

Lymphvasculogenesis and Lymphangioma – an Update

V Naveen Shankar, Ashwini. N Shankar and Praveena V

Kothiwal Dental College Research Centre and Hospital, Kanth Road, Moradabad, Uttar Pradesh, India

Abstract

Lymphangiomas are rare congenital benign lesions occurring mainly in the head, neck and oral cavity. They consist in localized centres of abnormal development of the lymphatics. A commonly used classification classifies these lesions into capillary lymphangioma or lymphangioma simplex, cavernous lymphangioma, and cystic lymphangioma or cystic hygroma. Histologically, these lesions are composed of dilated lymphatic channels, endothelially lined channels with or without an adventitial layer. These dilated lymphatic's can vary in size, depending upon the location and surrounding tissues.

Surgical resection still remains the best treatment for lymphangiomas; other treatment options, such as sclerotherapy have been proposed as an alternative to reduce the impact and complications of surgery.

Keywords: Lymphangiomas; Lymphatic endothelial cell; VEGFR

Introduction

Lymphangiomas are benign hamartomatous hyperplasia of lymphatic vessels. Lymphangiomatous lesions are a rare congenital malformation which usually appears within the first 2 decade of life [1]. they are typically superficial but may extend deeply into underlying connective tissue, rarely multiple lesions are also seen in infancy and childhood [2]. Prevalence of lymphatic malformations can be 30 per 10,000 births, but if only live births are included 1–3 Lymphatic Malformations per 10,000 live births are reported [3]. There has been various research studies on lymphvasculogenesis, etiology of lymphangioma and its treatment. Here is an attempt to update the knowledge on all such research works.

Lymphatic vessel development

The first description of the lymphatic system dates back to the seventeenth century, when the Italian anatomist Gasparo Aselli identified lymphatic vessels as “milky veins” in the mesentery of a “well-fed” dog [4].

However, the lymphvasculogenesis remained unclear until Florence Sabin in 1902 proposed a model based upon ink-injection experiments in pigs – that endothelial cells bud off from the veins during early embryonic development and form primitive lymph sacs. The peripheral lymphatic system then originates from these primary lymph sacs by endothelial sprouting into the surrounding tissues and organs, where local capillaries are formed [5].

This was challenged in 1910 by Huntington and McClure who alternatively suggested that lymph sacs arise independently of the veins – from mesenchymal precursor cells (lymphangioblasts), with consecutive establishment of venous connections [6].

The lymphatic vasculature runs in parallel, but develops secondarily to the blood vasculature, and both are lined by endothelial cells (ECs). The lymphatic vasculature is derived from venous ECs. Therefore, a prerequisite for the genesis of the lymphatic network is the formation of the blood vasculature. The development of the embryonic vasculature requires the differentiation of endothelial cells (ECs). First step in this process is the formation of endothelial precursors (angioblasts) from mesodermal progenitors during gastrulation. The ETS transcription factor Etv2 that leads to EC differentiation, and the Notch, BMP and

Wnt signaling pathways regulate its expression. VEGF signaling is also important during the differentiation of angioblasts into ECs. Subsequently, Notch signaling is required to promote arterial endothelial cell identity, and the expression of the orphan nuclear receptor COUP transcription factor II (COUP-TFII) promotes venous endothelial cell fate by downregulating Notch signaling. Upon its activation in a subpopulation of the venous endothelial cells, the SRY-related HMG-domain transcription factor Sox18 cooperates with COUP-TFII to activate expression of the homeobox transcription factor *Prox1*. *Prox1* expression is sufficient to specify lymphatic endothelial cell (LEC) fate. Later on, *Prox1* expression becomes independent of external stimuli, as it regulates its own expression and maintains LEC identity [7].

Guillermo Oliver et al. [8] proposed that the lymphvasculogenesis takes place in four stages comprising of competence, commitment, specification, and lymphatic vessel coalescence and maturation (Table 1).

Lymphatic competence

Competence is the capacity of cells to respond to an initial inducing signal; this stage seems to be autonomous and controlled by a developmental timer. Around 9-9.5 day of murine embryonic life all endothelial cells of the embryonic cardinal vein display the ability to respond to unidentified initiating and instructive growth factor(s) of lymphatic development [7,8]. At present, Lymphatic endothelial cell (LEC) competence is defined by the surrogate expression of lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) and vascular endothelial growth factor receptor-3 (VEGFR-3). LYVE-1 is expressed on blood endothelial cells (BECs) early in the phase of lymphatic competence. VEGFR-3 is broadly expressed on both early blood and lymphatic vessel endothelium and plays a critical

Corresponding author: Dr. V Naveen Shankar, No#110, 5th Ward, National College Road, Bagepalli, Chikkaballapura, Karnataka, India, Tel: + 00919286731312; E-mail: vnaveenshankar@gmail.com

Received April 27, 2011; **Accepted** July 20, 2011; **Published** July 24, 2011

Citation: Shankar VN, Shankar AN, Praveena V (2011) Lymphvasculogenesis and Lymphangioma – an Update. J Cancer Sci Ther 3: 149-153. doi:10.4172/1948-5956.1000078

Copyright: © 2011 Shankar VN. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Stage	Changes	Markers
Competence	LEC respond to unidentified initiating and instructive growth factor	VEGFR3 & 2 LYVE-1
Commitment/Bias	Polarization of localization LEC & subsequent budding	Prox1 LYVE-1
	Further differentiation to achieves complete autonomy, migrates peripherally	Neuropilin 2 (Nrp2), Podoplanin/T1 Secondary lymphoid chemokine (SLC) VEGFR3
Maturation	Organisation of primary lymphatic sac around tissues and organs	Desmoplakin and β -chemokine receptor D6

Table 1:

role in the development of both lineages of vasculature. With time, VEGFR-3 expression becomes limited to LECs as BEC expression is downregulated. With the attainment of vascular maturity, VEGFR-3 is largely restricted to the lymphatic endothelium [8,9].

Tammela and Alitalo said that transcription factor SOX18 is induced in the LYVE-1-positive lymphatic endothelial cell (LEC) precursors. SOX18 induces Prox1 expression, the first marker for LEC determination. At about this time, VEGFR-3 expression is downregulated in the blood vessels, but it remains high in the LEC precursors, which also begin to express neuropilin-2, rendering them more responsive to VEGF-C signals arising from the lateral mesenchyme. These signals are required for sprouting of the LECs [10].

In conjunction with primary VEGFR-3 ligands, VEGF-C and VEGF-D, angiopoietin-2 (Ang2) is believed to be responsible for lymphatic remodeling following differentiation, through interaction with the Tie2 receptor, to form functionally mature lymphatics [9].

Lymphatic commitment

Following the initial stage LECs acquire the ability to give rise to a particular cell type or structure. This stage is marked by the expression of prospero-related homeobox 1 (Prox1), a nuclear transcription factor whose appearance is exclusive to cells of committed lymphatic lineage. The Prox1-positive subpopulation of venous endothelial cells oriented in a polarized fashion along the cardinal vein. The mechanism of this differential and ordered expression remains unknown; nevertheless Prox1 is clearly necessary and sufficient for lymphatic commitment [7,8].

Francois et al. demonstrated that the homeobox transcription factor SOX18 is expressed in cardinal vein endothelial cells prior to Prox1, and that the Prox1 promoter contains SOX18-binding sites, indicating that SOX18 is required for initiation of the LEC differentiation program upstream of Prox [10].

Lymphatic specification and coalescence

Specification is the stage at which cells will differentiate into the desired phenotype, even if isolated and cultured alone.

As the LECs attains a higher level of differentiation, additional lymphatic specific markers are expressed, while those reflecting the assumed blood vascular lineage are increasingly suppressed. Committed LEC eventually achieves complete autonomy from the local microenvironment of the cardinal vein and migrates peripherally.

Under the further influence of Prox1, neuropilin 2 (Nrp2) and podoplanin/T1, LECs bud from the parental cardinal vein. This budding and migration seed the periphery for the formation of nascent lymphatic structures throughout the embryo. These are called primary lymph sacs [7,8].

Maturation

The primary lymph sac form capillaries around tissues and organs in a centrifugal fashion to constitute the lymphatic vasculature. The

cell continues to organize until the first few postnatal days. In the late stage of differentiation and maturation lymphatic markers such as desmoplakin and β -chemokine receptor D6 appear. These are thought to be among the last markers expressed [8,9].

Association of lymphatic vessels with the extracellular matrix

The elastic microfibril-associated protein Emilin1 is a component of the anchoring filaments in lymphatic vessels [10].

History and lymphangiogenesis

The first description of lymphangioma in the literature is credited to Redenbacher who, in 1828, referred to a lesion as a 'ranula congenita'. In 1843 Wernher coined the descriptive term 'cystic hygroma', hygroma being derived from the Greek 'hydro' = moist and 'oma' = tumor. He thought the fluid-filled sacs represented new growth of benign neoplastic tissue. In 1855 Rokitsansky postulated that a cystic hygroma was simply a collection of serous fluid held in place by surrounding tissue [11].

Florence Sabin, proposed centrifugal theory of lymphatic development, said that the human lymphatic system which originates from 5 primordial sacs: two paired jugular sacs; two paired sacral sacs; and an unpaired retroperitoneal sac. From these primitive sacs, endothelial sprouts propagate outward to form the peripheral lymphatic system. In support of this study Goetsch identified endothelial buds sprouting from the growing edge of the tumour and infiltrating surrounding tissue from histologic preparations of cystic hygroma. He felt this represented true neoplastic growth of the lymphatic system [11].

Several investigators have challenged this work, proposing instead a centripetal theory in which peripheral lymphatics develop from mesenchymal slits in sequestered portions of the primordial sacs. These sequestrations enlarge and ultimately join the venous system. Failure of this anastomosis results in formation of a cystic hygroma. This hypothesis, however, accounts for neither the- histologic findings nor the potential for rapid and extensive growth [11].

Now it has been widely accepted that lymphangiomas develop as a result of sequestration of portions of the primitive embryonic lymphatic anlage. These sequestered areas never achieve efficient anastomoses with the larger lymph channels; therefore functionally they exist as localized areas of lymphatic blockage, some appearing as lymphangiomas, others as cystic hygromas [12].

Recently Norgall et al. suggested that Immunohistological Characterization of lymphatic endothelial cells suggests an involvement of VEGFR- 3 and -2 in the etiology of the lymphangioma. Up-regulation of VEGFR-3 and -2 signalling are the major cause for the aberrant lymph vessel formation [13].

Classification

Lymphangiomas are classified as microcystic (capillary lymphangiomas), macrocystic (cavernous lymphangiomas), and cystic hygromas according to the size of the lymphatic cavities incorporated [14].

According to Kennedy et al Lymphangioma are classified based on their extent as [15]:

I. Superficial cutaneous lymphangioma

Lymphangioma simplex

Lymphangioma circumscriptum

II. Cavernous lymphangioma

Loose:

Mucous membrane of lips, cheek, and floor of mouth Compact:

Tongue, abdomen, or flank

III. Cystic hygroma—cystic lymphangioma

IV. Diffuse systemic lymphangioma

Lymphangioma—hemangioma.

De Serres et al. [16] proposed clinical staging system for lymphangiomas involving neck based on extent and location, the system classifies the disease as follows:

stage I, unilateral infrahyoid disease;

stage II, unilateral suprahyoid disease;

stage III, unilateral infrahyoid and suprahyoid disease;

stage IV, bilateral suprahyoid disease; and

stage V, bilateral infrahyoid and suprahyoid disease [16].

Clinical features

Lymphangiomas show neither racial nor sexual predilection and are most often diagnosed in the pediatric population. Discovery in adolescence or adulthood is reported but is distinctly uncommon [1,11].

Approximately 75% of all cases of lymphangioma occur in the head and neck region, and about 50% of all lesions are noted at birth. About 90% develop by 2 years of age [2,11]. Lymphangioma involving the head and neck occurred most commonly in the submandibular and floor of mouth regions. In the oral cavity tongue involvement is the most common site followed by buccal mucosa. Lips and Palate [1,3]. Instances of cheek, orbit, and eyelid involvement are also reported [2,11,16].

Associated anomalies include Turner's syndrome, congenital heart disease, cleft lip, spina bifida, and mental retardation [9].

When a lymphangioma is confined to fairly dense tissue, such as the tongue, it presents as a cavernous lymphangioma, but when it develops in the relatively loose fascia of the neck, a cystic lesion occurs [17]. The most prominent sign or symptom of all lymphangiomas is the presence of a mass. The mass may be small and unnoticed at birth only to present later [18]. These lesions commonly present with a slowly growing, asymptomatic, fluctuant, soft-tissue mass. The lesions are not attached to the skin or movable across deeper tissues, and readily transilluminate [14]. Frequently, rapid enlargement occurs following an upper respiratory tract disorder or incidental trauma at the site [11]. Most lesions, however, are recognized early on account of their size and associated symptoms of respiratory obstruction and problems with feeding, which are the second and third most common presenting symptoms. Difficulty in swallowing results from lymphangiomas extending to involve the oral cavity, oropharynx, and/or the hypopharynx [1,12,16].

Isolated tongue involvement can lead to macroglossia with dysphagia and airway obstruction. Airway and swallowing problems may persist after surgery in the neck on account of mucosal oedema, enlargement of internal lymphangiomas, and loss of neural innervation to the pharynx or tongue [18].

The clinical course of the pathology varies from a spontaneously regressing cyst to an aggressively invasive lesion. Spontaneous or traumatic haemorrhage of the cysts is the most common complication of the lesion [19]. Ultrasonography, CT and MRI can be used to define the relationship of the lesion with the neighbouring structures and to help plan surgical strategies [20].

Treatment options

The principal goal of Lymphatic malformations management is restoration or preservation of functional and aesthetic integrity. All treatment is based on a thorough initial assessment to detect the degree of functional impairment and/or disfigurement. Treatment timing relative to the age of the patient is somewhat debatable. Lymphangiomas of small dimensions, without functional impairment or cosmetic disfigurement, do not necessarily require treatment. The possibility of spontaneous regression in low-stage macrocystic lesions suggests that observational monitoring may also be appropriate in children with asymptomatic cervical Lymphangiomas, regardless of size [20,21].

Various modalities have been reported for the treatment of lymphangiomas. Procedures such as surgical excision, sclerotherapy, radiation therapy, cryotherapy, electrocautery, steroid administration, embolization, ligation, and laser surgery have all been used [12,20-22].

Surgery has been the main form of treatment, but total removal is not possible in all cases because of the extent of the lesion, which sometimes involves vital structures [23]. Complications include postsurgical fluid accumulation, infection, Horner's syndrome and peripheral nerve injury including damage to the facial nerve branches, the hypoglossal nerve, or the lingual nerve has been reported [24]. Saijo et al. reported that when facial lymphangiomas are diffuse and locally invasive, there is a 50% recurrence rate after the first excision, most likely due to residual anomalous tissue [25].

Furthermore, the infiltrating nature of these lesions and the involvement of vital structures make total excision nearly impossible in most cases. In such cases sclerotherapy has been recommended as a primary or adjunctive treatment for these lesions. Intralesional injection of Sclerosing agents such as tetracycline or doxycycline, sodium diatrizoate tetrahydrate (Ethibloc; Ethnor Laboratories/Ethicon, Norderstedt, Germany), ethanol, sodium tetradecyl sulfate, triamcinolone, sodium morrhuate, 50% dextrose, bleomycin sulfate, bleomycin emulsion, pingyangmycin, and OK-432 are used [21,25]. Prior to any sclerosant injection, the aspirated fluid should be examined to confirm the diagnosis. The fluid should be thin and tan in color.

OK-432 is a lyophilized mixture of group A *Streptococcus pyogenes* and benzylpenicillin. After injection, OK-432 remains confined within the malformation, resulting in obliteration of lymphatic channels with minimal local fibrosis. It is thought that endothelial damage occurs secondary to activation of the host immune system. The main disadvantage of OK-432 therapy is a theoretical risk of shock-like symptoms, particularly in those with penicillin allergy. Additional drawbacks include local edema and the need for multiple applications [21,25,26].

Bleomycin was initially developed as an anti-tumor agent in 1966. In addition to its activity as an inhibitor of DNA synthesis, bleomycin incites a mild inflammatory effect on endothelial cells. Bleomycin may be administered in one of two forms, as bleomycin oil or bleomycin hydrochloride (aqueous). Common immediate side effects of bleomycin sclerotherapy are slight local swelling and inflammation. However, the major concern with bleomycin use is the potential risk of interstitial pneumonia and pulmonary fibrosis [21,22,1].

Doxycycline, a broad-spectrum antibiotic, is also a metalloproteinase inhibitor. Based on this finding, it has been used as a vascular malformation sclerosant alone or in combination with ethanol. It is a safe and effective sclerosant for macrocystic LM. This agent creates an inflammatory effect and produces fibrosis similar to other agents. Potential complications include tooth discoloration when administered to patients less than eight years of age, electrolyte abnormalities, local infection, and pain [21].

All of these sclerosants can still cause severe swelling with airway compromise, skin breakdown, and other toxic side-effects. Also, it must be emphasized that treatment outcomes are based on multiple treatments, sometimes in excess of five to 10 treatments, and longterm follow-up is necessary [27].

Laser treatments can be useful to treat airway malformations as well as to treat the vesicular eruptions on the mucosal surfaces. Airway lesions may require redundant tissue excision as is often seen in the false vocal cord and supraglottis in order to prevent or decannulate a tracheostomy. The CO₂ laser can be used to accomplish these limited resections as well as to laser resurface oral mucosal vesicles, which can lead to pain and dysphagia [27].

Kennedy et al. [20] proposed a treatment plan according to him: Initial counseling to the parents and the child (if of sufficient age) is essential. The first sessions should include a thorough discussion of the malformation and all possible treatment options. If symptoms are life threatening, then surgical intervention is warranted. When a mass is the only sign or symptom, observation is recommended for at least 18 months to 2 years of age. By age 5 no sign of regression or apparent reduction in size in relationship to the growth of the child is seen. A surgical approach or the use of a sclerosing agent, such as OK-432, is two such options. If the lesion is below the level of the hyoid and mostly in the posterior triangle, surgery is the preferred. However OK-432 is a better choice for those enlarging hygromas above the hyoid that are beginning to invade the oral and pharyngeal mucosa. Smaller lesions in the submaxillary and parotid regions certainly can be managed safely with surgery [15].

For those patients who develop lymphangiomas later in life, Depending on the cosmetic concerns of the patient and the location of the lesion, we would favor waiting 6 months to 1 year before recommending surgery in these older patients [15].

Oosthuizen, Burns, and Russell in 2010 have proposed management algorithm (Figure 1 and Figure 2) [26].

Histopathology

Gross examination of excised lymphatic malformation tissue reveals cysts of various sizes, some interconnected and few isolated. The cysts contain serous fluid that may be clear, yellow, turbid or hemorrhagic. Older cysts are separated by thick walls, filled with hyaline and fibrous material whereas younger cysts are simply endothelial layers separated by minimal connective tissue. The intercytic stroma and capsule is made up of thin layers of smooth muscle in a connective tissue matrix of varying thickness containing iron pigment and nodules of lymphatics [12,24,28].

Lymphangiomas are unencapsulated lesions consisting of dilated, endothelially lined channels that may contain lymphocytes. The stroma consists of delicate collagen within which lymphoid aggregates are sometimes encountered. Some lymphangiomas also have a vascular component and may therefore contain some red blood cells. Cystic hygromas differ only in that they are usually composed of very large, interconnecting, endothelially lined, cyst-like spaces [29].

Electron microscopic study of the basal lamina appears as an electron-dense line which is composed of type IV collagen.” Immunostaining for type IV collagen and electron microscopic examination showed that the basement membrane of the lymph vessels was not continuous. These discontinuities may partially explain why sclerosing agents have not been effective in treating lymphangioma. Perhaps the discontinuous basement membrane allows sclerosing agents to permeate freely into the connective tissues, diluting the concentration of the agent and rendering it less effective [12].

Conclusion

Here is an attempt towards concised overview of lymphangioma

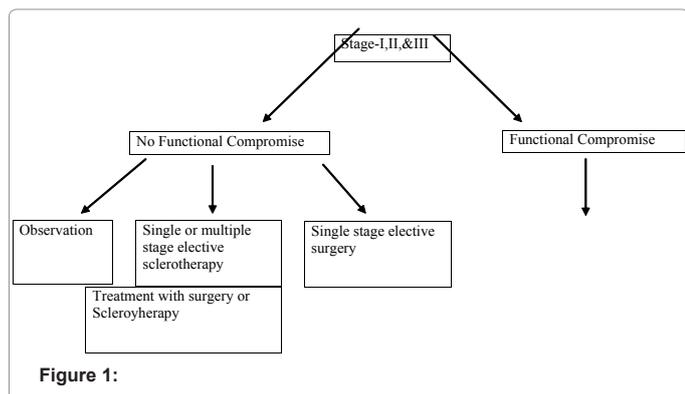


Figure 1:

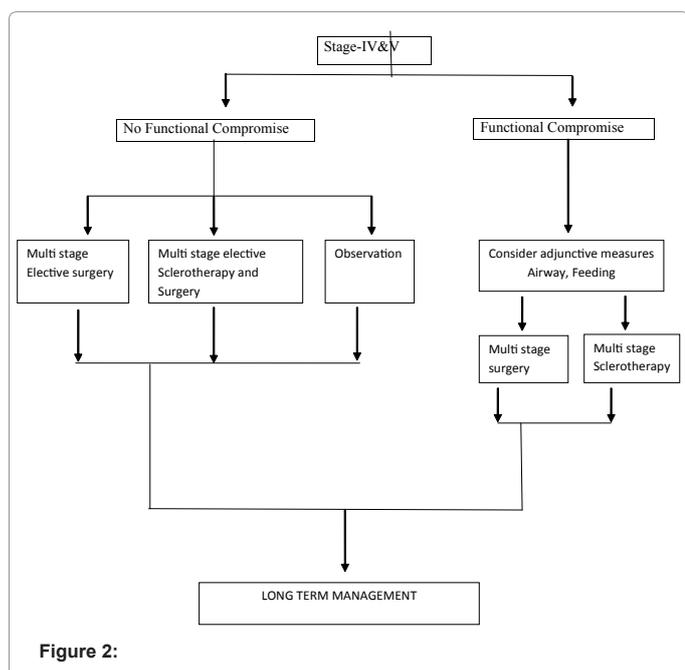


Figure 2:

covering the development of lymph vessels, lymphangioma and its treatment. This would help the clinician to best understand the disease process and its staging. Furthermore it helps in indulge/explore the different types of treatment options which are available.

Acknowledgements

Mr C.Vemanna, Mrs.V Seethamma, Mrs V.Roja Rani, Mrs V.Dhanurenuka, Mrs V.Chandrakala.

References

1. Filston HC (1994) Hemangiomas, cystic hygromas and teratomas of the head and neck. *Semin Pediatr Surg* 3: 147-159.
2. Joseph R, James S, Richard CRJ (2003) *Oral Pathology Clinical Pathological Correlation*. USA: Elsevier Sciences 4 th edn 169.
3. Forrester MB, Merz RD (2000) Descriptive epidemiology of cystic hygroma: Hawaii, 1986 to 1999. *South Med J* 97: 631-636.
4. Cueni LN, Detmar M (2006) New Insights into the Molecular Control of the Lymphatic Vascular System and its Role in Disease. *J Invest Dermatol* 126: 2167-2177.
5. Sabin FR (1909) The lymphatic system in human embryos, with a consideration of the morphology of the system as a whole. *Am J Anat* 9: 43-91.
6. Huntington GS, McClure CFW (1910) The anatomy and development of the jugular lymph sac in the domestic cat (*Felis domestica*). *Am J Anat* 10: 177-311.
7. Oliver G, Srinivasan RS (2010) Endothelial cell plasticity: how to become and remain a lymphatic endothelial cell. *Development* 137: 363-372.
8. Oliver G (2004) Lymphatic Vasculature Development. *Nat Rev Immunol* 4: 35-45.
9. Nakamura K, Rockson SG (2008) Molecular Targets for Therapeutic Lymphangiogenesis in Lymphatic Dysfunction and Disease. *Lymphat Res Biol* 6: 181-189.
10. Tammela T, Alitalo K (2010) Lymph angiogenesis: Molecular Mechanisms and Future Promise. *Cell* 140: 460-476.
11. Brock ME, Richard JH, Smith RJ, Parey SE, Mobley DL (1987) Lymphangioma. An otolaryngologic perspective. *Int J Pediatr Otorhinolaryngol* 14: 133-140.
12. Brennan TD, Miller AS, Chen SY (1997) Lymphangiomas of the Oral Cavity: A Clinicopathologic, Immunohistochemical, and Electron-Microscopic Study. *J Oral Maxillofac Surg* 55: 932-935.
13. Norgall S, Papoutsis M, Rössler J, Schweigerer L, Wilting J, et al. (2007) Elevated expression of VEGFR-3 in lymphatic endothelial cells from lymphangiomas. *BMC Cancer* 7: 105.
14. Grasso DL, Pelizzo G, Zocconi E, Schlee J (2008) Lymphangiomas of the head and neck in children. *ACTA otorhinolaryngol ital* 28: 17-20.
15. Kennedy TL, Whitaker M, Pellitteri P, Wood WE (2001) Cystic Hygroma/Lymphangioma: A Rational Approach to Management. *Laryngoscope* 111:1929-1937.
16. De Serres LM, Sie KC, Richardson MA (1995) Lymphatic malformations of the head and neck: a proposal for staging. *Arch Otolaryngol Head Neck Surg* 121: 577-582.
17. Ward FE, Hendrick JW, Chambers RG (1950) Cystic hygroma of the neck. *West J Surg Obstet Gynecol* 58: 41-47.
18. Berry JA, Wolf JS, Gray WC (2002) Squamous cell carcinoma arising in a lymphangioma of the tongue. *Otolaryngol Head Neck Surg* 127: 458-460.
19. Guarisco JL (1991) Congenital head and neck masses in infants and children. *Ear Nose Throat J* 70: 75-82.
20. Kennedy TL, Whitaker M, Pellitteri P, Wood WE (2001) Cystic hygroma/lymphangioma: A rational approach to management. *Laryngoscope* 111: 1929-1937.
21. Perkins JA, Manning SC, Tempero RM, Cunningham MJ, Edmonds JL Jr, et al. (2010) Lymphatic malformations: Review of current treatment. *Otolaryngology - Head and Neck Surgery* 142: 795-803.
22. Bai Y, Jia J, Huang XX, Alsharif MJ, Zhao JH, et al. (2009) Sclerotherapy of Microcystic Lymphatic Malformations in Oral and Facial Regions. *J Oral Maxillofac Surg* 67: 251-256.
23. Jian XC (2005) Surgical Management of Lymphangiomatous or Lymphangiohemangiomatous Macroglossia. *J Oral Maxillofac Surg* 63: 15-19.
24. Fliegelman LJ, Friedland D, Brandwein M, Rothschild M (2000) Lymphatic malformation: Predictive factors for recurrence. *Otolaryngol Head Neck Surg* 123: 706-710.
25. Mikhail M, Kennedy R, Cramer B, Smith T (1995) Sclerosing of Recurrent Lymphangioma Using OK-432. *J Pediatr Surg* 30: 1159-1160.
26. Oosthuizen JC, Burns P, Russell JD (2010) Lymphatic malformations: A proposed management algorithm. *Int J Pediatr Otorhinolaryngol* 74: 398-403.
27. Buckmiller LM, Richter GT, Suen JY (2010) Diagnosis and management of hemangiomas and vascular malformations of the head and neck. *Oral Dis* 16: 405-418.
28. Ozen IO, Ramazan SM, Demirogullari KB, Sonmez K, Turkyilmaz Z, et al. (2005) Surgical treatment of cervicofacial cystic hygromas in children. *ORL J Otorhinolaryngol Relat Spec* 67: 331-334.
29. Marx RE, Stern D (2003) *Oral and maxillofacial pathology: a rationale for diagnosis and treatment* 1st Ed. Quintessence Publishing Co, Inc Chicago 436.