. Lymphangioma extending into the oral cavity, oropharynx, and/or the hypopharynx results in difficulty in swallowing. Isolated tongue involvement can lead to macroglossia with dysphagia and airway obstruction. Sometimes, the airway and swallowing problems may even persist after the surgery in the neck region because of mucosal edema, enlargement of internal lymphangioma, and the loss of neural innervation to the pharynx or tongue [6].

Lymphangioma of the tongue is more often associated with the involvement of the head and neck than the isolated lesion. The most common site on the tongue is its anterior two-thirds. Lingual lymphangioma usually involves the dorsum of the tongue and the tip of the tongue is a rare occurrence. The clinical presentation varies based on whether the lesion is superficial or deep. Superficial lesions present

as papillary lesions with an irregular pebbly surface due to the presence of several translucent vesicles of the same color as that of adjacent mucosa or gray, pink, or yellowish color with macroglossia, which is a pathognomonic feature of lymphangioma of tongue occasionally with a mild reddish hue. 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. This gives lymphangioma a tapioca pudding or frog eggs-like appearance. The deeper lesions manifest as diffuse nodules that are soft in consistency with negligible alterations in color or texture [1,8], and their consequences may result in swelling of tissues leading to pain, poor oral hygiene, increased salivation, extrusion of the tongue, upper airway obstruction[5].

However, isolated or associated tongue lesions can lead to macroglossia with excessive salivation, halitosis, dysphagia, airway obstruction, and orthodontic and cosmetic abnormalities [9], and when the lesion increases its size leading to swelling of the tongue, which eventually interferes with speaking and mastication, endangering life due to its secondary infection. The clinical presence of lymphangioma above the surface of the tongue takes the form of localized or diffuse or occasionally nodular swellings. It becomes easier to excise the lesion with different modes of tongue reduction when its extension is limited [3].

#### Histopathological features:

The histologic features of lymphangioma consist of dilated lymphatic vessels with infiltration into the adjacent soft tissue and present as lymphoid aggregate in their wall. The endothelial lining in these vessels is very thin with the spaces containing proteinaceous fluid and lymphocytes. The lymphatic space is filled with lymphatic fluid, red blood cells, lymphocytes, macrophages, and neutrophils and sometimes, secondary hemorrhage may be noticed in the lymphatic vessels[8]. In 1938, Goetsch et al. detected that the isolated lymphatic tissue contributes to cyst formation, which eventually enlarges by the accumulation of lymph caused by the projection of endothelial out-pouching from the cystic walls. This leads to severe tissue destruction and infiltration of the lesion into areas of least resistance, between muscles and vessels, infiltrating tissue planes resulting in atrophy, fibrosis of the muscles, and hyalinization of the tissues. Whimster et al., 1976 stated that the basic pathological mechanism is the collection of lymphatic cisterns in the deep subcutaneous plane. It was proposed that during the period of embryonic development, these cisterns originate from a poorly developed lymph sac that has lost its connection with the remaining lymphatic system. The lining of the sequestered primitive sacs is comprised of a thick layer of muscle fibers that undergoes rhythmic contractions. These rhythmic contractions raise the pressure inside these sacs, causing dilated or distended channels to come out from the walls of cisterns toward the skin. Later, it was proposed that vesicles seen in lymphangioma are due to outpouching of these dilated and distended protruding lymphatic vessels. Whimster eventually concluded that lymphangioma develops due to occlusion, sequestration, and enlargement of the poorly developed lymphatic vessels[3].

#### Classification:

Based on the histopathological appearance, Lymphangioma has been classified into

- (1) Capillary (simplex) consisting of small capillary-sized vessels. It involves a cluster of vesicles measuring about 2–4 mm. These clear vesicles range from pink to red to black due to secondary hemorrhage.
- (2) Cavernous consisting of large dilated lymphatic vessels. Cavernous lymphangioma appears as subcutaneous nodules, with a rubbery consistency. They have a clear dimension than capillary. The overlying skin has no lesions or changes. This variation is usually found on the tongue and floor of the mouth [10].
- (3) Cystic showing large, macroscopic cystic spaces Cystic lymphangioma is usually larger than cavernous and more commonly occurs in the parotid region in the head and neck [4].
- (4) Benign lymphangioendothelioma – In this variation, lymphatic channels appear to be dissected through dense collagenic bundles [11].

Based on their clinical presentation they are classified into

- a) Macrocystic - cavities  $> 2\text{cm}^3$
- b) Microcystic – cavities  $< 2\text{cm}^3$

- c) Mixed – a combination of macrocystic and microcystic [1].

#### Differential Diagnosis:

Lymphangioma is an important cause of macroglossia in children and the clinical differential diagnosis depends upon the extent of tongue involvement. Localized macroglossia can be caused by vascular malformations, lymphangioma, neurofibroma, Teratoma, Dermoid cyst, Lingual thyroid, Thyroglossal duct cyst, Heterotopic gastric mucosal cyst, Granular cell tumor, and Leiomyoma whereas generalized macroglossia can be caused by Hemangioma, Lymphangioma, Chronic steroid therapy, Hypothyroidism, Acromegaly, Amyloidosis, Idiopathic muscular hypertrophy, Down's syndrome, Mucopolysaccharidosis, and Diabetes mellitus [9].

#### Markers of Lymphangioma:

The use of light microscopy has been a long-term problem in differentiating lymphatics and blood vessels. Some of the pan-endothelial markers such as CD105, CD31, and CD34 are generally used in the identification of microvessels, but none of these are specific for lymphatic vessels. The detection of specific markers such as podoplanin, VEGFR-3 (Vascular Endothelial Growth Factor Receptor 3), PDGFs (Platelet Derived Growth Factors), D2-40, Prox-1, Lymphatic Vessel Endothelial HA receptor-1 (LYVE-1), and Ki67 has been implemented using recently introduced diagnostic techniques. This facilitates the study of prognosis, recurrence rate, and targeted therapy of the lesions with aggressive behavior with the tendency for recurrence. When contrasted with those of normal tissues, the Lymphatic Endothelial Cells (LECS) of lymphangioma have different molecular expressions of biomarkers.

The expression of the Prox-1 marker is the characteristic feature of immature lymphatic endothelial cells. Further studies have shown an increased reaction of LECs for VEGFR-3 (vascular endothelial growth factor receptor 3) and PDGFR-beta (platelet-derived growth factors- $\beta$ ) suggesting that lymphangioma responds to anti-VEGFR-3 and anti-PDGFR beta targeted therapeutic approach. D2-40 is a monoclonal antibody that is used to identify an oncofetal glycoprotein (M2A antigen) expressed by testicular germ cell neoplasm. This M2A is 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. Hence, the use of immunocytochemistry or molecular techniques becomes mandatory for the proper diagnosis of infantile lymphangiomas [12,10].

#### Investigations and Diagnosis:

The diagnosis of lymphangioma depends on the clinical features, histopathological examination, and imaging techniques. Ultrasound and angiography are commonly used imaging modalities. Usually, ultrasonography helps to identify the cystic nature and fluid component of a lymphangioma and angiography plays an important role in the diagnosis of lymphangioma by ruling out the vascular lesions [13]. An accurate demarcation of the lesion should be determined for proper diagnosis, surgical planning, and for assessing the recurrence [14]. Ultrasound imaging is the most commonly used aid that identifies unilocular or multilocular irregular cystic masses lined by a thin or thick smooth wall [3]. Some investigators have shown that Magnetic Resonance imaging can determine the extension of the lesion more accurately than ultrasound and Computerised Tomography (CT) scans. Lymphangioma is difficult to differentiate from muscle on T1-weighted and hyperintense compared to fat on T2-weighted MR images [14].

#### Complications:

Whenever lymphangioma shows rapid growth an underlying factor such as an associated tumor or respiratory tract infection may be responsible [6]. The complications of lymphangioma may affect the patient broadly in four dimensions such as aesthetic, occlusal, functional, and psychosocial aspects [10]. Depending on the location of the lesion, complications may arise such as extrusion of the tongue, difficulty in speech and mastication, and obstruction of upper airways [1]. Complications related to an infection can occasionally result in Ludwig's angina associated with an infected base of the tongue [11]. Postoperative complications include Seroma formation, Infections, minor bleeding, recurrent cellulitis, and lymph fluid leakage [13]. Due to such complications, as well as difficulty in achieving complete resection of the lesion, early diagnosis and intervention are necessary for reducing functional, psychological, disturbances and cosmetic disfigurement [12,15].

**Management:**

The main objective in the management of lymphangioma of the tongue is the preservation of the taste sensation and the restoration of tongue size for articulation [8]. The treatment depends upon the size of the lesion, histologic type, involvement of anatomical structures, and infiltration into the surrounding tissues. The localized macro cystic lesions can be easily excised whereas the diffuse microcystic lesions which do not respect tissue planes are difficult to eradicate. The treatment modalities for lymphangioma include administration of steroids, surgical excision, radiation therapy, cryotherapy, electrocautery, sclerotherapy, embolization, ligation, laser surgery with Nd-YAG, CO<sub>2</sub>, and radiofrequency tissue ablation technique [1].

In some cases, the use of laser photocoagulation in removing superficial lymphangioma and controlling the tongue size. Surgical excision can be considered the treatment of choice as the lesions are encapsulated or partially circumscribed. Simple drainage, aspiration, and excision have been tried with varying success rates. Aspiration is temporarily effective but leads to infection. Most surgeons consider surgical excision as the treatment option but the patient can suffer post-operative complications such as wound infections, unacceptable scar formation nerve injuries, prolonged lymphatic drainage from the wound, and incomplete resections because of infiltration of adjacent vital structures, and recurrence. The recurrence rate is around 39% because of its infiltrative nature and is often a worry in achieving complete resection. Therefore, nonsurgical therapy particularly sclerosing agents should be considered [5,12].

Sclerosing agents like bleomycin, tetracycline, cyclophosphamide, hypertonic saline, and OK-432, a lyophilized incubation mixture of penicillin G potassium and *Streptococcus pyogenes* used to treat lymphangioma of the tongue [3]. Bleomycin is an antiviral, antibacterial, antitumor glycopeptide. Its biochemical action is when the core is oxidized, the DNA strand scission occurs with the release of free radicals. It has a sclerosing effect on the vessel endothelium. The intralesional injection of bleomycin is used in treating lymphangioma of the tongue. However, when treating the extensive involvement of the posterior third of the tongue, airway protection with tracheostomy or sedation is necessary to prevent chewing the swollen tongue during treatment. These patients require ICU admission and post-injection intubation until the mucosal swelling subsides. Therefore, treating large tongue lymphangioma with bleomycin should be done cautiously [16].

Vascular endothelial growth factor (VEGF) is a serum protein almost absent in normal lymph endothelial cells that are significantly increased in proliferative lymphangioma vessels promoting angiogenesis. The intralesional administration of steroids can cause a significant increase in mast cell density and cytokine concentration, decreased fibroblast growth factor, and decreases platelet-derived growth factors A and B and interleukin-6. These mechanisms alter the cellular functions without significant inflammatory reaction leading to regression of the lymphatic malformation but do not alter VEGF.

In particular, OK-432 is considered the first line of treatment because it does not cause perilesional fibrosis and is particularly more effective for macrocystic lymphatic malformations when compared to microcystic lesions and mixed lesions [3]. Sometimes, the use of sclerosing agents can lead to adverse effects such as fever and swelling at the site of injection [16].

In a case reported by Hwang J, Lee YK, and Burm JS, lymphangioma involved the base and posterior part of the tongue that hindered the surgical excision and required airway protection during sclerotherapy, combination therapy with Triamcinolone, Bleomycin, and Bevacizumab was suggested that enabled low dose of each drug, reduced local and systemic adverse effects caused by single therapy and maximized the synergistic effect during treatment. The effective initial ratio of Triamcinolone (40 mg/mL), Bleomycin (1 mg/mL), and Bevacizumab (25 mg/mL) are 1:2:1 or 1:3:1 where Triamcinolone prevented the edematous changes, inflammation, and the airway obstruction occurred after administration of high-dose Bleomycin alone. Both the steroid and Bleomycin helped reduce the size of the lesion. Hence, intralesional combination therapy can be the choice of treatment in case of extensive tongue lymphangioma where intubation is not mandatory [16].

Another treatment modality includes Radiofrequency ablation which

is a unique energy delivery technique. Radiofrequency energy produces a controlled rise in temperature within the tissue causing denaturing of local proteins and it avoids the vaporization of tissue that commonly occurs with laser and cauterization techniques. This controlled raise in temperature is considered unique because it is not generated by the probe itself but caused by vibrations within individual cells themselves. Hence, the mucosa or skin remains undamaged during the treatment. Since the energy dissipates rapidly from the electrode in a ratio of 1/radius, the volume of the treated tissue is to be precisely chosen. This can be an advantage in the treatment of lymphangioma which spares the critical anatomical, and neurovascular components and the sensitive mucosal surfaces. Other advantages are the treatment delivered is not limited by the diffusion of injected agents as seen in sclerosing therapy and it is also a minimally invasive technique that avoids significant pain and morbidity. This offers a clear convenience over the alternative methods [17].

**CONCLUSION:**

Although lymphangioma is benign and rarely encountered on the tongue, early recognition and diagnosis allow for proper initiation of treatment to avoid serious complications that obstruct the airway. Also, proper follow-up is necessary in order to prevent its recurrence.

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