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Maxillofacial Vascular Anomalies in Pediatric Patients: A Review Article

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Abstract:
Vascular anomalies represent a wide spectrum of pathological lesions than may involve blood, lymphatic, capillary, or combined vessels in any part of the human body, with various clinical presentations, different prognoses, and multiple treatment options. Vascular anomalies have been categorized by the classification system of the International Society for the Study of Vascular Anomalies (ISSVA) into two types: vascular neoplasms (hemangiomas), and vascular malformations. Diagnosis and management of vascular anomalies is a challenging, especially given the great concern for children and their parents. Approximately 60 % of them occur in the face, causing functional, esthetic, psychological problems to the child. The interest in the field of vascular anomalies has increased significantly during the last few years, due to the continuous update in knowledge of vascular anomalies. Accurate diagnosis and treatment most of the time involve multiple specialties, owing to the complexity of these lesions. The aim of this review article is to provide a clear understanding of vascular anomalies and their subtypes that can be encountered in clinical practice by oral and maxillofacial surgeons, their clinical aspects, diagnostic tools, and treatment options.

Key Word*: Maxillofacial, Vascular Anomalies, Hemangiomas, Vascular malformations, Pediatric*

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I. History, Terminology, and Classification

Vascular anomalies (VAs) are a group of complex vascular pathological lesions that may involve blood, lymphatic, capillary, or combined vessels of any part of the human body, with various clinical presentations, different prognoses, and multiple treatment options. The term "anomaly" was derived from the Greek word "anomolia", meaning "uneven" or "irregular"; vascular anomalies refer to any possible deviation from the normal vasculature; this deviation may be neoplastic (hemangiomas), or congenital (vascular malformations). For decades, vascular anomalies had been called by words like; "birthmarks", ''strawberry'', ''cherry'', "port-wine stain'', or "angel's kiss." These terms can be traced back to the false belief of maternal impressions; it was believed that the pregnant woman emotions and experiences during pregnancy would cause a permanent birthmark on her child; such as, she had craving for strawberries, watched the slaughter of an animal, or directly contacted animal or human blood. [1]

Vascular anomalies are typically diagnosed in pediatric patients; observed by parents of the infant. Approximately 60 % of vascular anomalies occur in the face. Vascular anomalies in the oro-facial region usually present within the soft tissues; they can increase in size to affect the facial bones, but, they are rarely formed within the bones.[2] Intraosseous vascular anomalies are extremely rare, representing only 0.5 –1%; they occur most commonly in vertebrae, followed by facial bones (mainly within the jaw bone), and less commonly long bones. [3] Intraosseous hemangiomas or vascular malformations within the jaws can cause life-threatening hemorrhage during and after tooth extraction. [4]

Vascular anomalies had been first classified by Mulliken and Glowacki [5] in 1982, based on the endothelial cell biologic characteristics; into hemangiomas (vascular tumors) and vascular malformations.

Hemangiomas or "vascular tumors" are characterized by increased proliferation of vascular endothelium (high endothelial cell turnover), whereas, "vascular malformations" (VAMs) demonstrate congenital dysplasia of vessels, with normal endothelial cells. Vascular tumors include benign tumors, such as, infantile haemangioma, congenital haemangioma, tufted angioma, pyogenic granuloma, border line tumors; kaposi sarcoma and kaposiform hemangio-endothelioma, and malignant tumors; such as, angiosarcoma. Vascular malformations are classified according to the dynamics of the blood flow within their vessels, and the predominant abnormal vessel type into: low-flow lesions, including; venous, lymphatic, capillary, and combined vascular malformations, or high-flow vascular malformations; such as, arterio-venous malformations and arterio-venous fistulas. This early classification was followed by the International Society for the Study of Vascular Anomalies (ISSVA) in their workshop in1996, later; the ISSVA classification was updated in 2018 to include the syndromes associated with vascular anomalies. [6]

The ISSVA classification strictly respects the difference between hemangiomas, as neoplastic lesions, and vascular malformations, as non-neoplastic lesions; this difference is very important for accurate diagnosis, effective treatment and improved outcomes. On the contrary, the World Health Organization (WHO) classification [7] of the vascular lesions in 2013 did not differentiate between hemangiomas and vascular malformations. The term "Hemangioma" was inaccurately used in the WHO classification to describe different vascular malformations; such as, "cavernous hemangiomas" for venous malformations, "lymphangiomas" for lymphatic malformations, "capillary hemangiomas" for capillary malformations, and angiomas for arterio-venous malformations. Therefore, the WHO terminology is actually misleading, and should no longer be used for vascular anomalies. Nowadays, the ISSVA classification is considered the standard classification system accepted worldwide in the field of vascular anomalies; because it is formulated by a large multidisciplinary group of different specialties, and it provides a common scientific language that can be used internationally. [8]

Hemangiomas

Hemangiomas are benign neoplasms of the vascular endothelial cells. Hemangioma is a Greek word composed of "hema" means blood, "angio" means vessel, and"oma" means tumor; meaning blood vessels tumor. Epidemiologically, hemangiomas are the most common pediatric tumor; affecting up to 10% of all infants, [9] and up to 30% of prematurely born infants that have birth body weight < 1500 gram.[10] In addition, hemangiomas have characteristic high female predilection (female-to-male ratio 5:1), more common in Caucasian ethnic group, twins, and with advanced maternal age. [11]

Clinically, they are not visible at birth; they are usually noticed within the first few weeks after birth. Hemangiomas have a characteristic clinical cycle that consists of 3 stages: [1] rapid proliferation phase at 6 – 9 months, [2] plateau (stationary) phase at 10 – 12 months, and [3] spontaneous involution phase after the first year of age until partial or complete resolution at 5 – 10 years of life, commonly with fibro-fatty scar. Histologically, in the proliferation phase, hemangiomas are characterized by rapidly proliferating endothelial cells lining the inner surface of blood vessels, with high turn-over rate. Later, in the involution phase, hemangiomas show thinning of the vascular endothelial lining and progressive deposition of fibro-fatty tissue (**Fig. 1**). [12]

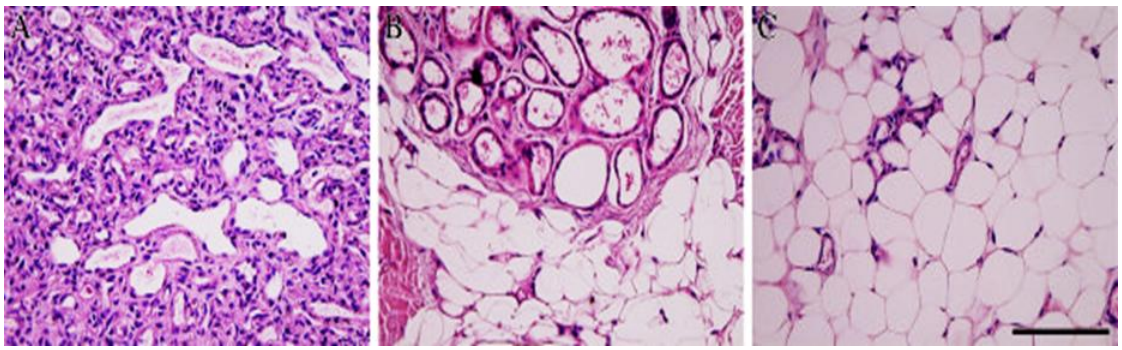

Fig. 1: Phases of Infantile Hemangioma: (A) proliferating phase: densely packed tumor endothelial cells, (B) involuting phase: disorganized vasculature, (C): involuted phase: tumor replaced by fat and/or connective tissues

From: Ji et al. Signaling pathways in the development of infantile hemangioma. 2014

About 60% of hemangiomas present in the head and neck region, specifically along the distribution of Trigeminal nerve, but they also occur in any part of the human body. During the proliferation phase, hemangiomas may bleed, ulcerate, or develop secondary infection. Furthermore, facial hemangiomas may affect

important functions of vital organs; such as, vision, hearing, respiration, speech, or feeding and growth of the infant\child. Large facial hemangiomas > 5cm may be a part of PHACES syndrome; it is an acronym for posterior cranial fossa malformations, hemangioma of cervico-facial region, arterial (Aortic arch) anomalies, cardiac anomalies, eye anomalies, and sternal clefting. Sometimes hemangiomas occur in visceral organs in the human body; most commonly in the liver, but may also affect spleen, lungs, heart, thyroid gland, kidneys, or urinary bladder. Infants who have 3 or more cutaneous hemangiomas are at high risk of having visceral hemangiomas; and should be investigated for liver hemangiomas with abdominal ultrasound. Multiple hemangiomas are more frequently encountered in preterm infants. Hemangiomas include infantile haemangiomas (IHs), congenital haemangiomas (CH), tufted angiomas (TAs), and kaposiform hemangio-endothelioma (KH). Infantile hemangioma is the most common type of all hemangiomas. Hemangiomas can be [1] superficial (cutaneous) present on the skin; commonly called strawberry birth marks, because of their characteristic bright red appearance, [2] deep (subcutaneous) present under the skin; making it bulge, or [3] combined (mixed), present on the skin and grow deeply. [13]

Hemangiomas are diagnosed mainly by their typical history and clinical appearance; imaging is rarely required. Ultrasonography (USG) is usually required in some cases to investigate presence of an arterial feeding vessel. Also, abdominal USG should be done in case of multiple hemangiomas, when presence of visceral hemangioma(s) is suspected. [14]

Historically, the management of hemangiomas was to "wait and see", for spontaneous involution in the second 6 months of the first year of the child life, or to do surgical excision. However, commonly the slow involution stage does not result in complete disappearance of hemangiomas; and the child is be left with residual fibro-fatty tissue; compromising child esthetics. Furthermore, about 25% of haemangiomas exhibit rapid growth rate, attaining very large size; become alarming to the parents, especially as their child approach school age, with potential risk of hemorrhage, ulceration, secondary infection, tissue necrosis and\or permanent disfigurement. In addition, rapidly growing hemangiomas can involve adjacent anatomical structures, affecting important functions; such as, occular region affecting vision, auditory canal affecting hearing, in the oral region affecting swallowing, feeding, and\or airway and breathing, which require immediate intervention. Therefore, treatment is essential during the proliferation phase of hemangiomas. Surgical excision of hemangiomas in the face is no longer recommended, as it usually results in scarring and facial disfigurement; affecting the child esthetics and psychology. [15]

Systemic and intralesional corticosteroids are both. Many side effects had been reported with systemic corticosteroid therapy in infants and children; such as, adrenal suppression, development of Cushing features, growth retardation, hypertension, and increased susceptibility to local and systemic infection. [16]

Intralesional corticosteroid injections are effective at reducing the size of proliferating hemangiomas, and have less adverse systemic effects compared to systemic corticosteroids. Intralesional corticosteroid injections are given with doses of 0.5-2 mg/kg, for up to 6 sessions, at 4 weeks interval. However, intralesional corticosteroid therapy is not the best treatment option for hemangiomas in the face, because of soft tissue and bone degeneration, local infection, ulceration and scarring at the site of injection, with subsequent esthetic and functional deformities. [17] Furthermore, more dangerous local complications have been reported; such as, central retinal artery occlusion and impairment of vision following periocular and forehead intralesional injections of corticosteroids. In addition to local complications, Cushing features have been reported in many cases. [18, 19]

After the effect of propranolol beta-blockers on hemangiomas has been first discovered in 2008 by the dermatologist Léauté-Labrèze, in 2014, the United States Food and Drug Administration (FDA) approved oral propranolol to be used for treatment of proliferating hemangiomas in children.[20]

Clinically, propranolol results in more rapid treatment response than both systemic and intralesional corticosteroids. In addition, oral propranolol does not cause the common complications of corticosteroids in pediatric patients; such as, adrenal suppression, growth retardation, Cushing features, and increased liability to systemic and local infections. [21] Today, oral propranolol is the first line choice for rapid treatment of the proliferating hemangiomas. Oral propranolol (Inderal 10 mg tablets) is given in a dose of 1-3 mg/kg/day. The treatment course lasts for minimum duration of 6 months for achieving satisfactory results.[22]

Vascular Malformations

Vascular malformations are congenital birth defects, which are formed during intra-uterine life at the 4th - 10th embryonic weeks. Hence, they have been also called congenital vascular malformations (CVMs). They are characterized by localized morphogenic defects in the walls of arteries, veins, capillaries, lymphatics, or combined vessels. They are formed due to abnormal vasculogenesis of angioblasts of mesenchymal origin that differentiate into endothelial cells, which then, differentiate into four types of vessels; arterial, venous, capillary, and lymphatic vessels. After birth, further growth of these abnormally formed vessels of vascular malformations occurs through angiogenesis process. Most vascular malformations are sporadic, usually presenting as a single lesion in the child, however, some of them are inherited (familial), presenting as multiple lesions associated with a syndrome. [23]

Histologically, unlike hemangiomas (**Fig. 3**) [24], vascular malformations are large dilated tortuous vessels, lined by one layer of endothelial cells (**Fig. 4**) [25] that have normal turn-over rate. [26]

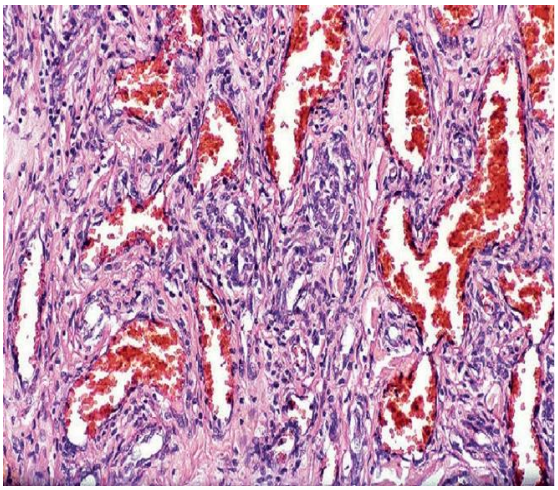

Fig. 2: Infantile Hemangioma proliferating endothelial cells lining normal blood vessels From: Rapini RP. Vascular Proliferations and Neoplasm.2012 [24]

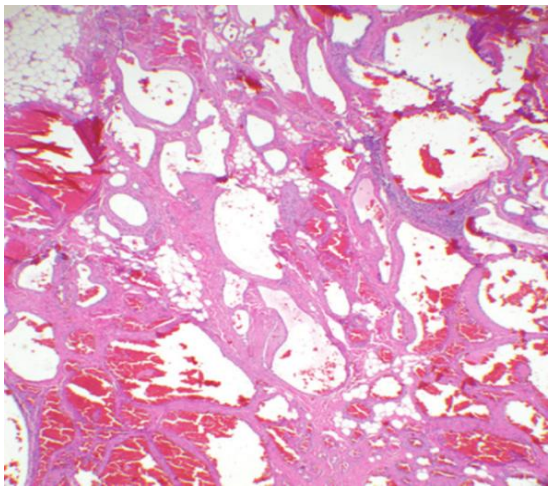

Fig. 3: Vascular Malformation malformed dilated vessels, lined by normal endothelial cells From: North PE. Histology of Vascular Malformations.2015 [25]

While hemangiomas are diagnosed mainly by their typical history and clinical presentation; usually without imaging, vascular malformations are diagnosed mainly by Ultrasonography (USG) and Magnetic Resonance Imaging (MRI), which are both are non-ionizing and non-invasive imaging techniques, particularly important for the safety of pediatric patients. [27]

Computed Tomography (CT) should be avoided in infants and children because they are more sensitive to the harmful ionizing radiation than adults, increasing the risk of cancers; including leukemia, thyroid cancer, skin, and brain cancers. However, CT may be indicated in some cases of intra-osseous vascular malformations. [28]

USG is a primary low-cost diagnostic tool, used to evaluate the blood flow dynamics; differentiating the high-flow from the low-flow vascular malformations. Also, it is used to guide sclerotherapy of deep vascular malformations, and during the follow-up stage to monitor the vascular lesions response to treatment. It can be easily done without sedation, which is commonly required for MRI, particularly for pediatric patients. However, USG has limited ability in showing the detailed anatomic extension of deeply located vascular malformations, and intra-osseous vascular malformations. MRI is commonly used for vascular malformations; it is superior to CT in demonstrating the relationship between the vascular lesion and its surrounding normal soft tissues; MRI images define the exact lesion size, extension into the adjacent important anatomical structures. [29]

Venous Malformations

Venous Malformations (VMs) have been previously termed "Cavernous Hemangiomas" by the WHO classification; despite they are not true vascular tumors. The correct medical term is venous malformations, according to the ISSVA classification. VMs are congenital vascular malformations; always present at birth, grow proportionally with the child growth rate, and they never involute spontaneously without treatment like hemangiomas. Histologically, they are formed of abnormal dilated tortuous vein-like channels, lined by endothelial cells with normal endothelial cells turn-over. These abnormal dilated veins are not closely packed

and the spaces between them "caverns" are filled with blood; hence the name "cavernous hemangiomas" has been used to describe venous malformations (**Fig. 4-A & B**). [30, 31]

Venous malformations are the most common type of vascular malformations; comprising up to 70% of all vascular malformations, with an incidence of 2 in 10,000 live births. About 40 % of VMs present in the head and neck region, 40% in the extremities, and 20% in the trunk. Clinically, they present as soft compressible swellings, their boundaries are usually not clearly defined, with a pathognomonic dark bluish\purple color of the overlying skin\mucosa, caused by the presence of venous channels. Unlike AVMs, they are non-pulsating; and not warmer than the non-affected areas. A characteristic clinical feature of VMs is their sensitivity to compression; they can be emptied or reduced in size and blanches by finger pressure. Also, these lesions become obviously enlarged in size; congested with venous blood, and their color darkens, during infant\child physical activity, crying, and with dependency (lowering the head). Spontaneous hemorrhage of these lesions is rare, but, they commonly show severe hemorrhage with minor trauma. In addition, they usually increase in size secondary to trauma, surgery, and\or hormonal changes during puberty. [32]

Without treatment, VMs will continue to increase in size throughout life; causing ischemia of the adjacent tissues due to the continuous uptake of blood inside the lesions, in addition to the esthetic and functional complications. Facial VMs commonly increase in size, causing facial disfigurement, functional, psychological and social problems in children. Furthermore, they may infiltrate adjacent tissues or pressure on vital organs; threatening important functions like vision. When VMs occur within the oral cavity, involving lips, cheek, tongue, floor of the mouth, para-pharyngeal space, or hard and\or soft palate, they can affect mouth opening, tongue movement, speech, or swallowing, feeding, nutrition, and subsequently the infant\child growth. In addition, the oral hygiene of the child gingiva and teeth is affected, because of the severe bleeding that occurs during teeth brushing and dental treatment. More seriously, they may affect breathing and cause life-threatening airway obstruction. [33]

Venous malformations that are combined with other low flow vascular malformations are usually a part of a syndrome called Klippel-Trenaunay syndrome (KTS). According to the updated ISSVA classification, KTS is a rare congenital disease of combined low-flow vascular malformation; characterized by classical triad of venous malformation and varicose veins, capillary malformation and\or lymphatic malformation, and unilateral lower limb (bone and soft tissue) overgrowth. Symptoms of KTS include poor wound healing, ulceration, paraesthesia, bleeding, deep vein thrombosis and pulmonary embolism. [34]

There are different treatment options of VMs; such as, sclerotherapy, Laser, sirolimus, or combination therapy for complicated cases. Historically, classical surgical excision had been the main treatment line; nowadays, it is not a recommended, and sclerotherapy had become the first line treatment for venous malformation; because of the high risk of life-threatening intra-operative hemorrhage. [35] This is caused by stagnation of the blood flow within VMs, which results in a continuous cycle of spontaneous intralesional thrombosis and thrombolysis; eventually resulting in consumption of platelets and coagulation factors; particularly fibrinogen (factor I); and subsequent disturbance of blood coagulation. [36]

Lymphatic Malformations

Lymphatic Malformations (LMs) have been termed **"**Lymphangiomas" by the WHO classification, despite the absence of the significant endothelial cells activity found in Hemangiomas. The term "Lymphangioma" was used, because it has been assumed that these lesions arise from an embryologic abnormal connection from the jugular sacs to the lymphatic system. Many authors still commonly refer to the cervical LMs as "Cystic Hygroma"; this term literally means a water tumor, the Greek word "hygro-" meaning fluid and "oma" meaning tumor; the term refers to the cystic nature of these lesions and the lymphatic fluid within these cysts. Scientifically, both terms "Lymphangioma" and Cystic Hygromas" are incorrect, because lymphatic malformations are not true neoplasms; there is no proliferation of endothelial cells lining lymphatic vessels, and they never regress spontaneously like hemangiomas. [37] In addition, although they are cystic lesions, their cysts are not always filled with lymphatic fluid. Currently, the correct medical term used, is lymphatic malformations, according to the ISSVA classification of vascular anomalies, as they are congenital low-flow vascular malformations, formed predominantly of abnormal lymphatic vessels. LMs are sub-classified into macrocystic (cysts > $2cm^3$), microcystic (cysts < 2 cm^3), and mixed. Macrocystic LMs were historically called "cystic hygromas", whereas, microcystic LMs were called "lymphangiomas". Macrocystic LMs usually present at birth, whereas microcystic and mixed LMs present later in life. Their cysts may be filled with lymphatic fluid and\or blood, or empty. LMs often increase in size, due to distention by the lymphatic fluid, caused by systemic or local infection; which results in sudden growth of the lesion that may compromise the airway. Also, they may contain malformed veins that bleed easily; and cysts become filled with blood.[38] Histologically, they are composed of abnormally dilated thin-walled lymphatic vessels, lined by normal endothelial cells (**Fig. 5 - A & B**). [39, 40]

Clinically, they appear as painless disfiguring swelling, with no pulsation, and covered by normal skin\mucosa. They are always present since birth and they usually increase in size and fluctuate during systemic\

local infections. Haemorrhage may occur within the cyst(s) of the lesion, which becomes bluish in color, and clinically similar to the bluish color of VM. About 60% of cases present at birth and about 90% are diagnosed by the age of 2 years. Sometimes, they are accidentally diagnosed during routine prenatal US examination, as they typically form between the 9^{th} and 16^{th} embryonic weeks of pregnancy. LMs usually present in the regions of lymph nodes; approximately 75 % occur in the head and neck (cervico-facial) region, followed by 20% in the axilla, and less commonly in the extremities. Oral LMs commonly occur in the anterior two-thirds of the tongue, associated with macroglossia, causing functional problems in feeding, speech, and oral hygiene in infants \ children.[41] Cervico-facial LMs are the most dangerous lesions, because they can compromise the airway and become life-threatening. Therefore, early diagnosis and intervention are very important to save the infant\child life. [42]

Treatment options include sclerotherapy, laser, sirolimus, surgery, or combination for complex cases. Complete surgical excision is clinically challenging and not recommended as a treatment option, because of their very thin wall of endothelium that can be easily torn during enucleation, leading to high recurrence rate. Also, the infiltrative nature of most lesions makes complete surgical excision involve surrounding important anatomical structures, leading to significant esthetic and functional complications, particularly in the head and neck region. Currently, sclerotherapy is the main line of treatment for LMs.[43] Carbon Dioxide Laser has shown satisfactory results in recent studies in treatment of microcystic LMs. [44] Sirolimus medication is an emerging treatment for extensive LMs that cannot be treated by sclerotherapy. [45]

Capillary Malformations

Capillary Malformations (CMs) had been commonly referred to as Port- Wine Stains (PWS), Salmon patch, or "angel's kiss". They have been considered hemangiomas in the WHO classification. Nowadays, they are classified by the ISSVA as low-flow vascular malformations, because they show normal rates of endothelial cell turnover, they are always evident at birth, and they never spontaneously involute. Histologically, CMs are formed of increased number of abnormally dilated capillaries, in the superficial dermis layer of the skin, containing large amount of blood and giving the characteristic pink to red appearance of the skin. (**Fig. 6 - A & B**). [46, 47] Clinically, they blanch upon pressure, and they vary in size from small to very large. Without treatment, they remain present for life, with no tendency toward involution. As the child grows, dermal capillary vessels become dilated and filled with erythrocytes; and their color changes from pink to red to purple. Their characteristic color and being superficial in the skin have led to their common name port-wine stain or salmon patch. They are less common than VMs and LMs. They occur in the head and neck region, commonly along the trigeminal nerve distribution, particularly, the ophthalmic and the maxillary nerves. Infants born with facial PWSs are at risk of having Sturge-Weber syndrome (SWS), a rare congenital neuro-cutaneous disorder consisting of: facial PWS, glaucoma, and lepto-meningeal angiomas (vascular malformation in the pia mater); causing brain ischemia, seizures and intellectual disabilities. Diagnosis of CMs is mainly made clinically; and imaging is not required. Treatment of CMs is mainly by laser, because they are too superficial. Different laser types have been used, and treatment options have improved significantly during the last few years. Currently, pulsed dye laser is considered the gold standard treatment for facial CMs; it has shown excellent results, especially if treatment is started as early as possible in life.[48] Recently, topical sirolimus was tried with laser, with satisfactory results in many case reports. [49]

Arterio-venous Malformations

Arterio-venous malformations (AVMs) have been inaccurately termed angiomas or arterio-venous hemangiomas in the WHO classification. According to the ISSVA classification, they are now classified as high-flow vascular malformations; because they have normal endothelial cell turnover, they are evident at birth; which means they are formed during embryogenic development, and they never involute spontaneously. Histologically, the AVMs is composed of a nidus (network) of abnormally formed vessels, with direct connection between artery(ies) and a vein, without capillaries in between (**Fig. 8- A & B**).[50, 51]

Normally, the vascular system consists of arteries, veins, and capillaries in between. The arteries carry oxygenated blood from the heart to different body tissues; then, arteries divide many times, and ultimately they connect to the capillaries, which connect the branches of arteries to the branches of veins. Capillaries are small microscopic blood vessels, where oxygen in the blood is given to the tissues, and the waste products are taken from body tissues into the blood back to the heart. The arteries have thick walls; created to carry high pressure blood from the heart to the tissues; this high pressure is necessary pump blood through the arteries to the tissues, thereby maintaining systemic tissue perfusion. On the other hand, veins have thin walls; created to carry back the low pressure blood from body tissues to the heart. Therefore, arteries and veins are very different in structure, and they should not be in direct communication. In AVMs, the arteries and veins are directly connected and the high pressure blood goes from the arteries directly into the veins. Veins within the AVM have thin walls and are under high systolic blood pressure; thus they can rupture at any time; causing significant bleeding. Over time, the AVM grows larger in size and its blood flow extensively increases, reducing blood

flow to the surrounding tissues, which can result in tissue necrosis, esthetic and functional impairment. Moreover, AVMs may be associated with congestive heart failure, due to the increased cardiac load, caused by the continuous high blood flow into the lesion. Clinically, AVMs present as red firm warm swellings, pulsating on palpation, with bruit or thrill (abnormal audible vascular sound associated with blood flow in the artery; which can be heard on auscultation with stethoscope), and due to its high vascular blood flow. Unlike venous malformations, AVMs do not empty completely on compression, and refill quickly on relieving the digital pressure. They often affect head and neck region, most commonly affecting the brain, the mid-face or the oral cavity; followed by the lungs, and the extremities. Intraosseous AVMs of the mandible are rare and often diagnosed when extensive bleeding occurs during extraction of teeth. Pediatric AVMs of the central nervous system usually present with seizures and\or headache. AVMs occurrence rate is about 14% among all patients with vascular malformations, but their true prevalence in the pediatric population is still unknown, because they rarely have clinical manifestations in children. However, AVMs have a higher rate of rupture in children than in adults; the severe hemorrhage is usually the first sign that the child has a high flow vascular malformation. Multiple AVMs are associated with Osler-Weber-Rendu syndrome, or hereditary hemorrhagic telangiectasia (HHT), a rare genetic disease, characterized by spontaneous recurrent epistaxis usually at age 10 years, muco-cutaneous telangiectasia (small AVMs) on the lips, buccal mucosa, tongue and fingers, visceral AVMs in lung, liver, or brain, and iron deficiency anemia. Among all types of vascular malformations, AVMs are considered the most aggressive lesions and the most difficult to treat, due to the complexity and high cost of treatment procedures, the high recurrence rate. [52, 53]

AVMs can be treated by endovascular embolization with\without surgery within 48 hours, endovascular laser therapy, gamma knife radiotherapy, or sirolimus medication. Embolization is the most common treatment of AVMs; numerous embolic agents have been used with varying efficiency, such as polyvinyl alcohol (PVA) particles, acrylic glue, Onyx®, metal coils; or combination of embolic agents, which are delivered into the AVM nidus through a catheter inserted through a blood vessel. These materials block blood flow to the lesion. Embolization is done through the artery or the vein connected to the AVM. When the feeding vessel is blocked, the blood flow to the AVM is reduced, which results in reduction of the lesion size. AVMs of the mandible in children can be treated by curettage and immediate replantation of involved bone to avoid morbidity of the conventional treatment (embolization, involved bone resection and reconstruction). [54]

Sclerotherapy with ethanol or other sclerosing agents alone may reduce the size and symptoms of AVMs; but it cannot make the AVMs disappear like venous and lymphatic malformations. In addition, AVMs that undergo incomplete surgical removal are commonly at high risk of recurrence and progression. Therefore, some AVMs are managed only by clinical observation and follow up; and the treatment is delayed until complications occur. This is because sometimes any therapeutic intervention may be more dangerous than leaving the AVM without treatment, particularly if the AVM is very large in size or present in a dangerous or inaccessible site. [55]

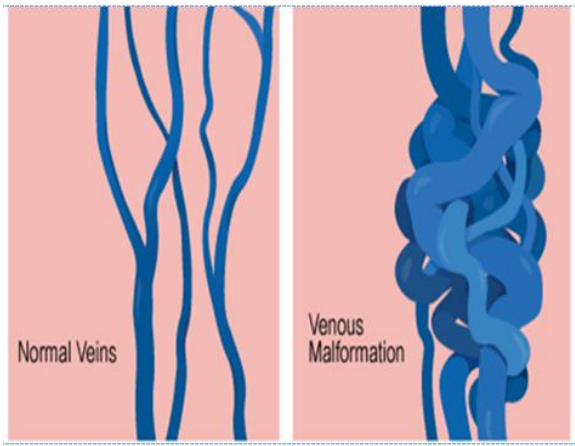

Fig. 4-A: Venous Malformation (VM)
From: https://kidshealth.org [30]

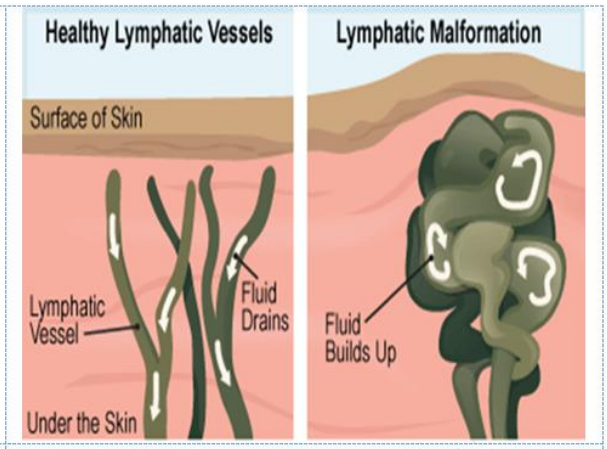

Fig. 5 – B: Lymphatic Malformation (LM)
From: https://kidshealth.org [39]

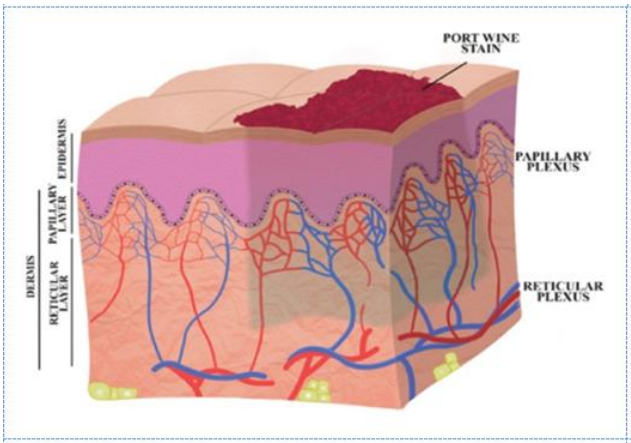

Fig. 6-A: Capillary Malformation (CM)
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From: Van Raath MI. Site-specific pharmaco-laser therapy [46]

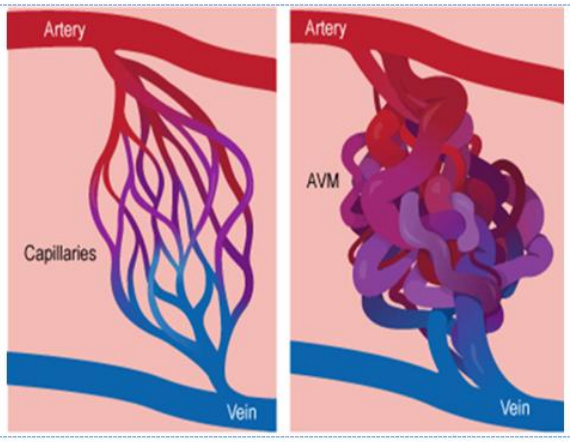

Fig. 7-A: Arterio-Venous Malformation (AVM)
From: https://kidshealth.org [50]

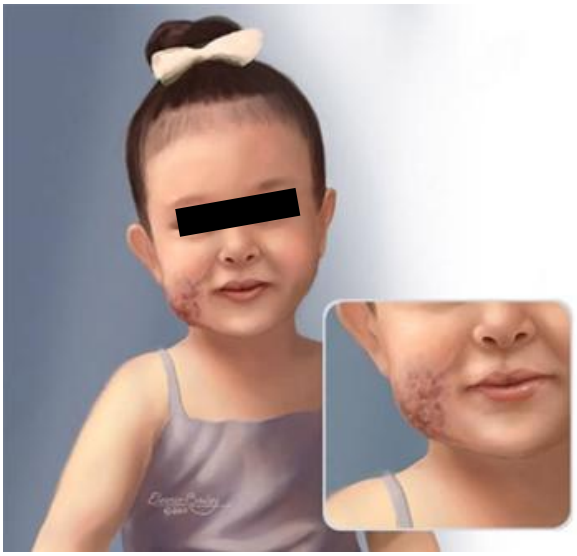

Fig. 4 – B: Venous Malformation (VM)
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From: https://www.hopkinsmedicine.org [31]

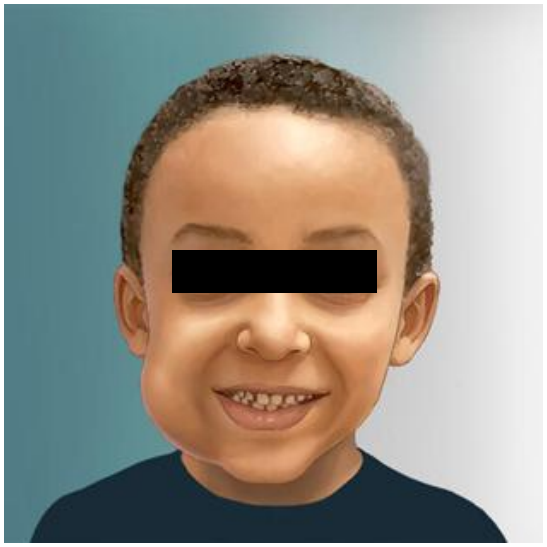

Fig. 5 – B: Lymphatic Malformation (LM)
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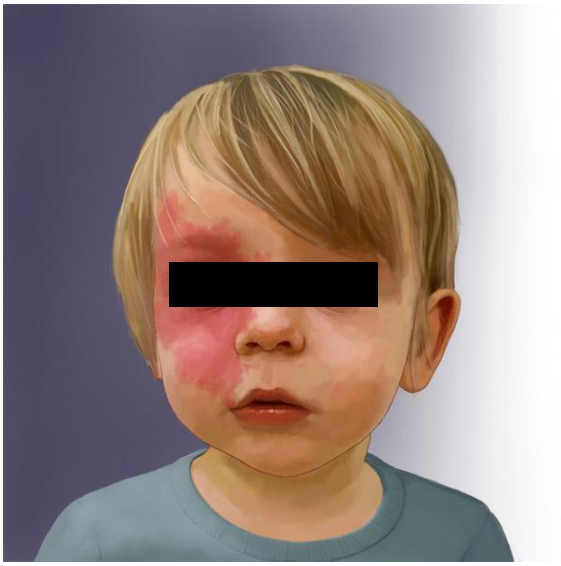

Fig. 6 – B: Capillary Malformations (CM)
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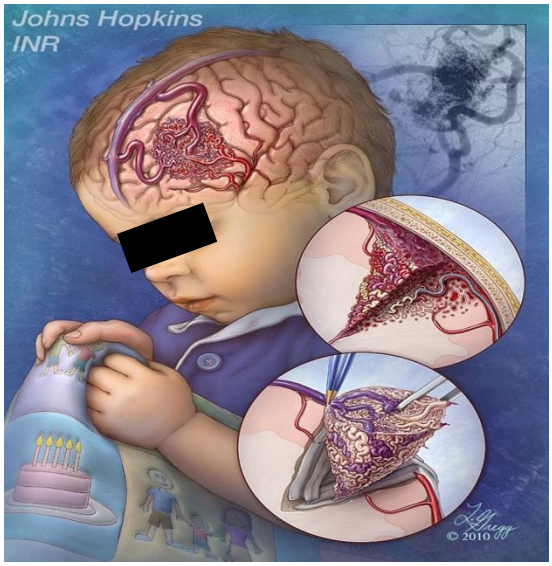

Fig. 7 – B: Arterio-Venous Malformation (AVM)
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From:
https://www.sciencedirect.com/science/article/abs/pii/S1546084311001131 [50]

Complications of Vascular Malformations: [56]

- Life Threatening hemorrhage (with minor trauma – after tooth extraction) \ infection \ aspiration pneumonia \ airway obstruction
- Function Impairment: involvement of vital organs; such as, orbit (vision), tongue – nasal cavity – palate (speech\snoring\ obstructive sleep apnea) – para-pharyngeal space (feeding\swallowing\breathing), or facial nerve (muscles of facial expression)
- Esthetic Problems: facial disfigurement
- Oral Hygiene Impairment: hemorrhage during teeth brushing \ dental anaesthesia \ dental treatment
- Psychological & Social Problems: facial disfigurement

Treatment options of vascular malformations include surgery, laser therapy, sirolimus, sclerotherapy, or combination for large or complex cases. [57, 58]

Unfortunately, vascular malformations are frequently confused with hemangiomas. Inappropriate diagnosis leads to subjecting many infants\children to the medical complications of propranolol and corticosteroids, as well as, delaying the appropriate therapy. Vascular malformations do not respond to systemic and intralesional corticosteroids, which have been used to treat hemangiomas, because the mechanism of action of corticosteroids depends on inhibition of Vascular Endothelial Growth factor (VEGF) expression. [59] In addition, vascular malformations do not respond to β-blockers (oral propranolol), which is the main treatment of hemangiomas, because the mechanism of action of propranolol relies on blocking Vascular Endothelial Growth factor (VEGF) and basic fibroblast growth factor (bFGF), the key regulators for angiogenesis; thus, inhibiting the proliferation of vascular endothelial cells of hemangiomas and reducing the size and color of hemangiomas.[60] The serum levels of VEGF and bFGF are significantly higher in hemangiomas than vascular malformations; this explains the positive response of hemangiomas to propranolol and corticosteroids compared to vascular malformations.[61]

Surgery

For many years, surgical excision for small localized lesions and surgical de-bulking for large diffuse lesions had been the classic treatment of vascular malformations. Nowadays, this is not recommended as it carries the potential risk of injuring adjacent important anatomical structures; causing esthetic and functional complications, particularly in the head and neck region, because: [62]

- Vascular anomalies involving important vital anatomical structures (facial nerve, muscles, bones, or vital organs) that should be preserved for facial esthetics and function, making total surgical excision difficult or impossible, or may result in significant complications, as scarring, severe facial disfigurement, nerve injury, and\or loss of function.[63]

- Intra-operative life-threatening hemorrhage that may exceed 1500 ml of blood, particularly with VMs and AVMs, caused by excessive consumption of platelets and coagulation factors; resulting in disturbed blood coagulation. [36, 64, 65]
- Incomplete surgical excision of lymphatic malformations, because of their very thin walls, which is usually torn during enucleation, in addition to the infiltrative nature of most vascular malformations, which results in high recurrence rate after surgery. [66]
- Surgery most of the time aggravates some vascular malformations, causing recurrence of the lesion with a larger size. Surgical intervention stimulates angiogenic growth factors; such as, vascular endothelial growth factor (VEGFs), fibroblast growth factors (FGFs), angiopoietin-1 (ANGPT-1) and angiopoietin 2 (ANGPT-2), which have been reported as the most important regulators for angiogenesis. [67]

The complications of surgery had been the driving force to search for new treatment options for these lesions; such as, sclerotherapy, laser, and sirolimus medication, which are less invasive, have less severe complications, and have shown better results than surgery.

Laser Therapy

Laser therapy of vascular anomalies has begun in the 1980s; then, different types of lasers, with different wave-lengths, have been used for treatment of hemangiomas and vascular malformation; such as, Diode, Neodinium YAG (Nd YAG), carbon dioxide (CO_2), and pulsed dye laser (PDL). Laser is the first line treatment modality for capillary malformations, but for venous and lymphatic malformations, it is considered a second line treatment option and may be used to treat discoloration or scarring after sclerotherapy.[68] Over the last 10 years, PDL has been considered the best therapy for PWSs. [69, 70] Laser energy is selectively absorbed by different chromphores of the target tissue that absorbs most of the laser energy; such as, Melanin, Hemoglobin (Hb), Hydroxy-apatite (HA), and water. For vascular anomalies, the main chromophore that absorbs laser photons is the Hb in RBCs within blood vessels in the vascular lesion; causing photo-thermal coagulation, destruction of vessels, and reduction of the vascular lesion size. However, photo-thermal coagulation of Hb occurs at 60-70°C, which may cause thermal damage and scarring of the facial skin. Also, this high temperature of photo-thermal coagulation is painful and dangerous in the moving infant\child; which usually requires GA in pediatric patients. Another important point is the limited penetration depth by laser for deep vascular lesions; this usually necessitates multiple sessions of laser therapy, usually at 3 -4 weeks interval. In addition, Laser safety is of great importance; the eyes are the most vulnerable organ to laser damage, especially that most vascular anomalies are present in the face. Unfortunately, safety eye goggles with suitable size for pediatric patients are not usually available in many laser companies. Hence, dangerous complications in pediatric patients related to laser safety, unpredictable effects on the growing bones and soft tissues, insufficient research for the different types of lasers, and the high cost of laser equipment limit the clinical use of laser for vascular anomalies in children. [71]

Sirolimus

Sirolimus (SRL) is fermentation product of *Streptomyces hygroscopicus*. It was initially known as Rapamycin; as this compound was isolated from soil sample in Easter Island that was known by its native name as Rapa Nui. It has immuno-suppressive effect; and it had been used to prevent organ transplant rejection and to coat coronary stents. In 1999, sirolimus was FDA approved to be used as an immuno-suppressive drug after kidney transplantation. Recently, it was introduced as a new therapeutic option of vascular anomalies that do not respond to other treatment modalities. [72] Regarding the mechanism of action of sirolimus, it inhibits the mammalian target of Rapamycin (mTOR); which is responsible for angiogenesis, cell proliferation, and progression of vascular anomalies. Recently, several case reports have been published of sirolimus as a new medical treatment for complicated vascular anomalies; such as, kaposiform hemangio-endotheliomas, Klippel-Trenaunay syndrome, and extensive infiltrative lymphatic, venous and veno-lymphatic malformations that do not respond to conventional treatments, and sirolimus has shown significant improvement in symptoms of these lesions. Sirolimus is administered with oral dose of 0.8 mg/kg twice daily or 2 mg/kg once daily. [73] However, the clinical use of sirolimus is not the standard treatment modality of vascular malformations. Safety of sirolimus is a major concern, due to the adverse side effects related to its immuno-suppressive properties: neutropenia, increased risk of infection, impairment of wound healing, fever, nausea, diarrhea, toxicity, and infection-related deaths. In addition, recurrence commonly happens when sirolimus medication is discontinued as was reported in many cases. Therefore, long-term studies are needed to evaluate the safety of sirolimus in pediatric patients. [74]

Sclerotherapy

The Greek word "skleros" or sclerosis means hard and "therapy" refers to treatment. Sclerotherapy is defined as targeted elimination of small vessels of varicose veins and vascular anomalies; by the injection of a

liquid sclerosing agent either intra-vascular injection into the blood vessel lumen, or intra-lesional injection into the surrounding interstitial space; leading to endothelial cells permanent injury, fibrous changes, thrombosis, and ultimately occlusion of the blood vessel. It is a simple, cost-effective treatment modality used for both therapeutic and esthetic purposes. Sclerotherapy had been used to treat varicose veins for more than150 years; later, it was used to treat vascular malformations. [75] Before sclerotherapy, surgery was the only treatment for vascular malformations. However, it has been associated with severe intra-operative bleeding, incomplete excision, postoperative scarring, esthetic and functional impairment, and recurrence. On the other hand, sclerotherapy is a simple, low-cost, minimally invasive technique. Therefore, intralesional sclerotherapy is generally preferred over surgery to avoid esthetic and functional complications. Today, it is the gold standard treatment of low flow vascular malformations. Many sclerosing agents have been used; such as, ethanol 95%, ethanol-amine oleate (EO) 5%, bleomycin (BLM), and 3% sodium tetradecyl sulfate (STS). [76, 77]

Ethanol

Ethanol (95% Ethyl Alcohol) was the first and most commonly used sclerosing agent to treat vascular malformations, because of being the most powerful sclerosing agent due to deep penetration of tissues, with the least recurrence rate, its availability, low cost, and long shelf-life. Regarding its mechanism of action, Ethanol is believed to displace water molecules in the endothelial cell membrane, thereby; damaging structure integrity of endothelial cell membrane, causing thrombosis, occlusion of vessels, and severe inflammatory response. [78]

Although Ethanol is the most potent sclerosing agent for venous malformations; but, it is considered the most destructive agent among all sclerosing agents and it has the highest reported complication rates. Local complications of Ethanol sclerotherapy include; severe pain during injection that necessitates GA, marked tissue swelling severe inflammatory symptoms that may last up to 4 weeks), allergy, skin (ulceration and necrosis, nerve damage, and facial palsy; this is because Ethanol is severely irritating to the tissues. Therefore, other sclerosing agents are recommended for lesions in the face, fingers, toes, or genitalia. In addition, systemic complications of Ethanol include CNS depression, hypo-glycaemia, hypertension, deep vein thrombosis, pulmonary embolism, cardiac arrhythmia, and respiratory depression; which require close cardio-pulmonary monitoring during the procedure with general anaesthesia. These dangerous complications had limited clinical use of Ethanol sclerosing agent in last years, especially for vascular malformations located in the head and neck. [79 -81] Other sclerosing agents, such as Ethanol-amine Oleate 5%, (EO) and Bleomycin (BLM) have less sclerosing effect, but they have less extensive and less frequent complications than Ethanol 95% sclerosing agent. [82]

Ethanol-amine Oleate

Ethanol-amine Oleate (EO) 5% is an organic chemical compound, consisting of Ethanol-amine (primary amine & primary ethanol alcohol) as a basic substance, with oleic acid and benzyl alcohol 2% as a preservative. Its common brand name is Ethamolin®. It is prepared as 50 mg per 1 mL of sterile aqueous solution; and it is available in 2 mL and 5 mL ampules. It has an alkaline pH range: 8 – 9. It is mainly metabolized mainly by the liver, rather than the kidneys. Ethanol-amine Oleate sclerosing agent was FDA approved and has been used for many years to treat oesophageal varices (a life-threatening disease, caused by liver disease, and results in severe bleeding from the esophagus into the throat). [83] Masaki et al [84] conducted their early study in 1990 to understand the pharmacological effect of EO on the vascular endothelium in animals. The authors observed by electron microscope that when EO is injected into the vessels, it destroyed the endothelial cells of vessels; and caused accumulation of fibrin and platelets on the damaged vessels, thrombosis and occlusion of vessels within few minutes. From this animal experiment, the authors assumed that when EO is injected, the Ethanol-amine portion causes acute irritation, dose-related inflammatory reaction of the vascular endothelium, thrombus organization, the Oleic acid portion transiently activates coagulation through the release of tissue factor and activation of Hageman factor; leading to occlusion of the blood stream, sclerosis of blood vessels, and eventually collapse and disappearance of oesophageal varices or varicose veins. Johann et al [85] conducted the first clinical trial in 2005 to assess the effectiveness of EO intralesional sclerotherapy in 30 patients having oral vascular anomalies (hemangiomas and vascular malformations). The authors reported that all lesions responded with total clinical resolution, and concluded that EO is an effective sclerosing agent for treatment of oral vascular anomalies.

Later, in 2008, Das and Hoque [86] conducted their study to describe the outcome of EO intra-lesional sclerotherapy of venous malformations. The dose range of EO used in their study was according to the manufacturer instructions; 0.4 - 20 mL\session, with a dose of 0.4 mL/kg body weight. According to the authors, 71 lesions out of 76 lesions completely resolved and 5 lesions significantly improved, however, all patients experienced pain and swelling after injections to a variable degree, skin sloughing happened in 3 patients only and healed spontaneously, and there was no recurrence. Similarly, Alexander et al [87] conducted their study in 2014 to evaluate EO sclerotherapy for venous malformations in the head and neck region. The authors concluded that EO sclerotherapy is a safe and successful treatment for venous malformations of the head and

neck; and that its effectiveness and safety as a sclerosing agent exceeds other sclerosing agents. According to the available studies in the literature, EO 5% intralesional sclerotherapy of vascular anomalies is safe and effective in treatment of venous malformations, because of its low toxicity, availability, and reasonable price compared to other sclerosing agents. It is a mild sclerosing agent due to its lower concentration; and it has less frequent and less severe side effects than Ethanol 95% sclerosing agent. While Ethanol sclerosing agent causes severe tissue damage if extravasated, EO 5% does not deeply invade tissues and vascular walls; thereby, reducing the potential damage to adjacent soft tissues and nerves in the head and neck region. The safe dose of EO 5% is 0.4 mL\Kg, and the maximum dose is 20 mL\treatment session. It is given at 1 or 2 weeks interval; the dose is adjusted in each treatment session according to the patient body weight, and vascular lesion size, and the number of sessions is determined according to the clinical response of each lesion. [88-90]

Bleomycin

Bleomycin (BLM) is a glycopeptide antibiotic, isolated from the fermentation of *Streptomyces verticillus*, and it has cytotoxic and anti-neoplastic properties. BLM has various brand names, such as, Bleocel®, Bleocip, Bleocin, Bleocare, Bleotex, Bleochem, and Blenoxane. The term bleomycin is used to describe a family of glycopeptide antibiotics with a common bleomycinic acid core. Its pH range: 5.5 – 6; it is excreted mainly via the kidneys in urine within 24 hours. BLM is on the WHO list of essential medicines; the most effective and safe medicines needed in health system. [91]

Bleomycin was first discovered by the Japanese scientist Umezawa [92] in 1962, who found the antitumor potential of this drug while screening culture of *Streptomyces verticillus*; this discovery was published in 1966. BLM drug was launched in Japan in 1969. Later in 1973, Bleomycin was FDA approved in the USA and many other countries to be used, alone \ with other drugs, as a chemotherapeutic drug for treatment of Hodgkin lymphoma, non-Hodgkin lymphomas, testicular cancers, ovarian cancer, Kaposi's sarcoma, and squamous cell carcinoma of head & neck (SCCHN). In addition, besides the cytotoxic and anti-neoplastic properties of BLM, it has a sclerosing effect on the vascular endothelium of vascular anomalies. It is available from its manufacturer in 15 international units (IU) vial; it can be administered by intravenous, intramuscular, sub-cutaneous, intrapleural, or intralesional injections [93]

Jura et al [94] used BLM intra-lesional sclerotherapy injections for the first time in 1977 to treat macro-cystic LMs (cystic hygromas) in children, instead of surgical excision. The authors reported that BLM has showed complete cure of all cases included in their study.

Later in 2004, Muir et al [95] in their retrospective study of 95 patients evaluated the sclerosing effect of BLM on the endothelial cells of vascular anomalies; including propranolol- resistant haemangiomas and (venous and lymphatic) vascular malformations. In their study, the BLM dose per treatment session was 0.5mg/kg for children and 1 mg/kg for adults, the maximum dose per treatment session was 15 mg BLM, for both children and adults. BLM dose was adjusted according to the patient body weight and the lesion size, and the lesions were re-injected after 4 weeks. The authors reported complete lesion resolution in 80% of lymphatic malformations, 49% of venous malformations, and 32% of haemangiomas. Hence, Muir concluded that BLM has a high sclerosing effect on the endothelium of vascular anomalies; and recommended using intralesional BLM injections as a first-line treatment of lymphatic and venous malformations, as well as, hemangiomas, instead of invasive surgery; due to the satisfactory therapeutic results obtained and absence of serious complications in their study.

According to the available data in the literature, the mechanism of action of BLM, as a cytotoxic anti-cancer drug, involves inducing of breakage of DNA strands, leading to tumor cell death; [96] this explains the effectiveness of BLM intralesional injection during the proliferating phase of hemangiomas (vascular tumors). [97, 98] In addition, BLM as a sclerosing agent promotes occlusion and sclerosis of vessels, through a non-specific inflammatory reaction inducing irreversible damage of endothelial cells. [99]

Side effects that have been reported in oncology patients receiving intra-venous or intra-muscular BLM injections include: fever, dry cough, nausea, vomiting, weight loss, leukocytosis, hypotension, feeling weak, alopecia (hair loss), skin hyper-pigmentation, chest pain, and interstitial pulmonary fibrosis and impaired lung function (lung toxicity). On the other hand, the common side effects of intra-lesional Bleomycin, with safe doses, include: transient localized swelling (for 3-5 days), related to the inflammation induced by the injected BLM, and temporary overlying skin discoloration. Pulmonary toxicity is the most common life-threatening systemic complication of BLM; it has been reported in more than 10% and it is fatal in about 1 % of patients receiving intra-venous BLM for long time. The mechanism of BLM-induced lung injury is related to the low level of BLM hydrolase enzyme in the lungs, which is the responsible for the metabolism of BLM; this enzyme is present in all normal tissues in the human body except the lungs and the skin. Hence, the repeated administration of high doses of BLM and the genetic susceptibility lead to pulmonary accumulation of BLM and eventually lung fibrosis. Interstitial pulmonary fibrosis usually develops over a period of weeks to months; it is clinically presented in its early stage as central cyanosis, dyspnea (shortness of breath) or tachypnea (fast shallow breathing). With progressive lung injury, central cyanosis may occur.

This rapidly progresses into lung fibrosis, impaired lung function, respiratory failure, and death. Diagnosis of BLM-induced lung injury is established by previously mentioned systemic symptoms, in addition to chest x-ray, and pulmonary function tests. Unfortunately, there is no specific treatment of BLM pulmonary toxicity. Corticosteroids are the usual treatment, as it may improve the symptoms, but it will not reverse the interstitial pulmonary fibrosis. BLM induced lung injury is dose-dependent. The risk is significantly increased with total cumulative doses of BLM ≥ 400 mg in adults and ≥ 300 mg in children; which are the maximum lifetime doses of BLM. Other risk factors for BLM-induced lung toxicity include pre-existing lung disease, previous exposure to BLM within the last 6 months, chest irradiation, or renal disease. This is due to the fact that about 65% of the administered IV dose of BLM is excreted via the kidneys in urine. Renal disease leads to concentration of BLM in the lungs and pulmonary toxicity. [100]

In addition, patients who have been treated with BLM in the past 12 months should not receive high concentrations of oxygen in GA or hyperbaric oxygen therapy, because BLM increases lungs sensitivity to oxygen, which can lead to BLM-induced lung toxicity and respiratory failure. Therefore, parents are advised that before any future surgical procedure to inform the anesthesiologist that their child had received BLM. [101] Furthermore, Zorzi et al [102] reported that up to 59% of children that have cancer and are being treated with high cumulative IV doses of BLM, have abnormal pulmonary function tests (PFTs), 2 years after completing their BLM chemotherapy. The authors emphasized that pediatric patients are at higher risk for BLM-induced lung injury due to their incomplete lung development. Therefore, the Children's Oncology Group recommends annual check- ups and PFTs, at least for 2 years after completing the intravenous BLM for childhood cancer therapy. [103]

Fortunately, intralesional sclerotherapy injections of BLM do not result in a substantial amount of BLM in the bloodstream, unlike patients systemically treated with BLM. According to Ionescu et al, [104] there was no detectable BLM in blood samples taken from pediatric patients 24 hours after BLM intralesional injections. This have been also confirmed by Kumar et al, [105] who reported that intralesional sclerotherapy of BLM is done is in very small doses (≤15 IU\session) in comparison to the intravenous BLM doses administered in chemotherapy. The authors clarified that the systemic distribution of intralesionally injected BLM is significantly lower and it is safer than the intravenous BLM.

Based on the current data, intra-lesional BLM sclerotherapy of vascular malformations does not cause nerve damage, sever inflammatory response, ulceration, tissue fibrosis or necrosis; therefore, it is especially recommended for sclerotherapy of vascular anomalies in the head and neck. BLM sclerotherapy has been proven to be effective and safe treatment of low flow vascular malformations and hemangiomas, with varying degrees of response. According to the most available studies, conducted on BLM intralesional sclerotherapy of vascular anomalies, the safe adult dose of BLM intralesional injection is 1 U/kg, the safe pediatric dose is 0.5 U\Kg; and the safe maximum dose per treatment session is 15U\session; given at 4 weeks interval, and the number of treatment sessions is decided according to each vascular lesion response. The intralesional BLM dose given each treatment session is adjusted according to the patient body weight, and the vascular lesion size. [106]

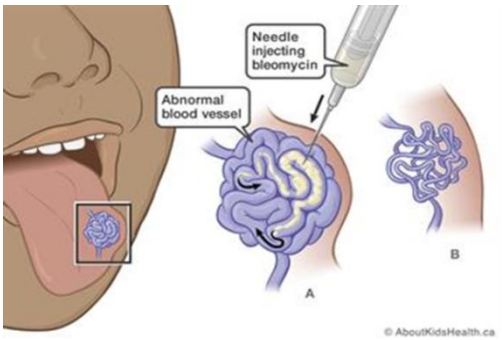

Fig. 8: Intralesional Sclerotherapy
From: https://www.aboutkidshealth.ca [107]

II. Recommendations

Maxillofacial surgeons, pediatric dentists, general practitioners and students in faculty of dentistry should have more knowledge in the field of vascular anomalies for appropriate diagnosis and treatment of maxillo-facial vascular anomalies. Most published research about vascular anomalies from Egypt, found in PubMed, was done by specialists of pediatric surgery, vascular surgery, dermatology, and interventional radiology; therefore, more research needs to be done in this field by maxillofacial surgeons and pediatric dentists in Egypt. I hope this review article would be a small step in that direction.

Declaration

This review article is a part of the PhD thesis of the first author (Sarah Arafat), in Oral and Maxillofacial Surgery Department, Faculty of Dentistry, Suez Canal University in Egypt, entitled "Comparative Study

between Bleomycin and Ethanol-amine Oleate Sclerotherapy in Management of Pediatric Maxillofacial Low Flow Vascular Malformations: A Randomized Clinical Trial".

Conflicts of Interest:
The authors declare that they have no conflict of interest.

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