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Oral lymphangioma: A review on its treatment aspects

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Abstract
Lymphangiomas are hamartomatous lymphatic mutations that happen when lymphatic tissue is sequestered at few areas that not associated with lymphatic channels. Lymphatic malformations of the head and neck, additionally called lymphangiomas or cystic hygromas, are a diverse group of lesions. The majority of lymphangiomas are present at birth, with 90% developing before the age of two. As much as 75% of these malformations arise within the head and neck region and are much less frequently stated within the oral cavity. In the oral cavity, most common location is the dorsum of tongue, followed by lips, buccal mucosa, soft palate, and floor of the mouth. Clinically, they manifest as painless, slowly growing pink or yellow soft tissue masses studded with transparent cystic vesicles. In addition to biopsy, imagistic studies and needle aspiration are rucial for the affirmation of the condition. Various treatment modalities had been advocated depending upon their type, size, and involvement of anatomical structures.

Keywords: Hamartomatous, head and neck, lymphatic vessel, macroglossia, MRI

Introduction
Lymphangiomas are benign malformations which are composed of cystically dilated lymphatic channels that don't interact or drain into different lymphatic channels or veins, ensuing in lymph accumulation. The first description of lymphangioma within the literature is credited to Redenbacher who, in 1828, mentioned a lesion as a ranula congenita. But, Virchow (1854) gave the primary accurate description of lymphangioma [1, 2]. This tumor may arise anywhere within the body, however the shoulder, armpit, stomach, neck, pharynx, eyelids, and conjunctiva are most often affected [3]. It is reported that approximately 75% of all cases of lymphangiomas occur within the head and neck region, at submandibular and parotid area, followed by extremities, trunk, and abdomen. Approximately ½ of the cases are present since birth. About 90% of those develop before the age of two years although, there are reports of its occurrence in adults. Occurrence of lymphangioma in oral cavity is rarely concerned. Intraoral lymphangioma occurs frequently on the dorsal surface and lateral border of the tongue, and barely at the palate, gingiva, buccal mucosa, and lips.Clinically, lymphangiomas are gradual developing, painless soft tissue mass. The treatment of lymphangioma relies upon on the extension of the lesion. The prognosis is good for most patients, even though large tumors of neck/tongue may also more over bring about airway obstruction and death [3, 4].

Embryology
Embryologically lymphatic system develops during the sixth week of embryogenesis from five primitive sacs that arise from the venous system which includes paired jugular sacs, paired posterior sacs and one retroperitoneal sac. There are two hypothesis for the origin of the lymphatic system in humans. Sabin proposed in the early 1900s that endothelial out pouching from the jugular sac spread to form the peripheral lymphatic system within the head and neck region. The subsequent hypothesis is that lymph tissues are deposited within the wrong area during embryogenesis and subsequently fail to hitch the conventional lymph system [5].
Y. Redenbacher initially portrayed lymphangioma in 1828, and lymphangioma of the tongue was represented later in 1854 by Virchow [2, 5].

The etiology of lymphangioma relies upon congenital or acquired in origin. Congenitally it arises from incomplete development and obstruction of the conventional lymphatic system during the sixth week of embryogenesis. The primordial lymphatic sacs fail to attach with the venous system [6]. This process leads to obstruction of lymph flow and cyst development. In contrast to infant lymphangioma, the aetiology of lymphangioma acquired in adulthood incorporate; trauma, inflammation, and lymphatic obstruction as possible pathogenic mechanisms [2].

Classification

De Serres, established a classification for lymphangiomas affecting the head and neck region based on the anatomical involvement as follows: [6]

- Stage/Class I: Infrahyoid unilateral lesions
- Stage/Class II: Suprahyoid bilateral lesions
- Stage/Class III: Suprahyoid or infrahyoid unilaterallesions
- Stage/Class IV: Suprahyoid bilateral lesions
- •Stage/Class V: Suprahyoid or infrahyoid bilateral lesions
- Stage/Class IV: Infrahyoid bilateral lesions

Lymphangiomas are classified based on their clinical appearance as microcystic (cavities smaller than about 2 cm^3), macrocystic (cavities larger than about 2 cm^3), and mixed (combining these two types) [7].

Lymphangiomas are classified histopathologically as follows: [4, 8]

- Lymphangioma simplex/Capillary - consist of small, thin-walled lymphatic vessels.
- Cavernous lymphangioma - composed of dilated lymphatics vessels with surrounding adventitia.
- Cystic lymphangioma - comprised of large, macroscopic lymphatic areas surrounded by fibrovascular tissue, and smooth muscle.
- Benign lymphangioendothelioma - shows lymphatic channels appears to be dissecting through dense collagenic bundles.

Clinical Features

Lymphangiomas are substantially uncommon but show a robust predilection for the head and neck region [6]. Intraoral lesions are not uncommon and typically affect the anterior two-thirds of the dorsal tongue. The lips, buccal mucosa, palate, and floor of mouth are other sites of occurrence. Most of the lymphangiomas are present at birth or within first 2 years of life [9]. Lymphangiomas of the tongue have a classic clinical appearance. Lesions of this location are usually superficial, that corresponds to the feature pebbly, translucent, and yellow vesicles stated to resemble frog eggs. Additionally, lesions frequently have a pink or purple hue that consequences from hemorrhage into the lymphatic channels. The anterior two-thirds on the dorsal surface of tongue is the most frequent site for intraoral lymphangiomas that can leadto Macroglossia [10]. These patients tend to have speech disturbances, terrible oral hygiene, and bleeding from tongue related with oral trauma. Lymphangiomas of the tongue may go unnoticed if they are small. Larger lesions might also compromise speech and/or eating. Bleeding may appear with minor trauma related with everyday oral functions such as eating, speaking, and hygiene, and some document a burning sensation associated with their lesion [11]. In intense cases, lymphangioma can be lifestyle threatening causing airway obstruction and death.

Microcystic lymphatic malformations can occur anywhere in the oral cavity, but they most commonly affect the dorsum of the tongue, causing macroglossia.

According to Wiegand S *et al*. [12], microcystic Lymphatic Malformations (LM) of the tongue are classified into four stages based on the extent of the lesion.

1. **Stage I:** Superficial microcystic lymphatic malformations of the tongue
2. **Stage II:** Lymphatic malformations of the tongue with muscle involvement (Stage IIA, involving a part of the tongue; stage IIB, involving the entire tongue);
3. **Stage III:** Microcystic lymphatic malformations of the tongue involving the floor of mouth
4. **Stage IV:** Extensive microcystic lymphatic malformations involving the tongue, floor of mouth, and further cervical structures.

Investigation

The differentiation of lymphangioma from other fluid-filled masses can also additionally require needle aspiration or biopsy. Needle aspiration indicates a blood tinged clear fluid which resemble lymphatic fluid that is then examined in microscope [13].

Histopathological examination of biopsy tissue indicates lymphatic vessels which are lined by thin endothelial lining with marked dilatations. This lymphatic area can also be additionaly seen empty or with proteinaceous materials and occasional lymphocytes, macrophages and neutrophils. Cavernous lymphangiomas consist mainly of dilated vessels, capillary lymphangiomas have vessels with the size of capillaries, and large cyst-like spaces are characteristic of cystic lymphangiomas [2, 6].

Differentiating lymphatics and blood vessels with the aid of light microscopy has long been a dilemma. Recently, numerous relatively specific antibodies for lymphatic vessels like podoplanin, vascular endothelial protein receptor 3, lymph vessel endothelial HA receptor 1, D2 40 and Prox1 are recognized. D2 40 is a monoclonal antibody which was used to distinguish 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 utilized as a solid marker to distinguish lymphatic endothelial cells [14].

Radiographic evaluation includes ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). US may be used routinely to assess the size and extension of the lesion. Both CT and US are beneficial to consider stable or cystic nature of the lesion whereas MRI has been found to be maximum useful in comparing the extension of the lesion [15].

Management and Treatment

In the past several techniques were used to manage lymphangioma. It includes, the following methods, Diathermy is a type of physical therapy that uses high frequency electrical current too deeply heat tissues. Typically, the terms "electrosurgery" and "electrocautery" are used to refer to surgical diathermy. In the past, diathermy was used to perform hemostasis following surgical removal of a lymphangioma [16].

Embolization has become a standard procedure over the few decades and it is now included in treatment protocols for oral lymphangioma. Embolization uses endovascular application of various chemicals or materials to achieve occlusion or a reduction in blood/lymph flow [17].

Radiotherapy was once used to treat lymphangiomas, but it is no longer an acceptable method due to the inability to completely eliminate the lesion, post radiation malignancy and damage to adjacent tissues. Radiation therapy has not been shown to be effective in the treatment of cystic hygroms [18, 19].

Based on the clinical appearance microcystic, macrocystic and mixed types of Oral Lymphangiomas, Various treatment modalities like careful Surgical excision, Radiofrequency ablation, Cryotherapy, Sclerotherapy, Laser therapy and Steroid administration have been implicated.

1. Surgical Excision

This is regarded as the preferred treatment. Surgery is suggested sooner rather than later because excision is technically easier before the tumour has invaded normal tissue and infection has caused fibrosis and scarring [20]. Most surgeons consider surgical excision to be the treatment of choice for oral lymphangiomas, with the approach differing counting on the clinicaltype. Macrocystic lesions, are more localized and respect tissue planes and are more easily excised. Alternatively, diffuse lesions like microcystic type, total excision with preservation of involved vital structures isn't always possible, because the lesion extends into surrounding tissue and infiltrates vital structures. Incomplete excision, is usually associated with recurrence [21, 22].

2. Sclerosants

Sclerosing agents are substances that cause marked tissue irritation or thrombus formation followed by local inflammation and tissue necrosis leading to fibrosis and tissue shrinkage. The most commonly used sclerosants are sodium tetradecyl sulfate (STS),OK-432,polidocanol, hypertonic saline, and chromium glycerin [23]. An important consideration in producing successful sclerotherapy is determining the minimum volume and minimum concentration of beneficial sclerotherapy. The only sclerotic agents in the United States approved by the Food and Drug Administration are sodium tetradecylsulfate (Sotradecol), sodium morrhuate (fatty acid in cod liver oil), and hypertonic saline (18%-30%).The effective sclerosing agent is one that induces panendothelial destruction and possesses no systemic toxicity. Side effects and complications of sclerotherapy include: purple-brown hyperpigmentation after therapy, telangiectatic matting, cutaneous ulcerations and necrosis, superficial thrombophlebitis, pulmonary embolism, and arterial injection [24]. Sclerotherapy appears to be the treatment of choice in the treatment of lymphatic malformations, especially recommended for microcystic lymphangiomas and macrocystic components of mixed lesions.

3. Coblation Technique

Radiofrequency ablation is a relatively new and different method of energy delivery. Coblation technique, also known as radiofrequency ablation, has been described as a successful treatment method Radiofrequency energy induces a controlled rise in temperature in tissues, causing local protein denaturation, while avoiding tissue vaporization that occurs with laser and cautery techniques. This controlled temperature rise is unique in that it is caused by vibrations inside the individual cells and not the probe itself, as during cauterization or laser use. This allows the skin or mucosal surface through which the transducer passes to remain undamaged during treatment [25]. Radiofrequency ablation offers a relatively new minimally invasive treatment option, mainly in stage I and II lesions, because it can be used to reach precise areas of tissue involvement. Many studies have shown that radiofrequency ablation is not commonly used to reduce lymphatic malformations of the tongue; only 8% prefer it for stage 5 LM and 72% consider it a third or fourth choice for the treatment of macroglossia caused by lymphatic malformations [26].

4. Laser

Laser therapy has been used to treat superficial lymphatic malformations, particularly in patients suffering from localised infection. The benefits of laser therapy include ease of use, less bleeding, less pain,a consistent effect and repeatable treatment. The most common lasers are carbondioxide (CO2) lasers, Neodymium-doped Yttrium Aluminium Garnet (Nd:YAG) lasers (wave length 1064 nm, near infrared light), pulsed dyelasers, and diode lasers. The CO2 laser is the most commonly used laser for surgical procedures in the oral cavity due to its high affinity for water and the high absorptive capacity of the oral mucosa. CO2 lasers typically emits at a wavelength of 10600 nm and have no color affinity. The interaction of laser light with tissue occurs through the conversion of light into heat in the presence of a fluids, primarily water. Several benefits of using CO2 lasers have been reported for oral surgical procedures, including coagulation of small blood vessels and lymphatics, drying of the surgical site, and reduced risk of metastases; relieve postoperative pain and minimal wound contraction and scarring due to the presence of small amounts of myofibroblasts; no sutures or wound, and others [27]. CO2 laser surgery appears to be an excellent option for definitive treatment of stage I and stage IIA lymphatic malformations of the tongue. CO2 laser surgery appears to be beneficial as part of a combined or stepwise approach in stages IIB, III, and IV disease [28].

5. Cryotherapy

The term Cryotherapy is derived from the Greek word "kryos" for frost, Cryosurgery is the local destruction of tissue by freezing. It has long been recognized as an excellent technique that, when used properly, can reduce pain and swelling while destroying lesions with minimal scarring. The mechanism of destruction in cryotherapy is as follows:

1. The formation of intracellular ice that leads to cell rupture.
2. Increased solute concentration in damaged tissue.
3. Inflammation of damaged tissue.
4. Vascular stasis at the treatment site.

Lymphangioma is considered to be very suitable for treatment by cryosurgery due to its high water content and inadequate blood supply [29]. The treatment takes much less time compared to surgical excision. Additionally, its effectiveness in eliminating pain is extremely important for palliative treatment. The use of cryotherapy can be seen as a treatment option for small lymphangioma in the oral cavity of adolescents and pediatric patients in the aesthetic zone, but it does not always lead to a complete solution or success [30].

6. Steroid Therapy

Corticosteroid therapy increases mast cell counts and cytokine levels and decreases platelet-derived growth factor and interleukin-6. This therapy contributes to the regression of lymphatic malformations, but does not alter VEGF. Vascular

endothelial growth factor (VEGF) is a serum protein that promotes angiogenesis. VEGFs are significantly increased in proliferating lymphatic vessels,almost absent in normal lymphoid endothelial cells. Bevacizumab, a recombinant human monoclonal antibody originally generated from mice immunized with recombinant human VEGF, binds to VEGF and prevents VEGF binding to VEGF receptors. VEGF blockade with bevacizumab is used as an effective treatment for capillary hemangiomas and diabetic retinopathy and has been shown to be a treatment for lymphatic system malformations [31, 32]. Treatment of tongue lymphangioma with injected steroids has been reported. Injected steroids induced a significant increase in mast cell density, decreased cytokine transcription, decreased platelet-derived growth factors A and B, and decreased basal fibroblast growth factor. These mechanisms alter cellular functions leading to the regression of lymphatic malformations without a significant inflammatory response. However, curative treatment is not guaranteed with injected steroid alone [33].

Medical Therapy

7. Sildenafil

Sildenafil has been shown in studies to be an option for the treatment of LM as a monotherapy or in combination with other therapies. The mechanism underlying sildenafil's effect in LM is unclear. Sildenafil's primary function as a selective type Phosphodiesterase-5 inhibitor (PDE5) is to inhibit the breakdown of cGMP, resulting in smooth muscle relaxation and vascular dilation. One hypothesis is that Sildenafil relaxes the perivascular smoothmuscle, causing the collected lymph to flow into the venous system and depressurize the LM. Sildenafil may also stimulate vasodilation, mediate lymphangiogenesis, and improve lymphatic dilatation and drainage by activating nitric oxide synthase. According to other reports, microcystic LM is resistant to Sildenafil. As a result, randomised controlled clinical trials are required to confirm sildenafil's efficacy in the treatment of LM [34].

8. Sirolimus

Sirolimus, also known as Rapamycin, is a macrolide drug that efficiently inhibits the activity of mTOR and blocks the PI3K/AKT/mTOR signalling pathway, which has been proven to enhance lymphangiogenesis. Recent research has demonstrated that Sirolimus can quickly reduce the expression of Prox1 and VEGFR-3 mRNA and protein, which may be related to the inhibition of Prox1 transcriptional activity, this lead to the prevention of growth of abnormal lymphatic vessels without having a significant impact on healthy lymphatic vessels [35]. According to a study, Sirolimus may be an effective alternative for the treatment of superficial LM because it can successfully treat patients with the condition. Sirolimus still causes a variety of side effects, such as metabolic toxicity and gastrointestinal problems. The majority of patients tolerate Sirolimus well, and there are typically no significant side effects. Therefore, Sirolimus may become a hotspot in the research of microcystic LM in the future [36].

9. Bleomycin Electrochemotherapy

Case studies have shown that Bleomycin electrochemotherapy effective in the treatment of infant capillary lymphangioma. Bleomycin based Electrochemotherapy can be considered a safe and effective alternative treatment option for infants with microcystic and combined lymphangiomas; however, more research into the method's efficacy and safety is required. Recent publications highlight the use of Bleomycin based Electrochemotherapy to treat benign vascular malformations. Bleomycin based electrochemotherapy was described by McMorrow *et al*. [37] in a case report in which a venous malformation was successfully treated with intratumoral delivery of bleomycin using electrochemotherapy and referred to the procedure as bleomycin-based electrosclerotherapy. [38]

10. Other drugs

A recent study identified Trametinib, a novel drug that inhibits Extracellular signal regulated kinase(ERK) phosphorylation and reduces endothelial cell viability, as a promising treatment option for Generalized Lymphatic Anomaly (GLA). As a result, these inhibitors could be used as a new targeted therapy for LM, but more clinical trials are needed to confirm their efficacy [39].

Bevacizumab, an inhibitor of VEGF-A, inhibits the proliferation of LM endothelial cells in a dose dependent manner and has been successfully used in the treatment of diffuse pulmonary lymphangiomatosis.Several studies have also reported that BMP and Wnt modulators, like dorsomorphin, LDN-193189 and calyculin A, may have certain therapeutic potential, supporting the participation of BMP and Wnt pathways within the study of LM therapy [40].

Other drugs, such as a Janus Kinase (JAK) inhibitor (ruxolitinib), a calcium channel blocker (amlodipine), and aATP sensitive Potassium activator (KATP) (minoxidil), may have therapeutic potential, but more clinical trials are needed to investigate their potential clinical benefit in the treatment of LM. Other drug therapies, such as Zoledronic acid and interferon- 2b, have also been used to treat patients with GLA, with some success. Prednisolone and Sunitinib have also been shown to be effective in treating LM as monotherapy or as part of a combination therapy [35].

11. Combined Treatment

Numerous studies have shown that a single treatment cannot provide adequate results for the majority of patients. There are several techniques for treating superficial microcystic mucosal LM, according to the literature, including laser ablation (the CO2 laser is the most commonly used), radiofrequency ablation, bleomycin sclerotherapy, and systemic Sirolimus. All of these methods can help to alleviate pain and bleeding symptoms. Surgical resection is the main treatment method, which can completely eradicate large cystic lesions and greatly reduce the size of large cystic lesions. Depending on the clinical types and anatomical sites, other treatment modalities are used to treat any remaining diseases and recurrence of lesions. Unfortunately, there is no published data to support the existence of multimodal therapy and and more clinical practise validation is still required [41].

Conclusion

The treatment modalities of Oral lymphangioma varies depending upon their clinical types, size, location and infiltration to the adjacent surrounding structures. Due to its infiltrative nature and difficulties in achieving complete surgical resection, several studies have reported that the recurrence rate of Lymphangioma is around 39%. Depending upon their anatomical location within the head and neck region, complication may arise such as tongue’s extrusion, obstruction of upper airways, difficulties in mastication and speech. Therefore, their early detection makes it possible to initiate anappropriate treatment and prevent the occurrence of complications.

Abbreviations

Phosphodiesterase-5 inhibitor (PDE5)
Extracellular signal regulated kinase (ERK) phosphorylation
Generalized Lymphatic Anomaly (GLA)
Janus Kinase (JAK) inhibitor
ATP sensitive Potassium activator (KATP)
Vascular endothelial growth factor (VEGF)
Carbon dioxide (CO2) lasers
Neodymium-doped Yttrium Aluminium Garnet (Nd:YAG)lasers
Sodium Tetradecyl Sulfate (STS)
Lymphatic Malformations (LM)
Magnetic Resonance Imaging (MRI)
Ultrasonography (US),
Computed Tomography (CT)

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