

# Bleb and Blister-Cystic Lymphangioma

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## ABSTRACT

**Abbreviations:** HPF: High Power Fields; VEGFR3: Vascular Endothelial Growth Factor Receptor 3; LYVE1: Lymphatic Endothelial Hyaluron Receptor 1; SMA: Smooth Muscle Actin; HHV8: Human Herpes Virus 8; CT: Computerized Tomography; MRI: Magnetic Resonance Imaging

## Introduction

Cystic lymphangioma represents as a benign vascular lesion constituted of an amalgamation of distended lymphatic channels. The essentially benign proliferation of lymphatic vessels may configure superficial or deep seated lesions or may diffusely incriminate various organs and physiological systems. Initially scripted by Rodender in 1828, tumefaction appears immune reactive to CD31 and D2-40. Contingent to site of origin, neoplasm is additionally designated as lymphatic malformation, lymphangioma circumscriptum, superficial cutaneous lymphangioma, cavernous lymphangioma, deep lymphangioma, cystic hygroma, cystic lymphangioma, intra-abdominal cystic lymphangioma, hemangiolympangioma or lymphangiomatosis, generalized lymphangioma and systemic angiomatosis. Cystic lymphangioma preponderantly appears within paediatric subjects or young adults. Majority (~90%) of lesions occur at birth or within first 2 years. Exceptionally, neoplasm may emerge within older adults and frequently represent as mesenteric lesions. Intra-abdominal neoplasms exhibit a mild male predominance [1,2]. Cystic hygroma is posited to concur with Turner's syndrome. Splenic lymphangiomas appear concordant with Klippel-Trenaunay syndrome.

Neoplasm is associated with a variant of Maffucci syndrome. Cystic lymphangioma is associated with trisomy 13, trisomy 18, trisomy 21 and various genetic syndromes as Noonan's syndrome [1,2]. Genomic

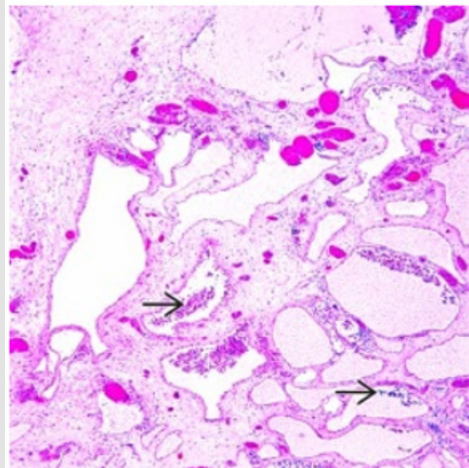
mutations within VEGFR3, FLT4, PROX1, FOXC2 and SOX18 gene may contribute to disease occurrence. Somatic mutations within PIK3CA gene are documented. Cystic lymphangioma occurring within superficial cutaneous sites frequently implicates proximal extremities or limb girdles. Commonly, deep seated lesions appear within head and neck region, pre-eminently upon tongue or floor of mouth followed in frequency by upper and lower extremities, axilla, groin or abdominal region [1,2]. Cystic hygroma is preponderantly confined to sites within head and neck region as posterior triangle of neck. Intra-abdominal lesions may appear within mesentery, omentum or retroperitoneum. Lymphangiomatosis may incriminate multiple visceral sites as pulmonary parenchyma, hepatic parenchyma or bone [1,2]. Cystic lymphangioma is posited to arise from anomalous development of the lymphatic system. Genetic triggers as genomic mutations within PIK3CA gene and diverse chromosomal mutations induce neoplastic genesis through various endothelial growth receptor pathways.

Preliminary, congenital lesions emerge as developmental malformations wherein sequestered lymphatics lack contiguity with normal lymphatic and vascular channels. Majority of neoplasms are contemplated to be malformations or hamartomas. However, genetic anomalies significantly contribute to disease emergence [2,3]. Clinically, superficial lesions may represent as aggregates of multiple, miniature vesicular lesions implicating diverse cutaneous surfaces. Lesions confined to tongue manifest as a tumour mass superimposed with peb-

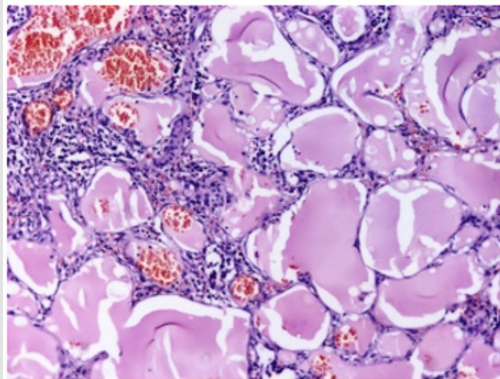
bly, vesicle-like nodules, akin to 'frog eggs'. Commonly, cystic hygroma represents as a unilateral, painless, diffuse, non pulsatile tumefaction confined to posterior triangle of neck. Deep seated lesions emerge as enlarged, painless, gradually progressive tumefaction. Intra-abdominal lesions may displace diverse visceral organs and induce intestinal obstruction [2,3]. Grossly, neoplasm manifests as a multi-cystic, spongy, translucent, reddish brown tumefaction. Cystic spaces are incorporated with watery, viscous or milky fluid [2,3]. Upon microscopy, tumefaction is composed of thin walled, distended lymphatic vessels of variable magnitude. Lymphatic articulations are layered by flattened endothelium with occasional configuration of papillary projections.

Lumina of the cystic cavity may be pervaded with eosinophilic, amorphous proteinaceous fluid commingled with infrequent lipid laden macrophages and lymphocytes. Lesions of extended duration exhibit interstitial fibrosis. Enlarged lymphatic vessels exemplify

smooth muscle within the walls [2,3]. The cystic tumefaction is encompassed with lymphoid aggregates which may occasionally configure reactive germinal centres. Intervening stroma frequently enunciates aggregates of mast cells and hemosiderin pigment deposits [2,3]. Generally, lymphangiomatosis is associated with anastomosing pattern of neoplastic evolution which dissects and circumscribes normal anatomical structures. Neoplasm may induce extensive granulation tissue and an inflammatory exudate, features which may obscure lymphatic genesis of the neoplasm [3,4]. Ultrastructural examination aids in confirming endothelial origin of neoplastic cells layering cystic cavities. Features as Weibel-Palade bodies or storage granules permeating endothelial cells may be observed [3,4]. Mitotic count is predominantly calculated from mitotically active areas, devoid of tumour necrosis. Mitosis may be quantified within 10 consecutive high power fields (HPF) upon 40x objective or 1 HPF x 400 = 0.1734 mm<sup>2</sup> area wherein appropriate high power fields encompassing 1 mm<sup>2</sup> area is contingent to individual microscope (Figures 1 & 2) (Tables 1 & 2).



**Figure 1:** Cystic lymphangioma demonstrating cystic cavity layered by endothelial cells and impregnated by proteinaceous fluid with circumscribed fibro-connective tissue infiltrated by chronic inflammatory cells [7].



**Figure 2:** Cystic lymphangioma delineating cystic cavity lined by endothelial cells and pervaded by eosinophilic, proteinaceous fluid with surrounding fibro-connective tissue infiltrated by chronic inflammatory cells [8].

**Table 1:** Mitotic score of soft tissue sarcomas [4,5].

Mitotic score	Mitosis/10 HPF	Mitosis / mm <sup>2</sup>
Score 1	0-9 mitosis/10 HPF	0-5 mitosis/mm <sup>2</sup>
Score 2	10-19 mitosis/ HPF	6-11 mitosis/mm <sup>2</sup>
Score 3	>19 mitosis /10 HPF	>11 mitosis/mm <sup>2</sup>

Note: HPF: high power field

**Table 2:** Tumour score associated with necrosis [4,5].

Score	Tumour necrosis
Score 0	Absence of tumour necrosis
Score 1	<50% tumour necrosis
Score 2	≥50% tumour necrosis

Note: Tumour necrosis is appropriately evaluated upon cogent gross examination and categorized upon histological sections.

Cystic lymphangioma appears immune reactive to podoplanin (D2-40), PROX1, vascular endothelial growth factor receptor 3(VEGFR3), lymphatic endothelial hyaluron receptor 1 (LYVE1), CD31, CD34, smooth muscle actin (SMA) or Factor VIII related antigen. Neoplastic cells expound enhanced expression of VEGFR3. Neoplastic cells appear immune non reactive to GLUT1, human herpes virus 8(HHV8) or c-MYC [4,5]. Cystic lymphangioma requires segregation from neoplasms as haemangioma, vascular malformation, atypical vascular lesion, acquired progressive lymphangioma, secondary lymphangiectasia, cystic lymphangioma-like adenomatoid tumour, parasitic cyst (echinococcal cyst), mesothelial cyst or soft tissue sarcomas. Besides, lesions as hematoma, abscess or lymphocele necessitate a distinction [4,5]. Cystic lymphangioma appears as a swollen, soft tissue mass which may be discerned with trans-illumination assay. Plain radiographs of abdominal lesions frequently demonstrate a soft tissue tumefaction which displaces loops of small and large intestine. Ultrasonography may be appropriately adopted to confirm the cystic or multi-cystic lesion and delineates a unilocular or multi-locular, anechoic tumefaction. Cystic or multi-cystic lesions may be sharply demarcated and traversed by intrinsic septa.

Tumour may be aptly discerned upon prenatal ultrasonography [4,5]. Computerized tomography (CT) depicts a cystic lesion of variable magnitude traversed by septa and devoid of image enhancement.

The cystic mass is pervaded with homogeneous fluid and may displace adjacent organs or viscera. Upon T1 weighted magnetic resonance imaging (MRI), a hypo-intense or hyper-intense tumefaction is permeated with proteinaceous substance or extravasation of red blood cells. T2 weighted imaging expounds a multi-loculated tumefaction with hyper-intense areas. Cogent ascertainment of the pre-eminently cystic lesion may be challenging upon assessment of miniature tissue samples on account of demonstrable bland cytological features [4,5]. Enlarged, symptomatic lesions may be optimally subjected to surgical extermination. Additionally, intralesional injection of sclerosing agents as bleomycin and OK-432 may be beneficially adopted. Neoplasm may be eradicated by radiofrequency ablation [4,5]. The pre-eminently benign lesion is associated with excellent prognostic outcomes. Inadequate surgical excision is associated with enhanced possible tumour reoccurrence. Deep seated lesions confined to various tissue planes delineate tumour relapse in up to 20% instances. Cystic lymphangioma is associated with complications as infection, haemorrhage, tumour rupture or intestinal obstruction. Diffuse lymphangiomatosis occurring within mediastinal organs or diverse viscera is accompanied by tumour associated mortality. Malignant metamorphosis remains undocumented [4-8].

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- Image 1 Courtesy: Basic medical key.
- Image 2 Courtesy: BMJ case reports.

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