Cervicofacial Lymphangiomas

The natural history of cervicofacial lymphangioma is the presence of a mass in the head and neck area. Cervicofacial lymphangioma is noted before birth, at birth, or in the first few months of life in fewer than 50% of patients with this condition. The initial appearance of cystic hygroma or lymphangioma in adulthood is less common. The growth rate of this neoplasm is variable. Slow progression followed by pseudoregression eventually gives rise to reappearance. Rapid growth or engorgement with lymph or blood is often associated with direct infection, trauma, or a secondary respiratory or skin infection. Spontaneous regression has been reported in as many as 15% of patients with cervicofacial lymphangioma. Malignant change has not been reported.

Problem. Cystic hygroma or lymphangioma is a rare neoplasm or congenital rest that appears in the head and neck region in more than 70% of cases. Whether patients with this neoplasm present in childhood or adulthood, the identification of a mass requires a diagnosis and management plan. Management may be complex and difficult because enlargement often results in functional and cosmetic problems. Attempts at a classification have been created to differentiate between the capillary, cystic, and cavernous forms of cervicofacial lymphangioma; however, the histologic appearance is not always uniform, which suggests a variable clinical and pathologic appearance of essentially the same disease. Determining location, persistence, growth patterns, and functional and cosmetic problems associated with lymphangioma usually requires a full diagnostic evaluation. Proactive therapy chosen on the basis of a careful clinical assessment follows the diagnosis.

Frequency. Cervicofacial lymphangioma is uncommon, representing fewer than 6% of benign tumors of childhood. Incidence has been reported to be less than 2.8 per 1000 population. No sex preponderance or side predilection has been reported.

Etiology. The origin of lymphangiomas is controversial. Theories include lymphangiomas as true neoplasms, hamartomas, or congenital dysplasias of the lymphatics. To determine the role of angiogenesis in the pathogenesis of lymphangioma, Sidle et al (2005) examined patients' specimens for expression of angiogenic inducer vascular endothelial growth factor (VEGF) and angiogenic inhibitor pigment epithelium-derived factor (PEDF) using immunohistochemical analysis. Staining patterns of VEGF and PEDF were evaluated. Histological evidence of increased angiogenesis, including microvascular density, stromal fibrosis, and inflammation, were graded in each

group and correlated with recurrence.

Lymphangioma specimens demonstrated histological evidence of increased angiogenic activity including multiple areas of increased VEGF staining combined with little PEDF staining. Recurrent specimens had increased histological evidence of angiogenesis as well as increased VEGF and decreased PEDF activity compared with nonrecurrent lesions.

They concluded that lymphangiomas exhibit tumorlike pathogenesis owing to the high expression of angiogenic inducers compared with the low expression of inhibitors. Recurrence may be influenced by this imbalance of angiogenic mediators. Further research with antiangiogenic therapy using agents such as PEDF analogues or anti-VEGF receptor antibodies is indicated.

However, most physicians favor the theory that dysplastic lymphatic tissue is sequestered in a target tissue space or organ during fetal development. Sabin (1909) proposed that lymphatics are derived from primitive veins by budding endothelial cells. Because jugular sacs are the largest formations, the high incidence in the neck correlates well with clinical studies and experience. Incomplete canalization of the lymphatics causes obstruction of lymph flow and cyst or cavern development. These formations are analogous to blood-containing cavernous hemangiomas. Target organs and tissues include the retroperitoneum, chest wall, lung, mesentery, pancreas, scrotum, tongue, floor of the mouth, larynx, neck, lip, mediastinum, parotid gland, adrenal gland, axilla, diaphragm, gallbladder, spleen, base of the skull, colon, breast, subdural space, and pelvis.

Pathophysiology. Macroscopically, lymphangiomas are large cavernous, cystic, or complex multilocular masses that extend into tissue fascial planes. Patients usually present with a painless enlarging mass. Cystic types infiltrate into the surrounding tissue by fingerlike multiloculated extensions. Within these multiloculated honeycombed cysts is a clear-to-cloudy, sometimes blood-tinged, fluid with the consistency of uncooked egg whites. Cyst walls are indistinct; penetration and decompression of the cyst is a common occurrence during surgical excision. In many cases, cervical fetal cystic hygroma may be diagnosed before birth by means of ultrasonography. Before 30 weeks' gestation, cervical cystic hygroma is almost always associated with chromosomal abnormalities and congenital cardiac malformations usually in the septated type. A high rate of spontaneous abortion is encountered in this type.

The different types of cervicofacial lymphangioma are classified as follows: Lymphangioma circumscriptum is a simplex superficial red macular or vesicular lesion of mucous membranes or skin.

Lymphangioma capillary type is a simplex lesion of dilated capillarylike channels. Lymphangioma cavernosa is a simplex lesion of dilated lymphatic channels with deep extension and without cyst formation. Lymphangioma cystica (ie, cystic hygroma) is composed of large lymphatic cysts that expand into adjacent soft tissue planes and are well defined, circumscribed, or lobulated. Lymphangioma complex is composed of multiloculated poorly defined cysts

extending to more than one anatomic area, tissue plane, or organ system.

P**resentation.** Children or, less commonly, adults usually present with a mass in the head and neck area. Approximately 90% of cases of cervicofacial lymphangioma become clinically apparent by the patient's third year of life. Common head and neck sites in childhood are the cervical area, floor of the mouth, and the tongue. Orofacial manifestations include mandibular of maxillary deformation, rotation, and malocclusion (ie, crossbite). In a study by Orvidas et al, the most common location involved was the submandibular region, followed by the parotid and cheek.

- Obtain a careful history.
- Perform a complete head and neck examination as well as a general examination.
- Lymphangioma in the head and neck generally involves a swelling or mass that is soft to palpation and well circumscribed or diffuse. It may have defined or ill-defined borders and is often associated with a bluish discoloration.
- Regional venous congestion and the absence of pain are common.
- Common additional symptoms and findings include diplopia, proptosis, respiratory distress, dysphagia, and dysphonia.

Differential diagnosis consideration. Differentiation from other cervical congenital masses or malignancy is necessary in children and adults. The presence of a mass in the larynx or trachea is usually associated with airway compromise and may require differentiation from a subglottic hemangioma. The presence of a mass in an anatomic location generates a differential diagnosis, particularly when combined with diagnostic studies. The cystic nature of the process and the bluish hue often associated with this growth frequently resemble characteristics of a hemangioma. Lesions in the floor of the mouth, particularly when bulging in the submental or submaxillary region, may simulate a plunging ranula. Other differential considerations in the head and neck/axillary region include a branchial cleft cyst, a thyroglossal duct cyst, an axillary lymphocele, a varix, a lipoma, a schwannoma, a parotid cyst, malignant tumors, or other growths capable of arising in this anatomic area.

Location of different classifications of cervicofacial lymphangioma. Cystic hygroma is more common in the neck, while the cavernous type usually appears in the lips, tongue, cheek, and the floor of the mouth. The anterior two thirds of the tongue is the most common intraoral site producing macroglossia. Enlargement of this congenital rest in the upper aerodigestive tract can result in airway distress, dysphagia, aspiration, and difficulty breastfeeding in a child. Cystic hygroma may be a solitary or complex opaque neck mass that spreads along multiple tissue planes.

Cavernous lymphangioma may be well circumscribed or diffuse. Extension into the skin produces a bluish discoloration. The diffuse form tends

to infiltrate into the surrounding tissue planes, around blood vessels and nerves with poorly defined borders. An attempt at staging has been reported. This system stages lymphangioma from early T1 to late T4 disease and is based on cosmetic changes, functional deficits, age of patient at diagnosis, and the number of sites involved.

Indication. Indications for therapy in the neonate with cervical lymphangioma are complex. Severe cosmetic changes do not necessitate immediate intervention unless functional impairment is occurring. Failure to thrive because of ineffective breastfeeding in a child and aspiration and airway compromise during the first 3 months of life are clear indications for immediate intervention. Rapid growth at any age is another indication for immediate intervention. Assess persistence or recurrence of disease in older age groups according to location, functional loss, and cosmetic impairment. Lymphangioma is best treated by means of surgical resection. However, surgical resection may be associated with a significant neurologic deficit and high rate of recurrence of the lymphangioma, which is reported to approach 81% in hygromas arising above the hyoid bone.

Complications. The principle contraindication to surgery is the circumstance in which further intervention will result in serious functional or cosmetic consequences rendering the quality of life below the standards of a reasonable functional life. This problem often arises in clinical situations in which previous therapy has resulted in significant complications that are often neurologic. Multiple recurrences usually indicate that the probability of cure from additional surgery is low. These recurrences are usually associated with lymphangiomas diagnosed in patients younger than 1 year or with lymphangiomas involving the lip, hypopharynx, larynx, tongue, and floor of the mouth **Imaging Studies.**

- Barium swallow and/or upper and lower GI series, when indicated
- Chest radiography
- Computed tomography
    - CT identifies a multiloculated cyst with smooth septa, which enhances uniformly after contrast injection.
    - CT fluid density ranges from -4 to 34 HU, depending on the lipid content and presence of blood.
    - CT contrast is unpredictable because enhancement occurs in only 50% of cases.
- Magnetic resonance imaging: MRI is the study of choice in the evaluation of head and neck lymphangiomas.
- Ultrasonography: For cervical lymphangiomas, the ultrasonogram depicts a cystic mass with smooth, thin, or irregular walls.
- Arteriography: This study is indicated in cases in which a hemangioma, an arterial vascular (A/V) malformation, paragangliomas/glomus tumors,

or vascular schwannomas are strongly suggested by means of conventional imaging studies.

- Screening ultrasonography and MRI
  - Screening ultrasonography has been a valuable tool to evaluate for fetal abnormalities, such as cystic hygroma, diaphragmatic hernia, bronchopulmonary sequestration, fetal airway obstruction, and other life-threatening birth defects.
  - MRI is helpful to corroborate these findings and refine the diagnosis.
  - This combination of imaging techniques is also useful when evaluating the abdomen in children and adults.
- Lymphoscintigraphy: This technique may help identify the source of lymph flow but is not available as a standard clinical study.
- Nuclear magnetic imaging (NMR) and MRI
  - These imaging studies delineate lymphangiomas more accurately with excellent identification of extent because of T2-weighted sequences. Images on T2 have greater signal intensity than muscle, cerebrospinal fluid, and fat.
  - NMR is the study of choice before surgical excision.
  - Gadolinium adds no additional imaging characteristics.

Other Tests. Depending on the anatomic location, other diagnostic studies may include the following: Full neuro-ophthalmic examination for orbital or central lesions; Laryngoscopy, bronchoscopy, and/or esophagoscopy for lesions of the upper aerodigestive system; Abdominal endoscopy and/or colonoscopy for lower GI lesions.

Diagnostic Procedures. Slim-needle biopsy usually yields straw-colored fluid, not the cellular material necessary for histologic diagnosis. Tissue diagnosis, as a direct and final correlate to imaging studies, is the best and most consistent confirmation of lymphangioma.

Histologic Findings. Excluding simplex circumspecta, lymphangiomas may histopathologically be classified into 2 types—the cavernous type and the cystic type. However, histologic characteristics of both types are the usual finding. The cavernous variety tends to involve the lips, tongue, and floor of the mouth. On histologic examination, these masses are composed of dilated cystic spaces containing blood or lymph lined by endothelial cells with a scant-to-dense fibrous stroma. Cell types in the stroma include lymphocytes, lymphatic tissue, fat, or muscle. Spaces vary in size, from capillary to cavernous channels often resembling a Swiss-cheese pattern. Indiscreet margins with no encapsulation correlate with the gross appearance in lobulated cystic types, which have multiple fingerlike extensions into the surrou**Medical Therapy.** Alternate therapy has been proposed as the primary treatment for lymphangiomas, particularly for sensitive areas (eg, the orbit) and, more

commonly, for recurrent disease after surgical therapy.

Radiation therapy has been effective but abandoned because of later malignant transformation or retardation of growth sites.

Carbon dioxide laser therapy has been effective in managing upper airway lesions and superficial mucosal microcystic lesions.

Intralesional sclerotherapy with group A *Streptococcus pyogenes* of human origin (OK-432) has had some success controlling lymphangiomas. The mechanism suggested is the stimulation of increased permeability of the endothelium, accelerating lymphatic fluid drainage and size reduction of the lymphangioma. Peral Cagical et al consider OK-432 the treatment of choice, especially in cases where surgical treatment is associated with the possibility of serious functional or cosmetic side effects.

Somnoplasty shows promise for reduction of tongue lymphatic malformations.

Occasional reports have described the use of triamcinolone, cyclophosphamide, bleomycin, fibrin glue, and alcohol (Ethibloc). Results have been inconsistent, and success is limited.

Surgical Therapy. The treatment of choice for lymphangiomas is surgery. The primary intention is to accomplish total resections. However, because of lesion size, lesion location, and a myriad of previously mentioned variables, total resection is not always possible. Nowhere in surgery is careful planning and attention to detail more important than when dealing with these elusive lesions. If significant cosmetic or functional deficits are probable, consider partial staged reduction or alternative therapy.

Combined sequential approach is recommended for mixed lesions as well as extensive lesions that involve both the mucosa and soft tissues.

The particular surgical procedure relates to the location of the lymphangioma and the structures involved.

Preoperative Details. The surgeon must prepare the patient with lymphangioma and the parents of a child who has lymphangioma for the potential problems associated with resection of a lymphangioma. Airway distress necessitates a tracheostomy, which, in a child, may be required for a considerable period. A careful preoperative consent and a discussion with the patient and family need to include the possible functional and cosmetic deficits that may occur as a result of the surgery. These potential deficits are determined by the age of the patient at onset and the complexity, size, and location of the lymphangioma. Acknowledging the probability of recurrence is important to avoid unpleasant confrontations at a later time. Consider second opinions to solidify the bond between the operating surgeon, the patient, and the famly.

Preoperative testing should confirm with a high probability that the diagnosis is correct. In borderline cases, open biopsy may be performed before definite surgery; however, this is rarely necessary. The responsible surgeon should be an experienced head and neck surgeon with a surgical background in

the resection of lymphangioma and all its ramifications.

Intraoperative Details. Slow deliberate dissection with meticulous attention to anatomic detail, excellent hemostasis, and wide field exposure is essential for a favorable outcome of surgery. Complex disease of the head and neck may require innovative exposures, such as midline mandibulotomy, craniofacial exposure, facial translocations, or degloving incisions. Because of the high incidence of nerve injury, a nerve stimulator is essential to identify at least the motor nerves. Immediately repair transection of a motor nerve (eg, facial) by a nerve graft. Attempts to identify the serpiginous pathways taken by lymphangiomas and hygromas by dye injection or casting with dental materials provide no assurance that disease does not remain. When penetration occurs, decompression flattens the saccular distentions, eliminating the identification and resection of additional disease. If this should occur, repair of the breach may allow for redistention. If not, terminate additional dissection.

Postoperative Details. Physical and psychological support is required, particularly when adverse cosmetic and functional problems occur as a result of surgery or the disease process itself. Tissue diagnosis should reassure the family and/or the patient that the process is benign. Standard postoperative care includes infection prevention, drain removal, airway maintenance, and proper nutrition.

Follow-up. Following discharge from the hospital, the frequency and duration of follow-up visits should be related to the nature of the surgery, its complexity, and problems generated by the surgery or disease process. After initial healing has occurred, a baseline MRI of the operative bed represents a snapshot to which perceived future problems can be compared. In view of the high recurrence rate, providing clinical care for a child with lymphangioma into early adulthood is recommended. For rare adult disease, 5 years is a reasonable time for follow-up evaluation and care. Beyond this period, individual considerations determine patterns of follow-up care.

Complications. The most common complication is incomplete resection and recurrence. A recurrence rate as high as 50% has been reported. Cranial nerve injury exceeds the rate of 20%; the facial nerve is the most common neural deficit reported. Ozen et al (2005) reviewed the medical records of 17 patients who were operated for cervicofacial cystic hygroma between 1985 and 2004 and documented the following 4 postoperative complications: 1 recurrence (6%), 2 facial paralyses (12%) and 1 collection of fluid (6%) at the resection site.

Additional complications include ocular motility problems, difficulty swallowing, aspiration, lingual and hypoglossal nerve injury, spinal accessory nerve loss, brachial plexus, and phrenic nerve injury. Secondary infection, cosmetic deficits, thrombocytopenia, and secondary airway obstruction have also been recorded.

Outcome and prognosis relate to age of onset, the number of sites

affected, the size of the lesion, the location of the lesion, and cosmetic implications. Negative prognostic factors include an age of onset younger than 1 year, multiple lesion sites, large complex lesions, severe widespread cosmetic changes with extension into subcutaneous tissues, and incomplete excision. Lesions of the lip, tongue, floor of the mouth, and larynx/hypopharynx have a high rate of recurrence. The mortality rate is less than 6%.

Future and Controversies. Interferon alfa-2A has been shown to be effective in the treatment of hemangiomas. No studies have shown consistent success in the treatment of lymphangiomas. Genetic therapy for treatment and prevention, improved sclerosing therapy, and advances in molecular biology may eventually provide more acceptable and effective treatments. At present, surgical therapy continues to offer the best chance at a cure for cervicofacial lymphangioma. Unfortunately, this cure may come at a price.