Review

Diagnosing hemangioma and vascular malformations of head and neck

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Abstract

Understanding of vascular lesions or 'birthmarks' has been hampered by confusing erroneous terms employed to describe and classify these lesions. An analysis of various scientific articles and newer editions of medical text books revealed that significant confusion prevails among the medical and scientific fraternity over the usage of correct nosology for defining a vascular lesion. Hemangiomas are true benign neoplasms developing after few weeks of birth, characterized by endothelial cell proliferation, and they invariably undergo spontaneous involution by 9 years of age. Vascular malformations are developmental anomalies of vascular plexus that are present from birth, characterized by normal endothelial cell turnover rate, and persists throughout life. The clinical appearances of the vascular lesions are similar and it is often difficult if not impossible to correctly diagnose these lesions. Even after the implementation of International Society for the Study of Vascular Anomalies (ISSVA) classification since 1996, the medical fraternity still persists with the old confusing nomenclatures while diagnosing and reporting vascular lesions. As a clinician and academician it is important to differentiate between the vascular lesions as they show different clinical, pathological, and biological behaviour, thus requiring different management and treatment modalities. In this review the authors advocate the usage of correct nosology for

defining specific vascular benign lesions to avoid inaccurate diagnoses and potential mismanagement.

Introduction

The earliest attempt at classification of vascular lesions was made by Virchow (1863) and Wegner (1877), who gave an anatomo-pathologic classification – (a) angioma, (b) lymphangioma.[1] Later researchers classified the benign vascular lesions (1) according to the type of fluid they contained – (a) hemangioma (blood-containing lesion), (b) lymphangioma (lymph-containing lesion), and (2) according to the size of the vascular channels – (a) capillary (small diameter vascular channels), (b) cavernous (large diameter vascular channels).[2] In 1982, Mulliken and Glowacki published the biological classification based on the endothelial cell characteristics, physical findings, and natural history of the vascular lesion.[3] Mulliken's classification differentiates vascular lesions with endothelial cell proliferation (hemangioma) from vascular lesions with structural anomalies (vascular malformation).[1-6] In 1996, this classification was adopted by the International Society for the Study of Vascular Anomalies (ISSVA) in their first workshop held in Rome.[4] The society modified the biological classification in their continuing workshops, and presently ISSVA differentiates vascular tumors from vascular malformations based on their history, clinical appearance, imaging and pathological features, and biological behaviour (Table 1).[3-5] The goal of this review is to advocate correct nosology for defining specific vascular benign lesions and to henceforth avoid the usage of out dated confusing nomenclatures by the medical and scientific fraternity that have led to inaccurate diagnoses, research, and mismanagement of these lesions.

Table 1. Modified International Society for the Study of Vascular Anomalies (ISSVA) 2007 classification

Vascular Tumor	Vascular Malformation
1. Benign Tumors a. Infantile hemangioma i. Focal. ii. Segmental. iii. Indeterminate. b. Congenital hemangioma i. Rapidly involuting congenital hemangioma (RICH). ii. Non involuting congenital	1. Slow (Low) Flow a. Venular Malformations i. Traditional (portwine stain). ii. Midline (Salmon stain). iii. Telangiectasia. b. Venous Malformations i. Unifocal. ii. Multifocal. iii. Bean (blue rubber bleb nevus)

hemangioma (NICH). c. Tufted angioma. d. Pyogenic granuloma and other dermatologic acquired tumors. e. Nasopharyngeal angiofibroma. f. Hemangiopericytoma-solitary fibrous tumor. 2. Intermediate Tumors 1. Kaposiform hemangioendothelioma. 2. Spindle cell hemangioendothelioma. 3. Hemangioendothelioma NOS (not otherwise specified).	syndrome. c. Lymphatic Malformations i. Microcystic. ii. Macrocystic. iii. Mixed. iv. Lymphedema. d. Complex Combined Malformations i. Capillary-lymphaticovenous malformations (Klippel-Trenaunay syndrome). ii. Proteus syndrome. 2. Fast (High) Flow a. Arteriovenous Malformations. b. Arteriovenous Fistula. c. Arterial Malformations.

Hemangioma

Hemangiomas are true benign neoplasms of endothelial cells.[1-6] They are the most common benign soft tissue tumor of infancy and childhood, occurring in 12% of all infants.[4-8] They are found in greater frequency in whites, girls, twins, premature infants, and are usually born to mothers of higher maternal age.[1,2,4-8] They occur most frequently in the head and neck region (60%), followed by the trunk (25%) and the extremities (15%).[4-6] ISSVA separates hemangioma into Infantile Hemangiomas (IH) and Congenital Hemangiomas (CH).[4-6]

Infantile Hemangiomas (outdated term - juvenile hemangioma) are not present at birth and arises during the first 8 weeks of life.[1,2,4-7] Initially the lesion clinically appears as an circumscribed area of discoloration or telangiectasia of facial skin.[4-7] It exhibits a high proliferative phase for 6-12 months and grows rapidly into a raised rubbery bright-red tumor (resembling a strawberry, hence outdated term strawberry hemangioma).[2,4-7] The proliferative phase is followed by a gradual involution phase and a spontaneous regression by the age of 5-9 yr.[4-7] 50% of all hemangiomas will completely involute by the age of 5 yr and 90% by the age of 9 yr.[1,2,4-7] 40% of involuted IH may clinically show scaring, wrinkling, telangiectasia, or loose fibro-fatty tissue at the site of their clinical appearance.[1,5] ISSVA categorizes IH depending on site of its occurrence as focal, segmental, and indeterminate, and depending on the depth of the lesion from the skin surface as superficial, deep and mixed.[4,6] Focal IH are the most common variant, appearing as localized raised tumor-like lesion that tends to occur at the area of

embryological fusion.[5,6] Segmental IH are flat plaque-like larger lesions that show a geographic segmental distribution, and Indeterminate IH shows characteristics of both focal and segmental IH.[5,6] Colour of the IH varies with the depth of the lesion and they can be bright red (superficial), purple, blue, or normal skin colour (deep).[1,2,5,6]

Congenital Hemangiomas are clinically present as fully developed lesions at birth, and either rapidly involutes during the first year of life or may never show involution.[1,2,5,6] These lesions do not exhibit a proliferative phase and usually do not grow after birth.[5,6] Rapidly involuting congenital hemangiomas (RICH) are present at birth either as red-purple colour plaques with coarse telangiectasia, as flat violaceous lesions, or as a greyish tumor surrounded by a pale halo with multiple tiny telangiectasia.[1,2,5,6] RICH undergo a rapid regression phase and completely disappear by 12-18 months of age.[1,5,6] Non- involuting congenital hemangiomas (NICH) are present at birth as pink or purple coloured plaque-like lesions with prominent overlying coarse telangiectasia and peripheral blanching.[1,5,6] NICH does not show a regression phase, may grow proportionately with the growth of the child, and can be mistaken for a vascular malformation.[1,5,6]

Infantile hemangiomas appear more common (70%) than CH (30%).[1,5,6] Apart from hemangiomas of soft tissue scientific literatures have reported central hemangiomas (hemangioma of bone) and intramuscular hemangiomas.[1,6-8] Many researchers, in addition to the World Health Organization (WHO) believe that most if not all such proposed lesions are vascular malformations and are not true neoplasms.[8] ISSVA classification has not been applied for the categorization of osseous or intramuscular vascular lesions.[8] 30% of large facial hemangiomas (>5 cm diameter) are associated with PHACE syndrome, an acronym that stands for posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular anomalies, cardiovascular anomalies, and eye anomalies.[5]

Vascular Malformations

Vascular malformations (VMs) are localized defects of vascular morphogenesis that results in formation of abnormal, tortuous and enlarged vascular channels, the exact etiopathogenesis of which remains unknown.[11,12] VMs are always present at birth, although they may clinically be apparent only later in life and they persist throughout life, growing slowly and commensurately with the child's development by distension and hypertrophy.[6,13] Majority of them are asymptomatic and are sometimes found only as an incidental finding during autopsy.[6,13] Unlike hemangiomas they do not have a growth phase, unless in response to trauma, infections, changes in intravascular pressure, or hormonal changes during pregnancy and puberty.[6] VMs occur in 1-1.5% of births and have not shown any predisposition to gender or race.[6] The actual incidence of VMs may probably be more since many clinicians and diagnosticians erroneously

report them as hemangioma.[1,2,9,10] VMs are categorized depending on the dynamics of flow within the vascular channels into slow or low-flow and fast or high-flow VMs (Table 1).[4-6]

Venular Malformations (VrM): In older classifications these malformations are denominated as Capillary Malformations, while in 1999 Waner and Suen based on their identification of the anomalies of these lesions in the post-capillary venules (rather than in the capillaries) re-categorized them as Venular Malformations (VrM).[6] (1) Traditional VrM (portwine stain) occur in 0.4-1% of newborns without any gender predominance, and 83% appear as reddish-pink macules over facial dermatomes supplied by the branches of the trigeminal nerve.[6,11,14] 90% of these malformations afflict more than one dermatome, with the combined affliction of maxillary and ophthalmic dermatomes the most common.[6] With age the skin lesion darken in colour and thicken to produce a violaceous coloured lesion with cobblestone surface; along with hypertrophy of bone, gingiva, mucosa and lip, leading to interdental spacing, malocclusion, and unaesthetic appearance.[6,14] 30% of traditional VrM are associated with Parkes-Weber syndrome, characterized by arteriovenous malformations and fistulas of legs, arms, head and neck, that clinically appear as diffuse red-pink blotchy macules.[6] 10% of traditional VrM are associated with Sturge-Weber syndrome, characterized by VrM of maxillary and ophthalmic dermatomes, hemifacial hyperplasia, and ipsilateral leptomeningeal VMs of cerebral cortex that is characterized by gyriform 'tramline' calcification on skull imaging, convulsive disorder, mental retardation, and ophthalmic manifestations.[6,14] (2) Midline VrM (Salmon stain, stork bite, angel's kiss) appear as wedge-shaped pink macules on the midline of the forehead along the anatomic areas innervated by the supratrochlear and supraorbital nerves, and sometimes involving the glabella, supra-alar region and philtrum.[6] They never show hypertrophic growth and usually involute by the age of 1 yr in 55-65% of the newborns.[6] (3) Hereditary hemorrhagic telangiectasia or Osler-Weber-Rendu syndrome is an inherited autosomal dominant mucocutaneous disorder affecting 1 in 5-8000 due to mutations in ENG, ACVRL1, and SMAD4 genes.[15] Vascular anomalies range from telangiectasia of skin and mucosa to arteriovenous malformations of lungs, liver, gastro-intestine, and brain.[15]

Venous Malformations (VeM) appear as multi-septated vascular spaces that are histologically similar to veins but lack the mesothelial and endothelial elements that are characteristic of normal vascular channels.[6] (1) Unifocal VeMs have a reported incidence of 1 in 10000 live births, and affects any organ, cutaneous tissue, muscle, or bone.[11,14,15] The most common site of occurrence is the head, neck and limbs, with the tongue, palate, lips, and jaw bones being the most afflicted areas in the mouth.[6] Cutaneous lesions are soft compressive nodular lesions that empty on application of finger pressure, produce no thrill or bruit, are not warm to touch, and colour varies from purple for superficial

lesions to blue or normal mucosal colour for the deep lesions.[6,14,16] (2) Multifocal VeMs appear as multiple small <5 cm asymptomatic raised pink to dark blue superficial nodules.[16] The nodules usually involve only the superficial mucosa, and rarely invades the muscle, bone or deeper tissues.[16] Most of the VeM that are sequestered from the main vessel undergoes a spontaneous continuous cycle of thrombosis and thrombolysis, and these thrombus may undergo calcifications to form phleboliths that become painful on palpation and could be a radiologic marker for these type of malformations.[6,14,16] (3) Bean syndrome or blue rubber bleb nevus syndrome is characterized by multiple cutaneous, visceral, and musculoskeletal VeM.[16] Cutaneous malformations appear as small blue rubbery nodules (bleb) of palm and sole, and visceral malformations cause chronic intestinal bleeding leading to anemia.[16]

Lymphatic malformations (LMs) (outdated term lymphangioma) are reported to afflict 1 in 2-4000 live births.[14] Obstruction or sequestration of the primitive lymphatic vessels during embryogenesis produce ectopic lymphatic systems, and the resulting failure of drainage from these areas lead to increase in intravascular pressure and LMs.[18,19] 75-90% of all LMs occur in the neck, followed by the axilla and mediastinum.[2,6,18,19] Within the oral cavity the LMs are more commonly found on the anterior 2/3 of tongue, followed by palate, gingiva, and oral mucosa.[6,18] (1) Microcystic LMs (outdated terms include capillary lymphangioma, superficial lymphangioma, lymphangioma circumscriptum, lymphangioma simplex) in the oral cavity appear as multiple translucent non-compressible cysts or vesicles of <2 cm^3 containing viscous clear fluid, producing a pebbly or warty surface resembling "frog spawn" or "tapioca pudding".[6,14] (2) Macrocystic LMs (outdated terms include lymphangioma cavernosum, cystic hygroma, lymphangioma cysticum) usually presents as multiple cysts of >2 cm^3 and are commonly found in the supra-clavicular fossa of the posterior triangle of the neck, and in the cervical area just below the angle of the mandible.[6,14,19] They clinically appear as localized painless non-pulsatile swelling with no bruit or thrill, having a rubbery compressible consistency, and covered by normal appearing skin unless hemorrhage or communication with venous malformations produce a blue discolouration.[6,14,19] The affected side may show mandibular hypertrophy leading to prognathic jaw, class III malocclusion, and open-bite.[6,14] Sudden growth of macrocystic LMs may occur due to infection and compromise the airway leading to respiratory distress.[6] (3) Mixed LMs have the combined features of microcystic and macrocystic LMs.[6,14,17]

Arteriovenous Malformation (AVM) (outdated terms include cirsoid aneurysm, arteriovenous aneurysm) is the most common fast or high-flow VMs.[6] They represent a group of congenital malformations that create a direct communication between the arterial and venous systems, through a nidus formed by arteriovenous shunts, along with hypertrophy of the afferent arterial and

efferent venous system.[2,6,14,20] AVM is present at birth, but become clinically apparent only during the 4-5th decade of life and is often misdiagnosed due to delay in clinical presentation.[2,14,20] The most common site for AVM is the brain, followed by the head, neck, limbs, trunk, and viscera.[6] The majority of the head and neck lesions occur on the cheek, followed by the ear, nose, forehead and upper lip.[14,20] Oral lesions are more common on the gingiva, causing mobility of teeth and profuse periodontal bleeding.[14] They appear as purple-blue raised painful macule, are pulsatile with thrill and bruit, warm to touch, and grow commensurately with the persons growth.[2,14] AVM are firm to palpation, do not empty fully on compression, and refill quickly on reliving digital pressure.[6] They are associated with embolism, pain, bleeding, ulceration, and congestive cardiac failure due to increased cardiac load.[2,6,14,20] They may enlarge suddenly due to thrombosis, trauma, or infection.[2,6,14,20] Schobinger divided the development of AVM into four stages: I) *Quiescence:* characterized by pink-violaceous macule and arteriovenous shunt detectable by echo-Doppler ultrasound; II) *Expansion:* as in stage I, and pulsatile red macule with obvious presence of tortuous vessels; III) *Destruction:* as in stage II, dystrophic skin changes, ulceration, bleeding, continuous pain; IV) *Decompensation:* as in stage III, heart failure.[6]

Investigations

Diagnosis of most benign vascular lesions are made by a detailed clinical history (time of appearance, presence of precursor lesion, growth pattern, involution) and a good physical examination, with only a minority requiring imaging studies or histopathological examination for confirmation.[2,5,6,21] Imaging studies in the form of Doppler-ultrasound (US), magnetic resonance imaging (MRI), computerised tomography (CT), phlebography, nuclear imaging studies, single photon emission computerised tomography (SPECT), and multiplanar computed angiography help to diagnose and distinguish vascular lesions.[1,2,5,6,21-24] The imaging studies help to define the size, anatomic extent, volume, involvement of adjacent structures, and the presence of any collateral feeders, the detailed knowledge of which are absolute necessity before any therapeutic or surgical intervention is attempted.[5,6,21-24] Ultrasound are an inexpensive and non-invasive tool in evaluating the flow dynamics, but have limited ability in displaying the full extent of large lesions and in demonstrating intra-osseous extent or lesion.[22,24] Contrast enhanced MRI and computed angiography are the commonly used modality for evaluating vascular lesions.[24] Immunohistochemical studies after a scalpel-biopsy may help distinguish VMs from hemangiomas, and have shown that IH are Glucose Transporter (GLUT)-1 positive while CH like VMs do not express GLUT-1 protein.[1,4-7] In contrast to hemangiomas, VMs do not express proliferating cell nuclear antigen (PCNA), vascular endothelial growth factor (VEGF), fibroblast growth factor (FBF), type IV collagenase, and urokinase.[4]

Management

Inconspicuous hemangiomas are best treated with close observation over their lifecycle, as *90% of all these lesions involute by 9 yr.*[5,6,14] *Medical and surgical management are done for* vascular lesions that produce bleeding, ulceration, visual axis obstruction, airway obstruction, high-output cardiac failure, potential psychosocial conflict in the family, or risk for permanent disfigurement.[5,14,21,23] Many therapeutic modalities have been tried and proposed depending on the expertise of the surgeon or the interventional radiologist, and a detailed discussion is beyond the scope of this review. The method of management and the therapeutic agents used depends on the type and flow characteristics of the vascular lesion.[21,23] Treatment of vascular lesions include repeated *aspiration* for small lesions; *sclerotherapy* under fluoroscope with corticosteroids (myriad side effects can occur), interferon-α, OK-432, doxycycline, cyclophosphamide, or propranolol; *transarterial embolization* (for high-flow lesions) with polyvinyl alcohol, ethylene-covinyl alcohol, N-butyl cyanoacrylate, silicone balloons, platinum or stainless steel coils; *photocoagulation* with carbon dioxide, Nd-YAG laser, or flash lamp pulsed dye laser; and *surgical excision* for lesions that threaten life, cause functional impairment or disfigurement.[5,14,21,23] In few VMs ligation or proximal embolization of feeder vessels may be required as secondary intervention.[23]

Conclusions

Indiscriminate, inappropriate, and interchangeable use of the term hemangioma with VMs should be avoided. Hemangioma and its erroneous obsolete variants (strawberry, capillary, juvenile) are the most common maligned term used to describe a VMs.[4-6,9,10] The Greek suffix 'oma' means cellular proliferation of a tumor, and thus the term haemangioma or lymphangioma is erroneous when used for a vascular anomaly.[4] The widely accepted ISSVA classification that differentiates vascular lesions with proliferative endothelium from structural anomalies have to a great extend helped in standardizing the terminologies. In addition to overcoming obstacles in communication it is important that we adhere to the correct nosology, as the therapeutic guidelines, management, and follow-up of these lesions differ. Unfortunately it is difficult and sometimes impossible to determine clinically and histopathologically whether the vascular lesion is a malformation or a true neoplasm, with more than 50% of the vascular lesions being diagnosed, termed, and treated incorrectly.[1,2,9,10]

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