Vascular Anomalies in the Pediatric Patient

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Introduction

Vascular lesions are the most common congenital and neonatal abnormalities, affecting approximately one in 22 children.[1] Their medical significance depends on type, location, size, and associated signs and symptoms. The craniofacial region is the most common site for these anomalies. It is crucial the otolaryngologist understands the natural history of these anomalies in order to manage them successfully.

Classification

The classification of vascular anomalies offers an array of popular descriptive and pathologic terms. The system devised by the International Society for the Study of Vascular Anomalies (ISSVA)[2], 1996, divides vascular anomalies into 2 categories: **Vascular Tumors and Vascular Malformations,** based on cellular kinetics and natural history (**Table 1**).

Table 1: Classification of the pediatric vascular anomalies

VASCULAR TUMORS	VASCULAR MALFORMATIONS
Hemangiomas • Infantile Hemangioma • Congenital Hemangioma	Slow flow lesions • Capillary • Lymphatic • Venous
Vascular neoplasms • Kaposiform hemangioendotheliomas • Hemangiopericytoma • Angiosarcoma	Fast flow lesions • Arteriovenous malformations • Arterio-venous fistulae
	Macrocystic Microcystic Combined

1. Vascular tumors

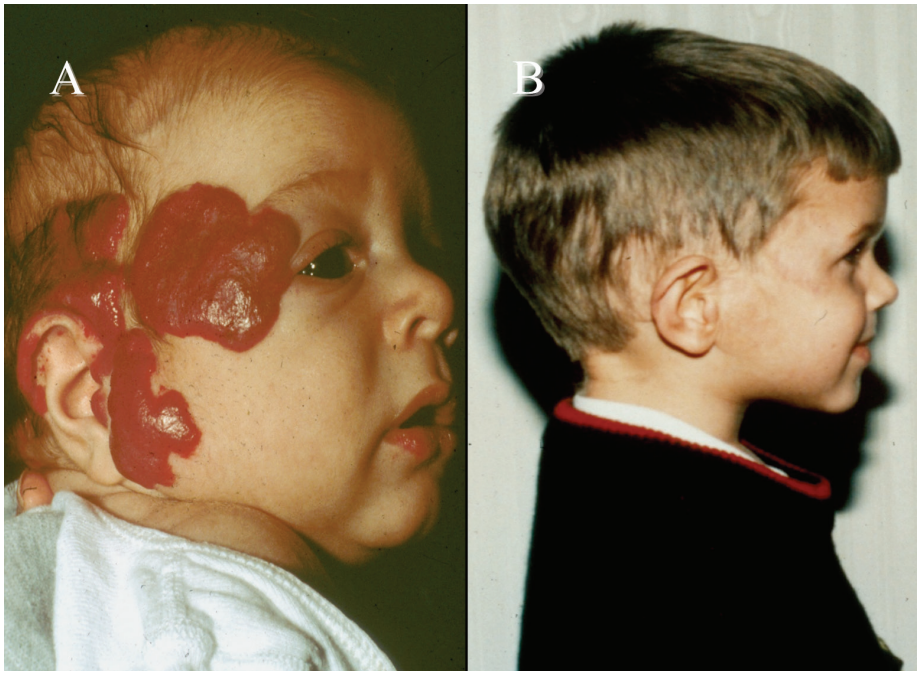
Infantile Hemangiomas (IH) are the most common benign tumors of infancy, affecting approximately 1 in 10 children.[3] Risk factors for development of IH include Caucasian ethnicity, low birth weight (< 1000g), and female sex

(2.4:1). Additional risk factors include prematurity, multiple gestation pregnancy and advanced maternal age.[4] Studies have showed a familial tendency, with a linkage to a locus chromosome 5q31-335. [4,5]

Clinical presentation

The majority of infantile hemangiomas appear during the first six weeks of life as a macular patch, blanched spot, or localized area of telangiectasia surrounded by a halo. IH vary in size from small innocuous tumors to large and deforming tumors. In the proliferative phase, IH tends to be firm and noncompressible, becoming softer and more compressible as they begin to involute.[6] Although, 85-90% of all IH eventually undergo spontaneous involution **(Figure 1A and B)**, it is important to realize that complete involution does not necessarily indicate complete resolution. Up to 40% of IH will leave residual textural changes and scarring characterized by fibrofatty residuum.[7] IHs can be localized, arising from a single point, or segmental, which are larger and present a higher risk of complications and associated anomalies.

Figure 1: (A) A 6-month-old infant with extensive hemangioma involving the parotid auricle and temporal region (proliferating phase). **(B)** Same patient following complete involution of the hemangioma when the patient was four years of age (involution phase).



There are variants of hemangiomas called **Congenital Hemangiomas**, that are defined as tumors that are fully developed at birth and do not exhibit the usual postnatal rapid proliferation. There are two types of congenital hemangiomas:

Rapidly Involuting Congenital Hemangioma (RICH), that defines a group of tumors that rapidly regress by one year of age, and the non-involuting congenital hemangioma (NICH) sub-type that fails to regress and grows in proportion to the child.[2]

Pathogenesis

The **pathogenesis** of IH is poorly understood and it is believed to be multifactorial. North and colleagues[8] were first to note that the endothelial-like cells of the IH expressed **GLUT-1**, the erythrocyte-type glucose transporter protein. This protein appears to be an exclusive marker for IH and is highly expressed at all stages. It is used to distinguish IH from other vascular lesions as congenital hemangiomas.[6]

Complications

The majority of IH are uncomplicated and do not require medical or surgical intervention. Risk factors predictive of complications of head and neck IH are listed in **Table 2**.[6]

Table 2: Risk factors predictive of complications

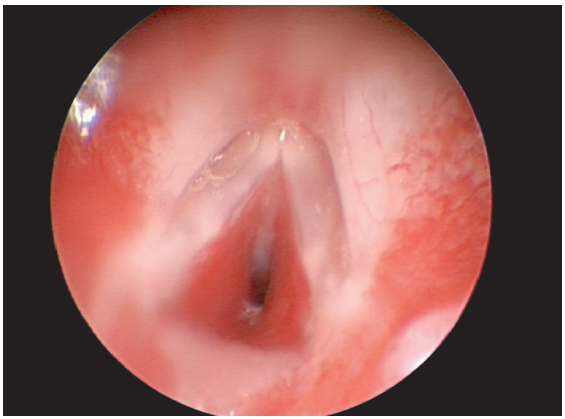
Location	Associated Risk
Periorbital, retrobulbal	Visual axis occlusion, astigmatism, amblyopia
Nasal tip, ear, large facial	Cosmetic disfigurement, scarring
Perioral	Ulceration, feeding difficulties, cosmetic disfigurement
Neck	Ulceration
Large facial	PHACE syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, sternal clefting)
Multiple hemangiomas	Visceral involvement, congestive cardiac failure
Beard distribution: preauricular areas, chin, anterior neck and lower lip.	Subglottic hemangioma

Visual obstruction of the visual axis by a hemangioma can result in deprivation amblyopia and failure to develop binocular vision. Any infant diagnosed with a hemangioma in the periorbital region should have a prompt ophthalmologic examination.

Subglottic Hemangioma is the most common airway vascular lesion and accounts for approximately 1.5% of all congenital laryngeal anomalies.[9] It is a potentially life-threatening lesion that usually presents after the first 6 weeks of life.[10] Over 50% of these infants have an associated cervicofacial cutaneous hemangioma. The patients typically present with biphasic stridor. As the size of the hemangioma increases, there is a reduction in the subglottic airway, with subsequent insidious onset of respiratory distress. On other occasions, the child may present with a

protracted episode of croup. A lateral radiograph of the neck or a fluoroscopic study of the upper airway shows a smooth, usually posteriorly based, round swelling in the immediate subglottic space. Diagnosis requires direct laryngobronchoscopy, which demonstrates the hemangioma as a smooth, easily compressible mass in the subglottic space. On rare occasions, it may extend circumferentially around the subglottic space **(Figure 2).** Biopsy of this lesion is *not* necessary to make the diagnosis. Further evaluation of the distal airway is important to rule out other hemangiomas.

Figure 2: Endoscopic view of a circumferential subglottic hemangioma.



Local complications such as **ulceration and bleeding** during the proliferative phase in infancy may necessitate active treatment. **Bleeding** is often sudden, punctate, and frightening. Parents should be taught how to compress the area with a clean pad, applying pressure for 10 minutes. Repeated bleeding is rare and if it occurs, a mattress suture may be indicated. **Ulceration** is particularly common in hemangiomas of the lips and secondary infection invariably accompanies ulceration. Superficial ulceration usually responds to daily cleansing and application of a topical antibiotic ointment while deeper ulceration may require dressings; these lesions often take several weeks to heal. Pharmacologic therapy may be indicated for extensive and/or refractory ulceration.

Congestive cardiac failure is a life-threatening complication that is typically seen with multiple cutaneous hemangiomas, and with hemangiomatous proliferation within the viscera, typically the liver. High-output congestive cardiac failure can also occur with large cervicofacial hemangiomas. Despite multimodality treatment, the overall mortality rate is reported to be as high as 54% with this complication.[6]

Management

Radiological imaging is not always required but can be useful to confirm the diagnosis, particularly if there is clinical concern regarding involvement of the subglottic region.[11] MRI is the procedure of choice, and contrast and gradient studies should be included. MRI typically shows a well-organized mass, arranged in a lobular configuration.

Pharmacologic Therapy

Hemangiomas are benign lesions. Most require no treatment. Watchful waiting and parental reassurance usually suffice. Hemangiomas that require treatment are those that cause significant cosmetic deformity, functional compromise (periorbital and subglottic), high-output cardiac failure, platelet-trapping thrombocytopenia

(Kasabach-Merritt syndrome), or other major system compromise. Pharmacologic therapy is primarily with corticosteroids. Propranolol has recently shown some benefit.

Corticosteroids

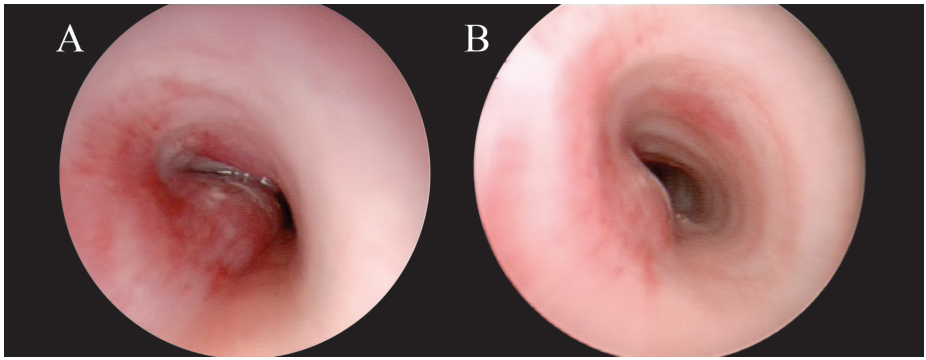
High-dose corticosteroids remain the first line pharmacologic agent for the treatment of hemangiomas that threaten vital function or cause significant complications. They have been shown to have up to a 60% response rate.[10] Although their mode of action is unclear, they are thought to increase the sensitivity of the hemangioma to physiological vasoconstriction. They may also block estradiol receptors, which are thought to enhance growth, within the hemangioma. Corticosteroids can be administered orally, topically, intralesionally, and intravenously. The duration of treatment and approach to tapering corticosteroids is variable, and is dependent on the treatment response, age of the child, inherent growth characteristics of the hemangioma, and complications associated with therapy. Adverse effects are common, and include irritability, gastro-intestinal upset, sleep disturbance, hypertension, glucose intolerance, cushingoid facies, adrenal suppression, immunosuppression, bone demineralization, and growth retardation.[6]

Intralesional corticosteroids can be considered for small protuberant hemangiomas in the face, particularly for upper eyelid and nasal tip lesions. Steroid dose is based on the size of the lesion and the infant's weight.

Propranolol

Propranolol is a non-selective beta-blocker that has recently been introduced as a novel treatment for infantile hemangiomas. Since this initial report in 2008[12], there have been numerous reports demonstrating a rapid response to oral propranolol in both cutaneous and airway hemangiomas after primary treatments were unsuccessful. The mechanism of action of propranolol is unclear, but may involve down-regulation of angiogenic factors and up-regulation of apoptosis. Reported side effects include hypoglycemia, hypotension and bradycardia. Prior to comencing treatment wiht propranolol, the patient should also be evaluated by a cardiologist. It is recommended that baseline investigations such as an electrocardiogram and glucose levels be obtained. Patients are typically hospitalized during the initiation of treatment. Propranolol appears to be an effective therapeutic strategy in cutaneous and airway hemangioma in patients who do not show any response to conventional corticosteroid therapy **(Figure 3A and B)**. However, optimal dosing levels are not yet clear and long-term side effects may have not yet become evident. Future studies with regards to the longterm use of propranolol in this conext are essential. A standardized universal protocol for the use of propranolol in the treatment of infantile hemangioma has yet to be determined.

Figure 3 (A) Endoscopic view of 14-week old female with a large mid-tracheal infantile hemangioma obstructing her airway by 90%. This hemangioma was unresponsive to corticosteroid therapy. **(B)** Endoscopic view in the same patient, one week after starting propranolol therapy, showing a 70% reduction in the size of the hemangioma.



Surgical Therapy

Surgical excision is indicated for removal of the fibro-fatty residuum or skin laxity that remains after complete regression of a hemangioma. There are, however, indications for earlier operative intervention, such as visual problems unresponsive to corticosteroid therapy, early excision of an obstructing subglottic hemangioma or even surgery for psychological indications. In instances in which the hemangioma is pedunculated and ulcerated, the lesion should be removed rather than waiting for involution.

Not all infants with a **subglottic hemangioma** require treatment, especially those with a small lesion that occupies less than 30% of the subglottic airway. The treatment of choice in this siutaion is watchful waiting until involution. After the initial diagnosis, close airway monitoring and regular follow-up is essential to monitor the behavior of the hemangioma and its rate of growth. For subglottic hemangiomas that require treatment, systemic corticosteroid therapy should be the first choice. If this fails, propranolol could be used, with caution. The carbon dioxide (CO_2) **laser** is a therapeutic option for infants who fail to respond to steroids. It is ideally suited for treating eccentrically placed subglottic hemangiomas or when such a lesion can be removed with one operative procedure. Newer laser delivery systems such as the flexible CO_2 laser can be helpful in reaching more distally located airway hemangiomas. The potassium-titanyl-phosphate (KTP) and neodymium: yttrium-aluminium-garnet (Nd:YAG) lasers have also shown some success.[10] To prevent subglottic stenosis, circumferential subglottic hemangiomas should be removed in stages.

Endoscopic and open surgical excision should thus be considered in patients with siginificant airway obstruction who are non responders to medical therapy or where medical therapy is contraindicated. Nowadays, a tracheotomy is rarely indicated for treatment of subglottic hemangioma. It is primarily reserved for patients with persistent significant airway obstruction despite medical and

open or endoscopic surgical therapy, multiple tracheal hemangiomas, or any other concomitant cause of airway obstruction such as vascular rings or tracheomalacia.[10]

1.Vascular neoplasms

Kaposiform hemangioendotheliomas (KHE) are rare vascular tumors mainly occurring in early childhood. KHE typically occurs in the proximal arms, legs and trunk. They can present as a slightly raised subcutaneous mass. Deeper soft tissue lesions may present as indurated masses and can involve multiple tissue layers. This tumor is associated with **Platelet-Trapping Coagulopathy - *Kasabach-Merritt Phenomenon*;** marked by profound thrombocytopenia (2,000 to 40,000/mm^3) resulting from active platelet trapping within the tumor, sometimes confounded by microangiopathic hemolytic anemia and secondary consumption of fibrinogen and coagulation factors.[13, 14]

Infantile Hemangiopericytomas are uncommon tumors that typically appear in the first year of life and are usually congenital. There is a male predominance by 2:1. The tumors presents as nodular lesions in the subcutaneous and dermal tissue of the head and neck. They may be confused clinically with infantile hemangioma due to rapid posnatal growth. Biopsy may be required for definitive diagnosis. Conservative treatment is recommended given the potential for spontaneous regression[15].

Angiosarcomas are malignant mesenchymal vasoformative neoplasms that arise in various soft tissues and visceral organs. They occur rarely in childhood and adolescence, and may affect multiple sites, including bone, skin, soft tissue and internal organs. Complete surgical excision is indicated. Prognosis is extremely poor.[16]

2.Vascular malformations

Vascular Malformations are not race or sex specific. They are classified either by the nature of the vessels (***capillary, lymphatic, venous, arterial or combined***) or by the type of flow within the malformation (***slow-flow, fast-flow and combined lesions***) (**Table 3 and 4**). Vascular malformations are also descibed as ***macrocystic or microcystic lesions***. Macrocystic lesions are lesions containing cysts greater than 1cm in size and commonly occur below the level of the mylohyoid muscle, and can involve both, the anterior and posterior cervical triangles. Microcystic lesions contain cysts less than 1cm in size, and are commonly found above the level of the mylohyoid muscle, involving the cheek, oral cavity, lip, and tongue.

The molecular mechanisms underlying the formation of vascular malformations remanin unclear. They are thought to be the result of **lymphatic dysmorphogenesis**.[17] In contrast to vascular tumors, histologic evaluation of vascular malformations shows no evidence of cellular proliferation, but rather a progressive dilatation of vessels of abnormal structure.

Clinical presentation

By definition, vascular malformations are present at birth and many, but not all, present in the nursery. Usually they grow commensurately with the child. **Venous** anomalies often expand sceondary to hormonal changes such as puberty or pregnancy, or secondary to trauma. **Lymphatic** malformations typically enlarge with infection or intralesional bleeding. Usually, both of them appear during

infancy while arteriovenous malformations more often manifest later in childhood. **Arteriovenous** malformations may also enlarge in association with trauma, puberty or other hormonal changes, or incomplete surgical excision. It is essential not to confuse these nonproliferative enlargements of vascular malformations with the proliferating phase of hemangioma.

Table 3. Histologic and clinical features of Vascular Malformations

Sub-type	Histology	Clinical features
Capillary malformation	Dillated capilaries or venule-sized vessels in the superficial dermis.	Present at birth. Port wine stain within the cranial nerve V1 area alone or extending into V2 and V3. (consider Sturge-Weber syndrome).
Venous Malformation	Dilated vascular channels lined by normal endothelium. Thrombosis is common. May be associated with phlebolith.	Variable. Isolated skin varicosity, localized spongy mass or complex lesion, infiltrating tissue planes. May or may not involve dermis. Common in lips, cheeks and skeletal muscles. Usually soft, compressible, non-pulsatile. Grows proportionally with the child
Lymphatic Malformation	Multiple dilated lymphatic channels lined by a single layer of flattened endothelium.	Congenital. Present at birth. Usually detected before 2 years of age. Associated with hypetrophy of bone and soft tissue
Arteriovenous Malformation	Arteriovenous shunts. Dysmorphic arteries of irregular calibre.	Rarely symptomatic in the neonate. More common during late childhood, or adolescence. Slow destruction of facial bones may occur.

Table 4. Characteristics distinguishing Vascular Tumors (Hemangiomas) from Vascular Malformations

	VASCULAR TUMORS HEMANGIOMAS	VASCULAR MALFORMATIONS
Clinical	Rarely present at birth Rapid post-natal proliferation Slow involution Female:male = 3:1 No skeletal involvement	Present at birth Grows slowly with patient No involution Female:male =1:1 Skeletal involvement – bone hyperthrophy and destruction
Histology	Plump proliferating endothelium (high turnover) Multi-laminated basement membrane Increased mast cell count Only IH express GLUT-1	Flat quiescent endothelium (low turnover) Normal basement membrane Normal mast cell count
Radiology	Well-organized mass arranged in a lobular configuration. MRI - fast flow in a proliferative-phase hemangioma CT with contrast - uniform intense enhancement	Vessels of a different caliber without intervening parenchyma. MRI - signal voids consistent with phleboliths Venous and arteriovenous malformations demonstrate diffuse variable enhancement. Lymphatic malformations typically show only rim enhancement or no enhancement.

Management

Radiologic Imaging

Like hemangiomas, the role of imaging in the diagnosis of a vascular malformation is not only to validate the clinical diagnosis, but also to determine the extent of the lesion and its relationship to surrounding tissue planes. Vascular malformations can now be diagnosed as early as the 4th month in-utero with the aid of prenatal ultrasound in combination with fetal MRI.[18] Post-natal imaging modalities include ultra sound (US), CT, MRI and infrequently conventional angiography.

Capillary Malformation

The flash lamp pulsed dye laser (PDL) is used extensively for treatment of capillary malformation in infancy and children. Significant lightening of the lesion is

achieved in 80% of patients, with the best results in younger children.[19] In selective cases, it may be possible to surgically excise the port-wine stain and obtain primary closure by skin advancement or skin grafting. There can be serious problems after excision and grafting, including scar hypertrophy at the junction of the graft and normal skin, and unpredictable pigmentation of the skin graft itself.

Venous Malformation

Most venous malformations do not require any specific treatment apart from reassurance and an explanation of the natural history of the lesion. Direct injection of a sclerosing agent into the center of a soft-tissue venous malformation is an accepted mode of treatment. Sclerosing agents such as 95% ethanol, sodium tetradecyl sulfate (1 or 2%), bleomycin, doxcycline and OK-432 are injected into the epicenter of the venous anomaly during occlusion of the arterial inflow and venous outflow. Injection of a sclerosing agent can be dangerous and should be done under general anesthesia with fluoroscopic monitoring by an experienced interventional radiologist. Local complications such as edema, full-thickness necrosis, or nephrotoxicity have been reported. Multiple injections are usually required, often at several month intervals. Unfortunately, venous malformations have a propensity to recur. Surgical resection is indicated for large or symptomatic venous anomalies.

Lymphatic Malformation

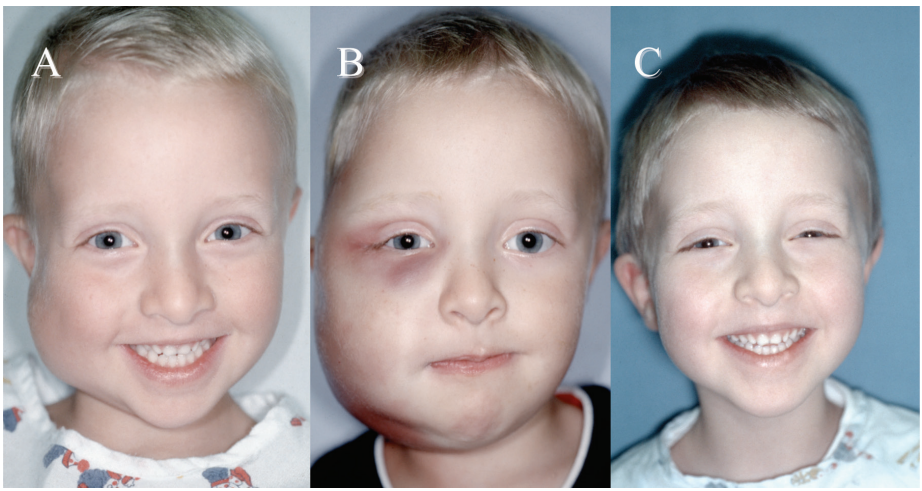
The two main treatment modalities for lymphatic malformations are surgical resection and sclerotherapy. Aggressive resection is never warranted, nor is an excessively conservative approach to be condoned.

Surgical resection: It is usually a good plan to wait until the lymphatic malforamtion has "declared itself" and its growth pattern has become evident, before embarking on surgical excision. This may mean waiting unitl the child is 1-2 years of age. ***Macrocystic lesions*** are more suited to surgical excision, and can frequently be removed in a single procedure. Surgery can sometimes be difficult due to scarring and fibrosis from sclerotherapy or infection, and anatomic distortion. ***Microcystic lesions*** are more difficult to manage surgically, because no distinct tissue planes exist between the malformation and the normal structures. Repeated procedures are often necessary, and complete removal is almost impossible. In cases where resection of a lymphatic malformation is planned, it is recommended typically at age 5-6 years, before the child starts school. In planning such a procedure, restrictions should be set for the extent of dissection, duration of procedure, and acceptable blood loss. Meticulous dissection is necessary because anatomic structures frequently are not in their normal position. Magnification and the use of the nerve simulator are essential. The disruption of the abnormal lymphatic channels frequently leads to prolonged wound drainage. Drains should remain in position for an adequate period to avoid re-accumulation of lymphatic drainage under the skin flaps.

Sclerotherapy is frequently used as an alternative to surgery in patients where surgical resection is not possible or indicated. It can be useful in relieving symptoms in up to 40% of patients, but is not generally curative and multiple treatments can be required. Sclerosing agents used in North America include 95% doxycycline and bleomycin. The procedure is usually performed under radiological guidance by the interventional radiologist. Swelling of the lesion following sclerotherapy is a

common side effect, and can be potentially very dangerous if the lesion is located in the airway or mediastinum, resulting in airway obstruction. For this reason, patients are typically observed in hospital for 24 hours following sclerotherapy. Other side effects include, local erythema and tenderness of the lesion **(Figure 4A, B and C).**

Figure 4: (A) A 3-year old male with a right parotid lymphatic malformation. **(B)** The same patient 36 hours after sclerotherapy treatment. **(C)** The same patient 4 weeks after sclerotherapy treatment showing a vast reduction in the size of the right parotid lymphatic malformation.



Laser is reserved for disease that is not readily resectable by sharp dissection. Lesions that involve the oral cavity, tongue and supraglottis can be candidate to CO_2 laser resection. The CO_2 laser may be helpful in localized lesions in the lip and buccal areas, which cause bleeding.

Radiofrequency coblation is a useful novel adjuctive treatment in patients who have large ulcerated microcystic lesions of the tongue or oral mucosa, and are troubled by recurrent bleeding and irritation. [20] Radiofrequency energy is applied through a wound to the mucosal surface of the lesion. It destroys tissue with minimal damage to adjacent tissues, diminishing regrowth of residual malformation and improving wound healing. Symptoms of bleeding, pain, infection and vesicle formation are dramatically reduced.

Arteriovenous Malformation

If an ateriovenous malformation is asymptomatic, no treatment is necessary. However, when complications such as pain, ulceration, bleeding, or heart failure are present, therapy is necessary. There is ***no place for proximal ligation*** of the feeding arterial system. The only therapy that holds any hope for long-term success is total resection of the tissue involved with the arteriovenous anomaly. Leaving behind residual and dormant anomalous channels only invites further collateral formation, shunting, and expansion.[10] Preoperative selective embolization will not diminish the extent of the resection, but will minimize intraoperative bleeding.

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