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## INVITED MEDICAL REVIEW

# Diagnosis and management of hemangiomas and vascular malformations of the head and neck

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**Vascular anomalies are congenital errors in vascular development. They frequently involve the head, neck, and oral cavity. Subdivided into vascular tumors (hemangiomas) and vascular malformations, vascular anomalies remain poorly understood. However, growing interest and recent advances in the diagnosis, management, and molecular characterization of these lesions are improving treatment strategies. The role of the multidisciplinary team cannot be overstated. This review provides both basic and up-to-date knowledge on the most common vascular anomalies encountered by physicians and practitioners. Because treatment options for vascular anomalies are widely variable and often debated, this report aims to provide a comprehensive approach to these lesions based upon current concepts and practical clinical experience.**

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## Introduction

Hemangiomas and vascular malformations are congenital aberrancies of vascular development causing identifiable birthmarks of the skin and mucosa and a variable degree of underlying soft tissue abnormalities. Under the global heading of vascular anomalies, these lesions predominately occur within the head and neck and affect approximately one in 22 children (Drolet *et al*, 1999; Haggstrom *et al*, 2007; Greene *et al*, 2008). Involvement of the oral cavity is common but frequently requires unconventional treatment strategies for their management. Depending upon the size and location, significant functional and esthetic impairment can result from the growth of 'problematic' hemangiomas or vascular malformations. Bleeding, pain, and disability are also common (Kohout *et al*, 1998). Thus, an in-depth understanding of the natural history of vascular anomalies is critical for practitioners who diagnose and manage these lesions.

Little is understood regarding the pathogenesis, molecular make-up, and origin of vascular anomalies. The field, however, is rapidly progressing. The identification of molecular contributors, genetic markers, and novel treatment protocols has emerged over the past decade that is changing the conceptual framework regarding the pathogenesis and management of vascular anomalies. However, the factors that have not changed are the complexity of vascular anomalies and the importance of a multidisciplinary approach, or therapeutic center, for the treatment and long-term follow-up of these patients.

In the past, patients and their families had been frustrated because of frequent misdiagnosis and mismanagement of vascular anomalies. The education of medical personnel encountering these lesions has been slow but continues to progress. This report, at the subsequent stage, also aims to provide comprehensive knowledge and therapeutic approach to the more common vascular anomalies discovered in the head, neck, and oral cavity. Treatment advances for these lesions, like beta blockers for hemangiomas, are discussed and further information regarding the origin and growth of vascular anomalies are explored.

## Classification of vascular anomalies

Vascular anomalies are soft tissue lesions of congenitally aberrant blood vessel growth that affect up to 10% of newborns (Greene *et al*, 2008). Previously termed 'angiomas' or vascular 'birthmarks', vascular anomalies are now divided into two main categories: vascular tumors and vascular malformations. Infantile hemangiomas comprise the majority of vascular anomalies and are considered the predominant vascular tumor type composed of rapidly proliferating endothelial cells (Drolet *et al*, 1999; Haggstrom *et al*, 2007). Other rare

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vascular tumors, of which the affected cell type may differ, include pyogenic granulomas, congenital hemangiomas, tufted angiomas, and a variety of hemangioendotheliomas. Blood vessel architecture is incomplete and surrounded by hyperplastic cells in hemangiomas and other vascular tumors.

In contrast, vascular malformations do not contain hyperplastic cells but consist of progressively enlarging aberrant and ectatic vessels composed of a particular vascular architecture such as veins, lymphatic vessels, venules, capillaries, arteries, or mixed vessel types. Vascular malformations are appropriately named by their predominant vessel type [e.g., venous malformations, arteriovenous malformations (AVMs)]. More importantly, the diagnosis and treatment strategies for vascular malformations are also based on their individual flow characteristics. Vascular malformations are therefore further subdivided into slow-flow and fast-flow lesions based upon the velocity of fluid motion through their system. Capillary, venous, and lymphatic malformations are considered slow-flow malformations while AVMs have fast-flow characteristics. Unlike hemangiomas, vascular malformations are uncommon, rarely regress, and continue to expand, and have high rates of recurrence following intervention (Kohout *et al*, 1998; Lei *et al*, 2007; Bai *et al*, 2009).

The current classification system for vascular anomalies can be attributed to Mulliken and Glowacki (1982) who based their concept upon the clinical presentation, biologic behavior, and histology of these lesions (Mulliken and Glowacki, 1982; Mulliken *et al*, 1982). The schema was subsequently accepted (1996) and revised (1997) by the International Society for the Study of Vascular Anomalies (ISSVA) and is now recognized worldwide as the official system for classification of congenital disorders of vascular development. Prior to the establishment of this system, vascular anomalies were often misdiagnosed, mismanaged, and poorly understood. Many disciplines are now involved in the treatment of these disorders, the majority of which affect the head and neck with frequent involvement of the oral cavity and upper aerodigestive tract.

## Vascular tumors

*Hemangiomas*

Infantile hemangiomas are congenital vascular tumors comprised of rapidly dividing endothelial cells affecting up to 10% of population with a greater incidence in Caucasians, female patients, and premature and low birth-weight infants (Haggstrom *et al*, 2007; Drolet *et al*, 2008). Their origin and pathogenesis remain incompletely understood. Frequently occurring as a solitary lesion in the head and neck, hemangiomas are considered the most common tumor encountered in infancy. In particular, they are the predominant tumor of the parotid gland and orbit in children (Torer *et al*, 2007).

Hemangiomas proliferate during the first 9–12 months of life and subsequently involute at a variable course over many years (Ronchese, 1953; Jacobs, 1957). Common dictum predicts that over 70% of lesions consistently and completely resolve by 7 years of age. This assertion has raised controversy concerning the approach currently being taken by the care providers on their management. Conservative observation has been historically employed to allow the majority of lesions, in inconspicuous sites, to dissipate on their own. Medical and surgical therapies have been uncommon unless functional problems arose such as orbital obstruction, airway occlusion, and ulceration. Nonetheless, a recent paradigm shift in the management of these conditions has occurred. Many practitioners now advocate early intervention to circumvent immanent esthetic sequelae from residual scarring and fibrofatty distortion. Undisputed indications for treatment of hemangiomas still remain and include ulceration, bleeding, exorbitant size, functional deficits, and congestive heart failure with massive disease.

Hemangiomas are sub-divided into two categories based on their clinical behavior and histology. The more common 'infantile' hemangioma develops shortly after birth and follows the expected course of proliferation with prolonged involution. They are variable in appearance and can present as isolated, multifocal, or segmental lesions. Positive staining for the histologic marker GLUT1 is highly specific and diagnostic for infantile hemangiomas. In contrast, the less understood 'congenital' hemangioma is rare, present at birth, and histologically GLUT1 negative, and does not follow the natural growth phase of its infantile counterpart (North *et al*, 2001). Congenital hemangiomas can either rapidly involute (rapidly involuting congenital hemangiomas; RICH) or never involute (non-involuting congenital hemangiomas; NICH). Surgical intervention is frequently necessary on the latter. As congenital hemangiomas are GLUT-1 negative, speculation as to their true nature has been raised. The remaining sections on hemangiomas center on the infantile type as encountered in greater than 90% of the cases.

*Pathogenesis*. Both infantile and congenital hemangiomas are the result of endothelial cell hyperplasia. The cause of the aberrant and focal proliferation of endothelial cells in hemangiomas remains unclear. The origin of hemangiomas, although still under debate, has been narrowed to embolic placental angioblasts or intrinsic endothelial progenitor cells with the ability to clonally duplicate in a precise milieu of cytokines and estrogen (Kleinman *et al*, 2005; Barnes *et al*, 2007). The placental theory of hemangioma growth originated from the work developed by North *et al* (2002) who discovered that the histology and molecular markers unique to placental tissue, namely GLUT1, Lewis Y Antigen, Merosin, and Receptor II were also present in infantile hemangiomas. In fact, staining for GLUT1 is now standard practice to pathologically delineate hemangiomas from other vascular anomalies when the diagnosis is in question (Leon-Villapalos *et al*, 2005). The placental theory suggests that fetal progenitor cells arise from disrupted placental tissue during gestation or birth and is further supported by the increased incidence of infantile hemangiomas

found following chorionic villis sampling, placenta previa, and preeclampsia.

The presence of circulating progenitor and stem cells, identified by their specific cell-surface proteins $CD133^+/CD34^+$, within hemangiomas and the blood circulation of these patients has recently brought to the fore the theory that these tumors arise from embryonic endothelial precursors (Yu *et al*, 2004). The source is suspected to be a single somatic mutation leading to clonal duplication of primitive endothelial cells (Bischoff, 2009). This concept has led to successful animal models of hemangioma development supporting the stem cell theory. In particular, stem cells isolated from human hemangiomas have been shown to develop into tumors histopathologically consistent with hemangiomas in nude mice (Khan *et al*, 2008). Although controversial, it is possible that both the theories regarding the origin of hemangiomas are correct. Hemangiomas likely arise from progenitor cells with directional preponderance to become placental-like tissue in specific organs such as skin and liver. However, the appropriate milieu of local tissue factors and cytokine signals must be present to foster their development.

Investigation into the pathogenesis of hemangiomas has been active for nearly a century. Much of the work has examined the factors contributing to hemangioma growth and involution. Environmental cues, perinatal events, disordered cytokine signaling, angiogenic factors, and genetic determinants have been explored. Growth factors specifically involved in angiogenesis and vasculogenesis have been natural targets for investigation. Subsequently, increased levels of common molecular contributions to endothelial cell migration and new vessel development have been discovered during the proliferative phase of hemangioma growth such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), insulin-like growth factor (IGF), and matrix metalloprotease-9 (MMP-9) (Chang *et al*, 1999; Kleinman *et al*, 2007). Estrogen and hypoxia-inducible factor also seem to play a critical role in regulating endothelial cell recruitment and proliferation in these lesions (Chang *et al*, 2007; Kleinman *et al*, 2007; Sun *et al*, 2008). Links to genetic errors in growth factor receptors such as FGFR4, PDGFRB, VEGFR2, and Flt-4 are also evident in cases of familial hemangiomas (Chiller *et al*, 2003). Although the origin may be under debate, the role of molecular signaling involved in vascularization is clear in hemangioma development. Similarly, and as would be expected, the levels of angiogenic markers also wane during the involution phase of hemangiomas. This decrease occurs along with increased concentrations of markers for apoptosis [Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)] and mast cells during hemangioma resolution (Frischer *et al*, 2004; Sun *et al*, 2007, 2008).

Recently, the identification of propranolol as a novel therapy in hemangiomas has shed new light on their pathogenesis (Frieden and Drolet, 2009; Sans *et al*, 2009). The mechanism of propranolol, although controversial, in reducing or eliminating the hemangiomas seems to center around the control of cellular apoptosis (Buckmiller *et al*, 2009; Sans *et al*, 2009).

*Clinical presentation and categorization*. Infantile hemangiomas become evident shortly after birth as well demarcated, red, vertically expansive lesions. They can be overlooked during the first month of life as they are difficult to differentiate from other common skin blushes seen in the newborn. During this period, they are flat, pink, and sometimes more pale or bluish than their surrounding tissue. In this light, and unlike vascular malformations, infantile hemangiomas are considered characteristically absent at birth. In time, however, progressive endothelial cell proliferation leads to skin and subcutaneous changes consistent with a growing tumor. The skin frequently becomes bright red, cobblestoned, and elevated during the proliferative phase of growth. Eighty percent of proliferation is felt to occur by 3 months of life (Chang *et al*, 2008). However, slower but continuous growth occurs up to 9 months in most patients. Rapid expansion can lead to adjacent skin and soft tissue ischemia, necrosis, and ulceration. Ulceration and subsequent bleeding is common in watershed areas, such as the lip and ear, and will appear within the first few months of life during the rapid growth phase (Haggstrom *et al*, 2006). Massive blood loss is uncommon and bleeding can typically be stopped by applied pressure to the site. Despite the appearance of superficial hemangiomas and the risk of ulceration in some areas, it is uncommon for hemangiomas to be more susceptible to injury or disrupt when exposed to minor trauma.

The visible portion of hemangiomas on the skin often represents only an element of a larger subcutaneous component. The bright red discoloration is persistent until the onset of involution when resurfacing is observed as variable graying of the overlying skin. Involution may occur as early as 6 months of age in isolated lesions and or much later when deep or segmentally distributed hemangiomas are present. In essence, depending upon the hemangioma, its course of involution is also variable (Chang *et al*, 2008).

Infantile hemangiomas are heterogeneous in their appearance and have further been classified according to their depth, number, distribution, and, sometimes, location. Superficial hemangiomas involve only the skin and will remain relatively flat throughout their growth phases. Compound hemangiomas involve both the skin and subcutaneous tissue while deep hemangiomas involve the subcutaneous surface and not the overlying skin. Rarely, if ever, do hemangiomas arise in muscle, and the diagnosis should be reconsidered if a vascular lesion is found at this site. Similarly, infantile hemangiomas are rarely present in adults, and the diagnosis should be questioned.

Hemangiomas are also described as either focal or segmental. Focal hemangiomas are classically reported as unilocular masses that undergo clear phases of growth and regression. Multifocal disease describes patients with numerous, and often small, hemangiomas distributed randomly throughout the body mostly involving skin, liver, and gastrointestinal (GI) tract.

The possibility of GI and liver hemangiomas is high when more than five hemangiomas are present. An abdominal ultrasound is necessary in these patients to locate GI involvement as they may cause liver dysfunction or GI bleeding.

Hemangiomas involving multiple contiguous cervicalfacial subunits with indistinct borders are termed as segmental hemangioma. Segmental hemangiomas are unique as compared with their focal counterparts. These entities, to a variable extent, involve the head and neck in the distribution of the trigeminal nerve. Extensive deeper components are typically present especially within the parotid gland and deep facial planes of the head and neck. Segmental disease is best illustrated by the characteristic 'beard' distribution hemangioma that involves lower lip, chin, cheeks and pre-auricular areas. However, periorbital, frontal, and auricular involvement is also found in segmental disease. Segmental beard lesions have been shown to have a 63% incidence of subglottic airway involvement and warrant a thorough airway evaluation (Orlow *et al*, 1997). Patients with a segmental distribution of their hemangiomas also need a thorough evaluation for PHACES syndrome, a neurocutaneous condition marked by the presence segmental head and neck hemangiomas (H) and one or more anomalies of the posterior cranial fossa (P), major cervical and intracranial arteries (A), heart and aorta (C), eye (E), and sternum (S) (Metry *et al*, 2009).

The segmental distribution of hemangiomas can also be found within the upper aerodigestive tract. In these patients, superficial and flat lesions are present along the mucosal surfaces of the floor of mouth, lip, tongue, pharynx, hypopharynx, and larynx (O *et al*, 2009). Rarely are the flat lesions symptomatic unless the trachea or subglottis is involved. In fact, subglottic segmental disease is typically more difficult to treat because of their diffuse nature as compared with focal lesions in the same area (Perkins *et al*, 2009).

*Management*. Prior dictum predicted hemangiomas to completely resolve in 50% of children by 5 years of age, 70% by 7 years, and 90% by 9 years (Ronchese, 1953). This suspected pattern led to conservative observation as the mainstay of therapy. However, long-term analysis of children with infantile hemangiomas has shown that disease-specific complications occur in 24% of patients and specific treatments are employed in 38% of patients to manage these lesions (Haggstrom *et al*, 2006). The paradigm of benevolent observation is waning as therapeutic options, disease understanding, and recognition of esthetic sequelae are emerging. Increasingly the medical community is recognizing that incomplete resolution is common in hemangiomas. For example, compound hemangiomas frequently leave fibrofatty residue and scar.

If inconspicuous, hemangiomas are left untreated and allowed to follow their natural course of proliferation and evolution. Problematic hemangiomas occur when they ulcerate, have massive growth, cause disfigurement, or impact normal function. Early intervention in these lesions is recommended. Common locations for problematic hemangiomas include the face, ear, orbit, lower lip, and airway (Wiatrak *et al*, 1996; Orlow *et al*, 1997; Pransky and Canto, 2004). Immanent sequelae are the course of their progressive enlargement. Thus, treatment often begins during the proliferative phase as rapid growth can lead to worsening function, obstruction, and/or esthetics.

Historic treatment options for infantile hemangiomas include systemic or intralesional corticosteroids, chemotherapeutic agents (vincristine, alpha-interferon), surgery, lasers, or a combination of these therapies (Bauman *et al*, 1997; Fledelius *et al*, 2001; Perez *et al*, 2002; Fawcett *et al*, 2004; Jalil *et al*, 2006; Pope *et al*, 2007; Buckmiller *et al*, 2008). Each treatment option has limited therapeutic benefit with its own side-effect profile and risks (Bauman *et al*, 1997; Adams, 2001; Goyal *et al*, 2004; Deboer and Boston, 2008). Intralesional steroid therapy, often requiring multiple injections, is an effective and safe first-line option for nasal tip and deep parotid lesions in the proliferative phase to control accelerated growth and terrible esthetic consequences (Buckmiller *et al*, 2008; Simic *et al*, 2009). Massive hemangiomas, liver disease with enzyme dysfunction, airway lesions, segmental disease, and periorbital involvement often require systemic therapy to control progression and devastating functional outcomes. Both systemic steroids and vincristine have been the workhorse for these conditions. Persistent therapy and careful regulation of side-effects requires frequent visits and multidisciplinary assistance (oncology, otolaryngology) until the onset of involution. Despite potential side-effects, steroids and vincristine have been successful in dramatically reducing and sometimes curing hemangiomas.

Definitive management for isolated lesions or fibrofatty remnants is surgical. Utilizing plastic surgical techniques and respecting relaxing tension lines can lead to excellent esthetic results. Residual telangiectasia and rubor following hemangioma involution is amenable to flash lamp dye laser (FPDL) therapy with low risks and superb outcomes. FPDL works by photothermal ablation of its chromophore hemoglobin that contributes to the superficial red discoloration in hemangiomas. Debate remains as to the benefit of early FPDL therapy to proliferating lesions. Intraoral lesions respond similar to their skin counterparts although these entities are uncommon. Ulcerative hemangiomas, frequently found on the lip, ear, neck, and anus, require early FPDL therapy to promote healing and epithelial resurfacing. One or two treatments are typically necessary to prevent further breakdown. Such lesions will require future excision of residual scar from the initial ulceration. Antibiotic ointment, before and after FPDL, is necessary to improve the health and prevent infection of ulcerated lesions.

*Subglottic hemangiomas*. Surgical and medical options for management of subglottic hemangiomas are numerous and remain under debate. These include systemic and intralesional steroids, endoscopic laser (carbon dioxide) therapy, airway dilatation, and surgical debulking

with airway reconstruction. In general, preservation of the mucosa of the subglottis is preferred, regardless of technique, in order to circumvent inevitable subglottic scarring and stenosis that can occur following minor mucosal disruption. Successful management of subglottic disease has been reported with each technique and the ideal approach remains unclear. However, several tenets can be derived from this and other series that should be observed when addressing subglottic hemangiomas.

Early airway evaluation and medico-surgical intervention should occur to prevent rapid obstruction of the subglottic lumen. Urgent tracheostomy is uncommon and should be avoided. Decannulation rates for early tracheotomies may not occur until the second to fourth year of life and override a critical period in voice and speech acquisition. Fibrofatty deposits, as found histologically in involuting hemangiomas, may contribute to persistent airway obstruction despite resolution of the initial hemangioma and will require surgical resection. For these reasons, when possible, treatment of obstructive subglottic lesions should be instituted early in the course of disease. In our experience, early and isolated lesions respond well to intralesional steroids, dilation, and overnight intubation. If this treatment is unsuccessful, systemic therapy can be effective (steroids or vincristine) in preventing tracheostomy. Subglottic disease appears to mirror the response of superficial lesions. If systemic therapy is employed in the treatment of superficial lesions, then one may reasonably follow subglottic disease by airway symptoms and response of the superficial hemangiomas.

The attributes of the subglottic hemangiomas also need to be considered before selection of treatment. Similar to facial hemangiomas, lesions of the upper airway may be either focal or segmental. This categorization is evident by segmental lesions involving numerous areas of the upper aerodigestive tract found in our patients. Segmental lesions are diffuse and superficial and involve several anatomic sites both along the pharyngolaryngeal mucosa. The lack of uniformity makes management difficult as treatment involves more than one site. If diffuse subglottic lesions are present, then systemic, or local, steroids may assist with temporizing or reducing disease until involution. Laser therapy may cause too much mucosal injury in segmentally distributed lesions. If a focal lesion is present in one anatomic sub-site, primary endoscopic intervention and surgical excision with thyroid ala laryngotracheoplasty are reasonable approaches.

*Propranolol*. Recently, Leaute-Labreze and colleagues (Leaute-Labreze *et al*, 2008; Siegfried *et al*, 2008) reported the serendipitous finding that hemangiomas regress in newborns treated with propranolol (2–3 mg $kg^{-1}$), a known non-selective beta-blocker used in treating infants with cardiac and pulmonary conditions. This finding has been supported by several case reports and a follow-up retrospective review by Sans and colleagues (Leaute-Labreze *et al*, 2008; Buckmiller, 2009; Denoyelle *et al*, 2009; Sans *et al*, 2009). Side-effects of this drug are rare and benign, making it a promising new therapeutic target. At our institution, we have followed over 30 patients with problematic hemangiomas with propranolol (2 mg $kg^{-1}day^{-1}$ TID dosing). Ninety-seven percent of patients have displayed improvement in the quality of their hemangiomas during propranolol therapy (Figure 1, Buckmiller *et al*, 2010). Minor but reportable side-effects have included somnolence (27%) and reflux (10%) in these patients. No serious adverse cardiorespiratory events have been observed. The mechanism of propranolol on reducing or curing hemangiomas remains unclear although the most likely mechanism is the pharmacologic stimulation of programmed endothelial cell death (apoptosis) (Buckmiller, 2009; Sans *et al*, 2009). We remain cautiously optimistic for the universal use of this drug for treating hemangiomas.

## Slow-flow malformations

*Venous malformations*

Venous malformations are slow-flow vascular anomalies composed of ectatic venous channels that will continue to grow throughout the patient's lifetime. The overall incidence of venous malformation is about 1 in 10 000

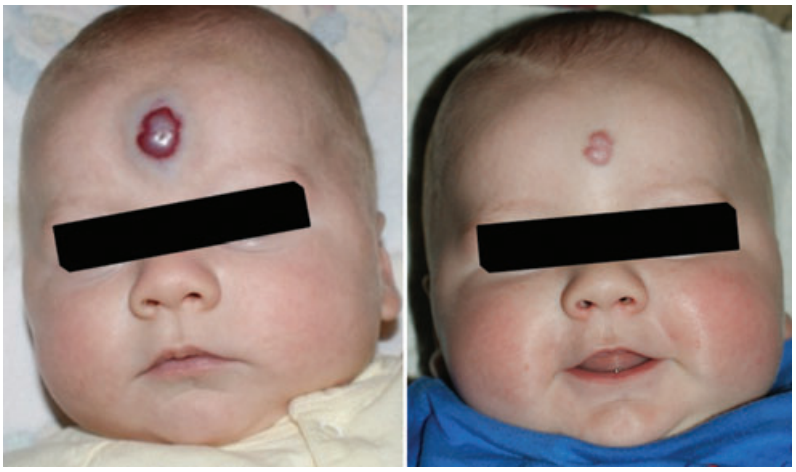

**Figure 1** Proliferative phase hemangioma before and after 3 months on propranolol

(Boon *et al*, 2004). This growth is usually commensurate with the patient's growth with a few distinct exceptions that will be discussed. These lesions commonly occur in the head and neck area with a predilection for the oral cavity, airway, and muscle groups. For the purpose of this article, emphasis in diagnosis and management will be limited to the head and neck region.

*Pathogenesis*. Venous malformations are caused by an error in development within the venous system. The vast majority of the lesions represent sporadic cases, and the etiology of these malformations remains an area of speculation and continuing research (Vikkula *et al*, 2001). Several syndromes can be associated with venous malformations including blue rubber bleb nevus syndrome, glomuvenous malformation (associated with glomulin mutation), and multiple cutaneomucosal venous malformation (mutations in the TIE2 receptor) (Boon *et al*, 2004; Garzon *et al*, 2007). There are also familial cases of venous malformations which are inherited in an autosomal dominant fashion and are linked to a locus on chromosome 9P (Boon *et al*, 1994). Somatic mutations in the angiopoietin receptors (TEK) have been found in a significant percentage of tested solitary and multiple sporadic venous malformations. These mutations lead to loss of function of the TIE2 receptor (Limaye *et al*, 2009). Ongoing research in these areas points to errors in vasculogenesis of which the TIE2 receptor is an important component. Other vascular growth factors such as tissue growth factor beta (TGFbeta) and beta fibroblast growth factor (betaFGF) also appear to be upregulated. This upregulation may represent evidence toward a proliferative component in these lesions as opposed to the accepted hypertrophy growth theory although ongoing research is needed to delineate the exact interactions of these findings (Pavlov *et al*, 2009).

The role of neural components in the development of vascular anomalies has been debated. The presence of increased neural cells has been found in both slow-flow and high-flow malformations. A recent study (Meijer-Jorna *et al*, 2009) found a significant increase in nerve components in venous malformations and more so in AVMs, while lymphatic malformation tissue showed almost a complete absence of neural tissue. Port-wine stains (low-flow capillary malformations) have also been studied and a significant decrease in the neural innervation of these vessels was found (Smoller and Rosen, 1986). Findings such as these suggest that neural elements in each of these lesions plays a role in the development, but the exact nature of that role remains unclear.

The matter by which malformations present at birth continue to grow is unanswered. It has long been accepted that these lesions grew by slow expansion (hypertrophy) rather than by proliferation (hyperplasia). Clinically, it can be difficult to predict how much growth will occur or where, as some lesions appear to expand well beyond their initial clinical boundaries and the patient may even develop multifocal lesions later in life suggesting that proliferation and actual invasion of surrounding tissue may be occurring. Recent findings of increased metalloproteinase-9 in intramuscular venous malformations suggest that invasion and vasculogenesis may indeed be a mechanism of growth beyond that of hypertrophy with increased hydrostatic pressure (Wang *et al*, 2009). Progesterone receptors were also found on venous malformations, which may explain their propensity for rapid growth during hormonal changes (Duyka *et al*, 2009).

*Clinical presentation*. Venous malformations are frequently obvious at birth and will cause a constellation of symptoms depending on the locations involved. The lesions vary in color depending on depth of involvement, from undetectable color differences to deep purple. The lesions fill with dependency and are compressible, which helps to distinguish them from lymphatic malformations on physical examination. Patients may present with complaints of pain and swelling and this is usually related to clot formation either from trauma or venous stasis (Mavrikakis *et al*, 2009). Frequently, patients will have their malformations misdiagnosed as hemangiomas (MacFie and Jeffery, 2008; Bruder *et al*, 2009; Lee *et al*, 2009b). This misdiagnosis not only delays treatment because they are told the lesions will regress, but it can result in inappropriate therapy such as interferon, which can have devastating irreversible side-effects. It is not uncommon for these misdiagnosed patients to seek medical treatment when they experience dramatic lesion growth during puberty or other hormonal changes.

Venous malformations have a propensity to occur in muscle groups but can also involve skin and mucosa. Areas frequently involved in the head and neck are masseter, temporalis, tongue musculature, as well as oral and airway mucosa. MRI remains the diagnostic modality of choice to assess extent and plan treatment for these lesions. The authors believe that early intervention, especially on extensive lesions, can not only help prevent many symptoms but also decrease the management complexity of a much larger malformation should the lesion be allowed to grow unchecked.

*Management*. Multiple treatment options exist for venous malformations, including conservative measures such as head of bed elevation and compression, laser therapy, sclerotherapy, and surgery. Decisions regarding which treatment courses to follow vary widely with various specialties and institutions. Because of the wide variety of management options and patient presentations, it is strongly recommended that patients with vascular malformations undergo treatment at a multidisciplinary center for treating vascular anomalies.

Conservative management of venous malformations is usually reserved for smaller isolated asymptomatic lesions and is also important in controlling the growth and symptoms of larger lesions being treated with other treatment modalities. Elevation of the head of the bed is important to decrease long periods of hydrostatic pressure in the malformation which can lead to expansion. It also can decrease symptoms of airway obstruction, swelling, and pain that are experienced throughout

the night and in the morning. Other helpful measures include warm compresses and ibuprofen for areas of thrombosis.

Laser therapy is a mainstay of management of mucosal and skin malformations. The Nd:YAG laser is the preferred laser at our institution, although the use of the KTP laser has also been described (Kishimoto *et al*, 2008). Patients with cervicofacial involvement will most often have an intraoral or airway component. Airway lesions can be managed with serial laser treatments endoscopically using a flexible fiber delivery system for the Nd:YAG laser. This fiber is attached to a telescope, and then all mucosal surfaces are treated resulting in shrinking of the lesion, thrombosis, and scar formation in the submucosa. These endoscopic treatments are continued every 3–6 months until satisfactory clearance of malformation and symptoms of airway obstruction are resolved. Patients will usually require future treatments when they become symptomatic, and a series of laser treatments can be restarted (Glade *et al*, 2009) (Figure 2). Surface non-contact Nd:YAG laser can be used to treat any intraoral involvement of the venous malformation. Serial laser treatments as often as every 3 months can be used to control the growth and diminish the size of the malformation in the tongue, buccal, palatal, and gingival areas.

Interstitial Nd:YAG can also be used to treat lesions that are deeper than is accessible by surface Nd:YAG laser, which can penetrate up to 7–8 mm. The authors use interstitial Nd:YAG in large tongue lesions with good results. The goal in massive tongue venous malformations is to decrease size to allow further treatment by surface laser only or to allow a more manageable resection if necessary. Care must be taken to avoid the neurovascular pedicle to prevent hypoglossal nerve injury. Ultrasound guidance may be useful to avoid these complications. Interstitial laser treatments are being used in other areas of the head and neck, but data is lacking about the safety of such treatments as control of the destruction instigated by the laser is difficult. Neural injury is thus of utmost concern especially in the areas of the facial nerve and other cranial motor neurons. Along similar reasoning, reports of radiofrequency ablation for treatment of facial venous malformations have also appeared in the literature. This treatment may be an alternative for managing venous malformation especially in more superficial neck lesions; in deeper neck and facial lesions, however, the potential for neural injury must be considered (Kim *et al*, 2009).

Sclerotherapy remains a good option for the treatment of venous malformations in the head and neck. A plethora of literature continues to emerge regarding different techniques and injectable substances (Schumacher *et al*, 2008). Ethanol and sotradecol are the workhorse sclerosants and have a long history of efficacy; however, there is controversy concerning the curative nature of sclerotherapy treatments (Lee *et al*, 2009a; Uehara *et al*, 2009). Multiple treatments are necessary and complications are recognized as common.

Sclerotherapy involves percutaneous injection of a substance to induce inflammation and thrombosis of the lesion which then will lead to more long-term fibrosis and hopefully decrease or eliminate the expansion of the lesion. It is important during injection that the sclerosing substance remain within the lesion and not washout to the main vascular stream to prevent embolic injury or cardiovascular collapse. To minimize washout, sclerosants have been developed to slow outflow from the malformation, such as sotradecol foam or ethibloc (glue), or the sclerosant is mixed with fibrin glue or ethyl cellulose (Schumacher *et al*, 2008; Chen *et al*, 2009). Bleomycin (pingyangmycin) and OK-432 have recently been used as sclerosants in Asia with promising results (Chen *et al*, 2009; Zheng *et al*, 2009).

Potential complications of sclerotherapy include skin and mucosal injury, airway compromise, infection, nerve injury, and cardiovascular collapse. While the more serious of these complications such as cardiovascular collapse and death are rare, problems with skin injury and scarring are more common. It is estimated that skin and soft tissue injury can occur in 12–30% of patients, and about 10% of patients will suffer some type of neuropathy although this is rarely permanent (Fayad *et al*, 2008; Lee *et al*, 2008). Agents such as Polidocanol, a more moderate form of ethanol, have been shown to be effective in smaller malformations with fewer complications than more toxic agents (Mimura *et al*, 2009). Overall, each agent has its own benefit and risk profile; therefore, agents are chosen carefully based on availability, physician comfort with the use of the agent, availability, and malformation being treated.

Surgical excision continues to be a good treatment option and in the authors' opinion remains the best chance for cure of the malformation. Excision of extensive lesions remains a challenge as venous mal-

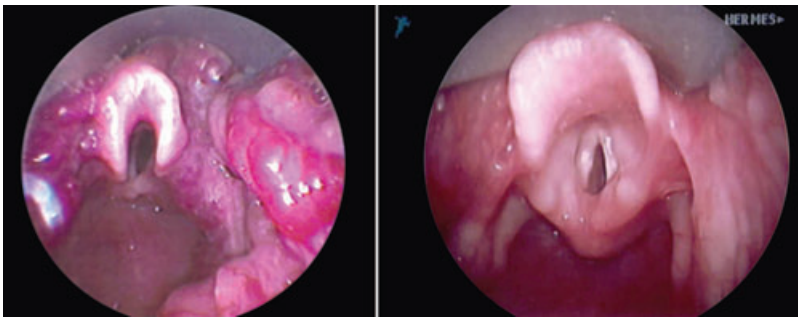


**Figure 2** Airway venous malformation before and after two endoscopic Nd:YAG laser treatments

formations are rarely well-defined lesions and intraoperative bleeding can make identification and preservation of important structures difficult. Preoperative sclerotherapy can be beneficial not only to decrease bleeding, which improves visibility and eases dissection, but also decrease blood loss and operative time (James C, Buckermiller LM, unpublished data). Management of small venous malformations may be controlled by sclerotherapy indefinitely and surgery may be saved for the failure of sclerotherapy in these cases. Large cervicofacial venous malformations present a much greater challenge, and one must be prepared to use multimodal therapy to keep the lesion under control. These lesions generally cannot be cured as doing so would leave devastating functional and cosmetic results. Therefore, therapy is used to control growth, maintain cosmesis, and decrease symptoms. In our experience with larger lesions, especially in patients undergoing hormonal changes, sclerotherapy alone will be inadequate to keep the lesion under control, and surgery is then considered to remove large portions of disease while maintaining function and symmetry (Glade *et al*, 2009).

Overall, venous malformations, although benign lesions, can present a diagnostic and management challenge. A multidisciplinary approach to treating these lesions is strongly recommended as there is no single superior treatment modality.

*Lymphatic malformations*

Lymphatic malformations are congenital collections of ectatic lymph vessels that form endothelial lined cystic spaces. Multiple classification systems have attempted to categorize these lesions, but only one system, the classification by Mulliken and Glowacki (1982), is based on clinicopathologic findings and has prognostic value. The main divisions in classifying these lesions are whether they contain macrocysts (≥2 cm), microcysts (< 2 cm), or both. Macrocystic lesions are more easily treated and carry a better prognosis than its microcystic counterpart.

*Pathogenesis*. The embryologic development of the lymphatic system remains an area of active investigation. As the development is not completely understood, it is difficult to fully understand the causal factors involved in lymphatic malformations (Blei, 2008). Several studies have been published regarding possible lymphangiogenic growth factor involvement in the etiology of lymphatic malformations (Wiegand *et al*, 2008). These factors include VEGF-C, vascular endothelial growth factor receptor 3 (VEGFR-3), and transcription factor Prox-1. VEGF-C and VEGFR-3 have been shown to be upregulated in lymphatic malformation tissue, and both are involved in lymphatic tissue proliferation (Itakura *et al*, 2009; Pavlov *et al*, 2009). In addition, Prox-1 is involved in upregulation of VEGFR-3 in the lymphatic endothelium and may also be involved in the separation of lymphatic vessels from the venous system during development. How these growth factors play a role specifically in the development of a lymphatic malformation is far from clear.

*Clinical presentation*. Lymphatic malformations can present in a wide variety of ways in the head and neck. Lesions can be focal, multifocal, diffuse, macrocystic, or micrcystic. The oral cavity and airway are commonly involved in more diffuse lesions. Lymphatic malformations are frequently diagnosed on prenatal ultrasound and may require special preparations for delivery if the perinatal airway compromise is suspected. Diagnosis is usually made in childhood, and if not obvious from birth, it may become apparent with infections such as upper respiratory infection or otitis media, which can cause swelling of the malformation caused by increased lymph flow. The lesion will typically grow slowly but as mentioned may rapidly swell with infections or with hormonal changes such as puberty. Patients may have complaints of deformity, pain, airway obstruction, odynophagia, dysphagia, speech difficulty, and possibly infection of the malformation itself. There is a subset of patients with lymphatic malformations who are lymphopenic and may present with a history of multiple infections requiring hospitalizations, although it is unclear how this is involved in the pathogenesis of the malformation in these patients (Perkins *et al*, 2007).

On physical examination, the lesions usually feel fluid-filled and are non-compressible, which can help in distinguishing them from venous malformations. Mucosal and skin surfaces can be affected with vesicle formation, which represents small external fluid-filled cysts. Vesicle formation causes problems with bleeding, weeping of lymph fluid, and pain. When examining a patient with lymphatic malformations, it is important to assess the extent of the lesion. In patients with more diffuse lesions, the airway must be examined. These patients can have mandibular overgrowth and dental and occlusal abnormalities, especially when the oral cavity and submentum are involved. Intracranial vascular anomalies have also been found in a significant percentage of patients with orbital lymphatic malformations, and therefore, an MRI/MRA of the brain may be warranted (Bisdorff *et al*, 2007). MRI remains the visualization method of choice for delineating the extent of the malformation, planning intervention, predicting outcome(macrocystic *vs* microcystic), and verifying diagnosis.

*Management*. There are sporadic reports of spontaneous resolution of a small percentage of lymphatic malformations, although this is quite rare. It has been proposed that the lesions that are most likely to resolve are small, macrocystic, and within the posterior triangle of the neck. Reports suggest that they usually resolve before 1 year of age (Perkins *et al*, 2008). In the lesions that fail to resolve, intervention is warranted as the natural history of these lesions is to progress and enlarge.

Sclerotherapy remains the mainstay in many centers when treating patients with lymphatic malformations. The literature is replete with different methods and sclerosing agents, suggesting that there is yet a perfect option to be identified. When reviewing the experience of various centers with different agents, it is important

to look at whether the lesions treated are microcystic or macrocystic, how many treatments are required, and the long-term follow-up results. Macrocystic lesions remain the easiest to treat as well as cure with either sclerotherapy or surgery. Long-term follow-up in many articles is lacking, thus skewing the data toward better outcomes. Lymphatic malformations tend to recur and can do so several years after reporting a cure with sclerotherapy so the literature must be analyzed carefully. A distinction may also be considered between radiographic cure and patient satisfaction with the latter ultimately being the more important (Alomari *et al*, 2006).

Ethanol and sotradecol have traditionally been used to treat lymphatic malformations with good results preferentially in macrocystic lesions. Multiple treatment sessions may be required, and there are sometimes weight-limited dose concerns with these toxic agents in small children. Complications can include skin breakdown, prolonged swelling, pain, and airway compromise. These complications should all be discussed with the family, and the potential for ICU admission mentioned (Ravindranathan *et al*, 2008). Shiels reports a method to improve results by placing an indwelling catheter in the macrocystic areas to provide continuous drainage of lymphatic fluid that may accumulate after the sclerosant is drained. This method attempts to collapse the cyst walls together and promote fibrosis and scarring within the lesion (Shiels *et al*, 2009). Building on this method, the sclerosant may be reintroduced over several consecutive days to induce more inflammation and improve results (Burrows *et al*, 2008).

Other sclerosants have been reported in an attempt to find an effective treatment while maximizing safety. These sclerosants include doxycycline, OK-432, and Bleomycin (Burrows *et al*, 2008; Nehra *et al*, 2008; Bai *et al*, 2009; Poldervaart *et al*, 2009; Smith *et al*, 2009). All agents show varying degree of efficacy dependent on the extent of the macrocystic components in the lesion as well as the proficiency of the sclerotherapist (Acevedo *et al*, 2008). Concerns still remain regarding complications with each treatment. Doxycycline can cause neural damage, OK-432 can be associated with sepsis, shock, myalgia, and Bleomycin still carries a warning of pulmonary fibrosis although this is related to total lifetime dose and the doses received for treatments of lymphatic malformation usually do not approach that level. 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 long-term follow-up data is lacking.

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 $CO_2$ 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 (Glade and Buckmiller, 2009).

Surgery is also an important consideration in the management of these complex lesions. As with sclerotherapy, surgery is more effective in producing a cure when the lesion is focal and macrocystic. Unlike sclerotherapy, microcystic lesions can be treated more effectively with resection with the goal of removing excess tissue thus creating a more normal appearance while preserving function. It is important to note that surgical excision of lymphatic malformations produces an abundance of dense scarring and care must be taken when resecting in areas such as the tongue and airway to prevent dysfunction secondary to scar formation (Figure 3). When operating on lymphatic malformations, it is important to resect all disease when possible as failure will result in regrowth.

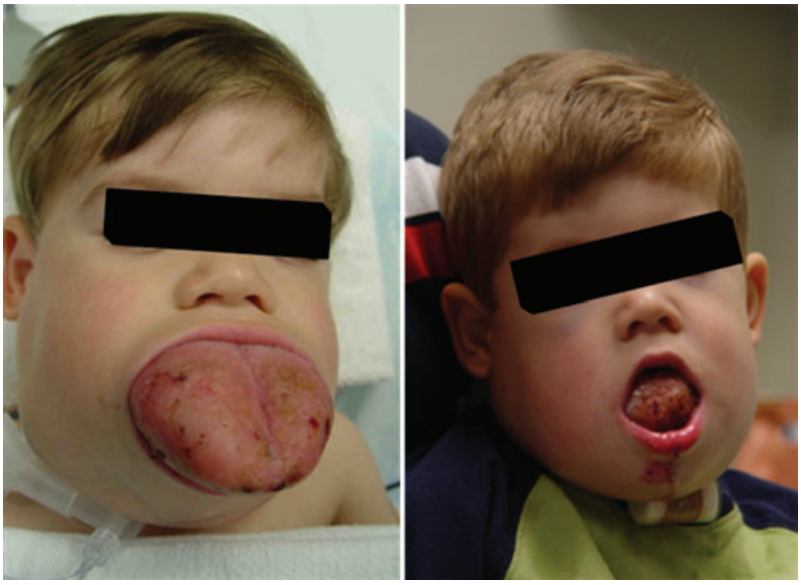

**Figure 3** Lymphatic malformation of the tongue before and after two conservative tongue reductions

Surgery is important not only for removing and hopefully eliminating the malformation but also for correcting the secondary deformities caused by the malformation. Secondary deformities are frequently seen in cervicofacial malformations which cause mandibular overgrowth with open bite deformities and various dental and occlusal problems from tongue enlargement. Careful surgical resection followed by orthodontic and orthognathic treatment is frequently required (Zeng *et al*, 2008).

Overall, complex lymphatic malformations may require many different treatment modalities to maintain good function and cosmesis while attempting to eliminate the disease itself.

## High-flow vascular malformations

*Arteriovenous malformations*

High-flow malformations can be separated into arteriovenous fistulas (AVFs) and AVMs. AVFs are the result of trauma and initially consist of one or several shunts between arteries and veins. AVFs are usually treated with surgery or with intravascular embolization. AVMs are generally felt to be congenital malformations consisting of a 'nidus' of abnormal capillary beds shunting blood from the arterial system directly into the venous system resulting in a high-flow vascular abnormality.

Arteriovenous malformations of the head and neck (extra-cranial) are high-flow lesions and among the most serious of the vascular malformations because they are difficult to diagnosis, treat, and cure. They grow throughout life with frequent, dramatic, and aggressive growth spurts as a result of various environmental influences. AVMs are very destructive, infiltrative, and often life-threatening secondary to massive bleeding. Clinically, extracranial AVMs behave differently from AVMs found in the brain. Most common areas of occurrence are the cheek, lips, neck, scalp, neck, ear, tongue, and mandible (Kohout *et al*, 1998; Seccia *et al*, 1999; Wu *et al*, 2005; Jeong *et al*, 2006). They frequently invade multiple cervical-facial regions as they expand.

*Pathogenesis*. Of all vascular anomalies, the pathogenesis of AVMs remains most unclear. It is unknown whether these lesions are congenital, and in case of congenital AVMs, the errors in vasculogenesis causing them are unknown. AVMs are usually present at birth but may not manifest until several years later. Rapid progression may occur during periods of hormonal fluctuations such as puberty, pregnancy, or hormonal therapy. We have recently demonstrated by immunohistochemistry the presence of progesterone receptors in most AVMs. Interestingly, using the same technique, estrogen receptors were not identified (Duyka *et al*, 2009). Follow-up polymerase chain reaction analysis revealed DNA for both progesterone and estrogen receptors in this tissue. These findings support the role of hormonal influence on the rapid growth of AVMs.

Trauma may also be a causal factor in AVM formation. A large number of reported cases of AVM in the literature did not present until over 40 years of age (Kohout *et al*, 1998; Lee *et al*, 2004; Wu *et al*, 2005; Kim *et al*, 2006), which has been the experience at the authors' institution as well. It is difficult to maintain the hypothesis of a congenital origin in these patients and yet consider the AVM to remain dormant for 40 years before manifesting itself. We have treated three patients with classical AVMs that had a definite history of trauma to a specific site and within a short time had symptoms and signs of a vascular abnormality. Treatment with surgery was undertaken several years after the traumatic event, and both clinically as well as histologically, these abnormalities were consistent with AVM. It is conceivable that these patients may have had subtle or minor trauma which caused an AVF to progress to an AVM (Jeffree and Stoodley, 2009).

Arteriovenous malformations vary in their histopathology and presentation, suggesting a spectrum of disease and not just one disease process (Richter *et al*, 2007). We are hopeful that, with gene array analysis as well as other molecular studies, we will be able to differentiate the different types and be able to differentiate the more aggressive lesions so that aggressive treatment can be instituted. Recent research by our group has shown that most AVMs have large numbers of 'stem cells' (Fan CY, unpublished data). The role that these stem cells play is not yet clear, but we are able to grow them in culture and hope to produce animal models with AVM. These stem cells may differentiate into new vessels, and part of the treatment plan may need to be directed towards these cells and could change the way we treat AVMs in the future.

Our Vascular Anomalies Team has unpublished data showing molecular changes in AVMs that are very similar to malignancies. It is our belief that an AVM is very similar to a malignancy and has the potential for independent growth as a tumor. This thought contradicts the long-standing belief that an AVM is not a tumor. We have discovered that AVMs can have large numbers of stem cells that could be responsible for the creation of new blood vessels. This finding may lead to new treatment options such as chemotherapy or antiangiogenic drugs. Much research is still needed to answer these important questions.

*Clinical presentation*. The diagnosis of AVMs can be made clinically in conjunction with imaging studies. Most AVMs presenting before the age of 20 will have a history that includes the presence of a vascular blush in the overlying skin as a child that then began to expand and bleed. The history shows that the vascular lesion grew more rapidly as the patient entered puberty or had other hormonal changes. Most patients are diagnosed with a 'hemangioma' and are either not treated at all or given inappropriate, ineffective treatments. Patients over the age of 40 will often give a history of recent onset of the lesions not having been noticed previously. They may also give a history of trauma to the involved area prior to noticing it. Bleeding, pain, and tissue destruction are often subsequent signs in AVM growth, and patients suffer significantly when the malformation reaches this stage.

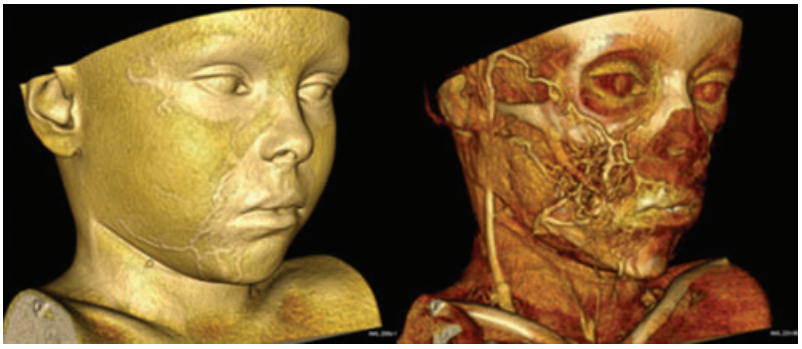

**Figure 4** Computed tomography angiogram demonstrating different layers within the arteriovenous malformation as well as feeding vessels

On physical examination, early AVM lesions may have an overlying vascular blush in the skin similar to an early port-wine stain. The underlying tissue is usually thickened and is not fluctuant or compressible but can be pulsatile. If mucosa is involved, it is usually thickened and vascular. The more advanced lesions may have obviously enlarged vessels in the skin and underneath and pulsation usually present. AVMs can invade the skin where ulcerations and bleeding are common.

Imaging studies are essential for the diagnosis and evaluation of AVMs. Magnetic resonance imaging (MRI) with T2-weighted processing will typically reveal a hyperintense, irregular lesion with numerous flow voids (Wu *et al*, 2005). A magnetic resonance arteriogram (MRA) and a computed tomography arteriogram (CTA) can give excellent images of the AVM (Ziyeh *et al*, 2005). We prefer a CTA because it requires less time, is less expensive, and provides superior imaging capability for surrounding normal tissue and bone as compared with conventional MRA. In addition, digital processing of CTA can provide three-dimensional images of superficial AVM and demonstrate their primary arterial feeders (Figure 4).

*Management*. Over the past 20 years, most published articles regarding AVMs were case reports discussing management (Erdmann *et al*, 1995; Kane *et al*, 1995; Bradley *et al*, 1999; Jackson *et al*, 2005; Wu *et al*, 2005; Jeong *et al*, 2006; Kim *et al*, 2006; Cohen *et al*, 2009). Many of the studies reported using arteriogram and embolization with varying substances, such as, glue, coils, and alcohol. Alcohol is considered the most effective embolic material with some possible cures reported in the literature (Jeong *et al*, 2006). Unfortunately, alcohol can cause significant swelling, potential nerve palsy, and cardiovascular collapse. On surface areas, alcohol can cause significant skin or mucosal ulcerations with sloughing of the tissue. Generally, however, alcohol embolization of AVM is safe in appropriately selected cases.

Onyx (ethylene vinyl alcohol copolymer) has been used successfully for treating the AVMs of the brain for over 10 years (Taki *et al*, 1990; Jahan *et al*, 2001; Mounayer *et al*, 2007; Panagiotopoulos *et al*, 2009). In the past few years, there have been several reports of using Onyx as the embolic material for extracranial AVMs (Arat *et al*, 2007; Cohen *et al*, 2009; Wu and Orbach, 2009). Onyx appears to have the advantage that the vessel occlusion is permanent. We have used Onyx for extracranial AVM in over 10 patients in the past year and have been impressed with the results thus far. Complications have included ulceration of mucosal surfaces, hyperpigmentation of skin, and nodularity of the tissues. Also, Onyx is very expensive and requires increased fluoroscopy time.

Surgical resection after embolization is another common treatment modality (Bradley *et al*, 1999; Seccia *et al*, 1999; Richter *et al*, 2007). This combination is indicated when the AVM is small and appears to be 'focal' and completely resectable. Surgery is also indicated in a very large AVM, which is life-threatening because of bleeding and invasion. In this scenario, embolizations have been attempted and were ineffective. Large AVMs are difficult to resect and this must be performed by experienced surgeons. Microvascular free flaps may be required to reconstruct the defects. Also, these procedures are typically palliative and not curative. It is recommended that after surgery, these patients have follow-up arteriograms and embolizations for any residual AVM. This follow-up may take multiple procedures using either Onyx or alcohol.

Many articles use the word 'cure' after treatment of AVM with embolization techniques or using preoperative embolization followed by surgery. Follow-up after treatment has been short, and if followed for 5 or 10 years, AVM recurrence is common. It has been our experience that some AVMs will show obvious recurrence within weeks or a few months whereas some other recurrences may not manifest for up to 10 years.

## Conclusion

Vascular anomalies represent a wide variety of vessel abnormalities. Their correct classification and diagnosis is imperative to accurately ascertain prognosis and direct treatment. Multimodal therapy is frequently indicated, and in complex patients, a referral to a multidisciplinary vascular anomalies team should be considered.

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