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Inconsistency in Classifying Vascular Anomalies: What's in a name?

Kristy S. Pahl, M.D.[1,2], **Kyung Kim, M.D.**[2,3], **Casey Sams, M.D.**[2,3,+], **Hortensia Alvarez, M.D.**[2,3], **Scott V. Smith, M.D.**[2,4], and **Julie Blatt, MD**[1,2]

[1]Division of Pediatric Hematology Oncology, The University of North Carolina School of Medicine, Chapel Hill, NC

[2]Vascular Anomalies Clinic, The University of North Carolina School of Medicine, Chapel Hill, NC

[3]Department of Radiology, The University of North Carolina School of Medicine, Chapel Hill, NC

[4]Surgical Pathology and Experimental Pathology, The University of North Carolina School of Medicine, Chapel Hill, NC

Abstract

Background—Vascular anomalies are a heterogeneous group of disorders seen in children and adults. A standard nomenclature for classification has been offered by the International Society for the Study of Vascular Anomalies (ISSVA). Its application is important for communication among the multiple specialties involved in the care of patients and for planning treatment, as well as for research and billing. We hypothesized that terminology still is not uniformly applied, and that this could have an impact on treatment.

Methods—We retrospectively reviewed the medical records of patients with non-brain lesions from our institutional vascular anomalies database seen 2010–2016 for whom at least one clinic visit, radiologic imaging report, and pathology report were available, to compare diagnoses among and within disciplines, and treatment recommendations. Diagnoses and referral patterns by community healthcare providers also were reviewed.

Results—Of 400 patients seen during the targeted time interval, 35 had clinical, imaging, and pathology reports. Agreement in terminology from initial clinic notes with imaging and pathology reports was noted in only 3 cases (9%). "Hemangioma" was often misused; "lymphangioma" and "cystic hygroma" persist as diagnostic labels. Community healthcare providers referred vascular malformations with a diagnosis of "mass" or "hemangioma" in 17/18 cases where that information was available. Incomplete or mislabeling of vascular anomalies sometimes delayed referrals to appropriate clinics, though it did not have a major impact on treatment.

Conclusions—An understanding of vascular anomalies as tumors or malformations is not uniform. Ongoing education will be needed to promote consensus terminology and facilitate referrals.

Corresponding Author: Kristy S. Pahl M.D., Division of Pediatric Hematology Oncology, The University of North Carolina School of Medicine, 919-966-1178 (tel), 984-974-8579 (fax), Kristy.Pahl@unchealth.unc.edu.

[+]Current address: Department of Radiology, Brown University School of Medicine

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Keywords

vascular anomalies; hemangioma; vascular malformation; Classification

Introduction

Vascular anomalies are a heterogeneous group of disorders that are common in both children and adults[1]. A standard nomenclature is important for communication among the multiple disciplines involved in the care of these patients. In 2014, the International Society for the Study of Vascular Anomalies (ISSVA) updated its classification scheme for vascular anomalies (www.issva.org)[2], a refinement of that initially proposed by Mulliken and Glowacki in 1982 [3]. This most recent classification (Table 1) divides vascular anomalies into vascular malformations (capillary, lymphatic [LM], venous [VM], arteriovenous [AVM], AV fistulas, combined lesions, those associated with major vessels, and those associated with other anomalies) and vascular tumors (including benign, locally aggressive, and malignant tumors). Although the ISSVA classification is widely accepted, our anecdotal experience suggested that its terminology still is not uniformly applied. This is concerning, since treatment for different types of vascular malformations and for tumors may be very different. We retrospectively searched our institutional vascular anomalies database for patients with non-brain lesions which had been evaluated clinically, radiographically, and histologically. Our results confirm that, even at a center with dedicated interest in the management of vascular anomalies, there is a lack of concordance among and within disciplines. Community healthcare providers also seem to be uncomfortable with terminology. Although discordant terminology did not change consensus treatment recommendations, it did sometimes result in inappropriate subspecialty referrals.

Methods

Vascular Anomalies Clinic

In 2008, the University of North Carolina at Chapel Hill (UNC) began to promote a multidisciplinary approach to patients with vascular anomalies with the development of a Vascular Anomalies Clinic. Patients referred to one of the more than 15 participating divisions and departments often are referred internally by the initial contact for same-day visits to at least one of the other divisions, as clinically indicated. Consults are concentrated among specialists with a specific interest in these problems. Selected cases are reviewed at a monthly clinical management and education conference.

Vascular Anomalies Database

A comprehensive UNC database was previously compiled (KP, JB) of both adult and pediatric patients who had been seen at UNC with a vascular anomaly between 2000–2016. This database was completed with the help of UNC's North Carolina Translational and Clinical Sciences (NCTracs) Center, which pulled patient names and medical record numbers based on relevant ICD-9 codes (747.60, 747.63, 747.64, 747.9, 759.9, 228). Patients with hereditary hemorrhagic telangiectasia are included in a separate institutional database and were not included here. Patients with intraparenchymal brain anomalies also

were excluded because their diagnosis has not been controversial among different neuroscience specialties. Five patients with brain AVM's recorded in our database and seen by members of the Vascular Anomaly Clinic in the same period showed 100% concordance the among initial clinician, pathology and radiology reports. These are not included in this series.

Medical records were reviewed (KP, JB) for confirmation that patients actually had at least one vascular anomaly. Data abstracted from the medical record included patient age and gender, site of anomaly, presence or absence of overgrowth or other syndrome, relevant providers by whom the patients had been seen, and outside referral diagnosis. Diagnoses were recorded from clinic notes, imaging and pathology reports. Whether the patient had surgery, sclerotherapy/embolization, or pharmacologic management (e.g., sirolimus) was noted. Both compilation of the database and medical record review were approved by a waiver from the UNC School of Medicine Institutional Review Board.

Patient Selection

Subjects were selected from the above database who had been first seen at UNC by at least one member of our Vascular Anomalies Clinic from 2010–2016, and for whom at least one imaging evaluation (magnetic resonance imaging [MRI], ultrasound [US], computerized tomography [CT], or arteriogram) and surgical pathology report from the same time period were available. Indication for biopsy was not always clear from the medical record, but the majority of patients underwent biopsy or excision of their lesion for either diagnostic or therapeutic purposes. Medical records were reviewed for diagnostic labeling (and corroborating ICD9 codes) by clinicians, radiologist, and pathologist. Clinical diagnosis at the time of first visit to a UNC Vascular Anomalies Clinic physician and what specialty made the diagnosis were recorded. The first imaging and pathology reports were used for comparison with each other and with the clinical diagnosis. Where serial reports were available, these were reviewed to track changes in diagnosis over time. Treatment recommendations and response to treatment were used to support the credibility of diagnoses and to explore to what extent these were altered by labeling.

Results

Of the 400 patients recorded in the database who had been seen from 2010–2016, 35 patients met eligibility criteria, having been seen by a clinician in one or more divisions and having had both imaging and a biopsy during the same time frame. Patient age at the time of initial evaluation at our center ranged from birth to age 64 years (median 6 years); 29 patients (83%) were first seen before the age of 18 years. Twenty-three patients (66%) were female and 12 (34%) were male. First clinical evaluations were by otolaryngology (n=10), pediatric surgery (n=7), orthopedic surgery (n=5), pediatric hematology/oncology (n=4), vascular interventional radiology (n=4), plastic surgery (n=2), vascular surgery (n=1), general surgery (n=1), and ophthalmology (n=1).

Location of vascular anomalies was head/neck (n=14, 40%), axilla (n=2, 6%), abdomen/pelvis (n=3, 8%), back (n=1, 3%), extremity (n=15, 43%). Two patients had more than one vascular anomaly, but in both cases all were confined to the head and neck region. None of

the patients was diagnosed with a syndrome, possibly reflecting better diagnostic criteria in such individuals making biopsy for diagnosis unnecessary. Initial imaging evaluations were by MRI (n=23, 66%), US (n=5, 14%), CT (n=4, 11%), or arteriogram (n=1, 3%), and 2 patients (6%) had had same-day MRI and US.

Table 2 summarizes the diagnostic labeling by the initial clinical service which examined the patient, as well as the updated clinical diagnosis noted by this same specialty at its last clinical encounter within the time frame of this study. Ten (29%) patients saw a second clinical specialist at their initial encounter at UNC, and the diagnostic labeling by this second clinician is listed, but was not followed over time. Pathology and radiology diagnoses are included in the table. Complete concordance among initial clinician, pathology, and radiology was seen in only 3/35 cases (9%). Clinical diagnoses often were noncommittal at the time of initial evaluation with labeling of lesions as a “mass” in 11 cases. However, chart reviews indicated strong suspicion of a vascular malformation, and often of a AVM, LM, or VM. In 25 of 35 cases (71%), clinicians changed their diagnoses over time. In most cases this was a refinement of the original diagnosis (e.g., “vascular malformation” to “VM”). Based on clinic notes, changes seemed to reflect incorporation of pathology results (12/25 cases) which hadn’t been available initially, and to a lesser extent of imaging studies which followed the initial clinical encounter. Ten patients were seen on the same day by more than one clinical specialty. Of these 10 individuals, 3 had both initial and second clinician agree in the diagnosis. This included 1 patient with an AVM, 1 patient with a LM, and 1 patient labeled as a hemangioma (which in actuality was a VM).

Pathology in most cases was based on hematoxylin-eosin staining without use of immune-histochemical stains. Pathology reports diagnosed AVM more frequently than did the other services (n=9, 25%). Of the 9 patients diagnosed with AVM by pathology, 5 did not have physical examination findings which supported an AVM diagnosis (i.e. no thrill or bruit) and/or imaging studies were not suggestive of a high flow lesion. In 4/9 lesions which pathology reports labeled as AVMs, either initial clinical or imaging documentation was not sufficient for us to be sure of that diagnosis. LM was the next most common pathologic diagnosis (n=6, 17%); of these 6 patients 2 had agreement in diagnosis between all disciplines. Of the remaining 4 patients diagnosed with LM by pathology, 3 were labeled as “lymphangioma” and 1 “lymphovascular malformation” by either initial clinician or radiologist, using non-ISSVA classification. In 5 cases (14%), the final report was “vascular malformation,” with no further specification. For 23 of the 35 patients, the only available pathology report was following either sclerotherapy, embolization, and/or sirolimus, which may have affected the pathology findings and diagnosis.

Imaging diagnosis differed from pathologic diagnosis in 26 of the patients (74%), from initial clinical diagnosis in 22 (63%) and from final clinical diagnosis in 26 (74%). The most common imaging diagnosis was LM (n=7, 20%), VLM (n=6, 17%) and hemangioma (n=5, 14%). In the group of 5 patients diagnosed with hemangioma by imaging report, 2 also carried this diagnosis according to clinical report, and none by pathology report. Four of the 5 ultimately were clinically classified as VM or VLM (with 3 treated with resection alone, 2 with sclerotherapy, and 1 with resection alone), and 1 as an AVM treated with resection alone. 10 of the 35 patients (29%) had more than one imaging evaluation during the study

interval. Of these 10 patients, 8 patients (80%) had a change in their imaging diagnosis over time, with different radiologists reading these images. These changing diagnoses were either from a general diagnosis in the first image changed to a more specific diagnosis (i.e. vascular malformation to VLM), from hemangioma to a specific vascular malformation, or even from one type of vascular malformation to another.

Referral information from community healthcare providers was available for only 18 of the 35 patients (51%). The most common referral diagnoses were “soft tissue mass” and/or symptoms related to the mass such as “pain” or “swelling” (n=14, 78%). Of the other 4 patients, 3 were referred with a diagnosis of “hemangioma,” and of these 1 was later determined to have a VM or VLM, 1 a VM, and the other 1 an AVM. The remaining patient was referred with a diagnosis of “vascular malformation” which was thought to be correct and with a final diagnosis of VM. Referrals were to a surgical specialty in 10/18 cases, 8 with a diagnosis of “soft tissue mass” or symptoms related to a mass; 2 patients were referred to surgery with a referral diagnosis of “hemangioma.” Referrals were to VIR in 4/18 cases, for a diagnoses of “hemangioma” (n=1) or “mass” not otherwise specified (n=3). Two of 18 cases were referred to PHO for evaluation of a correctly labeled “vascular malformation” and a “mass,” not otherwise specified. One patient was referred to ophthalmology for proptosis and found to have a retro-orbital hemangioma, and the other to otolaryngology for a mass.

Discussion

Our results confirm that even at a center with a cohort of individuals and disciplines with an interest in vascular anomalies, there often is a lack of concordance about what to call these lesions. Agreement at the time of initial evaluation to our institution-by clinician, radiologist, and pathologist- was noted in only 9% of patients. Even among clinicians from different disciplines, there were differences in how anomalies were labeled at the time of first visit to each. However, these differences usually were clinically insignificant, reflecting how specific the diagnosis was (e.g., “vascular malformation” without a commitment to VM or LM). Clinicians frequently changed their initial diagnosis over time to reflect input from other clinicians and newly available radiology and especially pathology reports

It is likely that these differences in part reflect a lack of familiarity with or a resistance to adopting ISSVA terminology by many disciplines and practitioners within disciplines who are involved with care of these patients. A 2011 report also noted non-uniformity in diagnosis based on review of the literature, with almost 21% of patients receiving improper treatment due to mislabeling[4]. In our series, improper labeling of vascular malformations as hemangiomas, as well as use of non-ISSVA terminology, was common across all clinical specialties, radiologists, and pathologists. This is despite the broad membership of ISSVA, which includes many disciplines involved in patient care. Misdiagnosis of vascular anomalies by referring providers has previously been documented[5], a finding that was replicated in our study. Community healthcare providers sometimes mislabeled vascular malformations as hemangiomas or recognized them as “masses” but not as malformations. Their frequent referrals of patients to surgical specialties, in addition to lack of familiarity with ISSVA nomenclature, may have reflected a lack of familiarity with the role of non-

surgical specialties in the management of these patients, or may simply have reflected a lack of familiarity with our multidisciplinary clinic.

It was reassuring that, apart from requiring redirection of patients to different clinicians in our vascular anomalies clinic, we did not see a major impact on treatment decisions. We agree with the prior report[4] that "although a vascular anomaly may be mislabeled, the physician could still understand…the treatment approach." However, our numbers are small and we may be underestimating the impact of imprecise labeling on treatment. It is of note that we more recently saw a child who had been evaluated at a community hospital where biopsy and MRI were said to show a hemangioma. The child was unsuccessfully treated with propranolol. She then was referred to pediatric surgery at our institution which recognized the lesion as a vascular malformation and referred her to pediatric hematology oncology and vascular interventional radiology. Although mislabeling can result in mismanagement, the risk of that is probably low given that treatment is usually deferred to tertiary care centers.

The ISSVA terminology is based on objective clinical[1], imaging[6–8], and pathologic criteria[9,10] which should facilitate labeling. It is usually easy to distinguish infantile hemangiomas (IH) from other vascular tumors and from vascular malformations based on their natural history. IH develop days to weeks after birth, proliferate for 6–12 months, and then involute. On the other hand, vascular malformations are present at birth (though they might not be appreciated early in life), grow with the individual, and do not involute. Vascular malformations can occur in the context of overgrowth syndromes which is not typical of vascular tumors[1,2].

On color doppler US, characteristics of hemangiomas vary depending on time at evaluation; during their proliferative phase, a highly vascular mass with both arterial and venous waveforms will be seen. As these lesions involute, they become less vascular. MRI features of hemangiomas also change over time. Initially these mass lesions will be T2 hyperintense and demonstrate avid enhancement with large draining veins. With involution, all that will be seen is amorphous residual soft tissue. Depending on the location of a vascular malformation, US can be diagnostic. LMs will typically show a multi-loculated anechoic or hypoechoic structure. AVMs may exhibit a nidus and will demonstrate both arterial and venous waveforms. VMs will classically show a compressible tangle of vessels with a low flow venous waveform. Flow characteristics are more easily discerned on MRI with magnetic resonance arteriography (MRA), particularly with the increasing use of time-resolved imaging which allows angiographic imaging in both the arterial and venous phases using a single contrast bolus. VMs will show gradual filling of engorged vascular spaces whereas an AVM will show the feeding artery and an early draining vein. On MRI, LMs will show enhancement of septations but the dilated lymphatic channels will not enhance[6–8]. Recommendations for standardizing imaging evaluations of vascular anomalies should be forthcoming from the Vascular Anomalies Special Interest Group of the American Society of Pediatric Hematology Oncology (I. Iacobus MD, personal communication).

In instances in which a diagnosis cannot be made by history or physical examination, pathology should be able to distinguish glucose transporter type 1 (GLUT-1) positive IHs

from congenital hemangiomas[9]. Other special stains help define vascular malformations, such as CD31 for endothelial cells, prospero-related homeobox (Prox-1), podoplanin or D2-40, and lymphatic vessel endothelial hyaluron receptor 1 (LYVE-1) for lymphatic endothelium, and CD61, which stains platelets trapped in Kaposiform hemangioendotheliomas[10,11]. Our experience enforces the need for these diagnostic criteria to have wider dissemination.

This report has several limitations. We used ICD-9 codes to identify potential patients for this study, therefore we may have missed subjects due to miscoding of diagnoses. We did include a comprehensive list of ICD-9 codes, including both broad and specific diagnoses, in order to minimize missed patients. This study does not reflect comfort with labeling the majority of hemangiomas. These usually do not require imaging or pathology evaluation, and therefore were not a part of this series. Dermatologists at our institution, who have had a longstanding leading role in managing our vascular tumors, and whose medical societies have adopted consensus statements[12], most certainly are attuned to what is and what is not a hemangioma. However, our results are likely to reflect those of other modest-sized vascular anomalies programs. An attempt at more comprehensive management of patients at our institution is fairly recent, and there has been a steep learning curve. In that regard, we are encouraged by what, even in this small series, appears to be improved concordance over time, which we attribute to improved institutional emphasis on education and multidisciplinary patient care conferences. Nonetheless, experience for different disciplines is likely to remain biased. The majority of patients at our institution with hemangiomas or malformations are seen by 6 divisions (vascular interventional radiology, pediatric dermatology, pediatric hematology oncology, otolaryngology, general and plastic surgery). Other divisions each have seen relatively fewer patients, due to referrals which usually are anatomically driven. As we expand our multidisciplinary approach and draw in more divisions to see or hear about each patient, we can anticipate improved concordance. Although we did not see major effects on treatment decisions, this is of more than academic interest and has implications for educating referring physicians and families, for research, and possibly for billing and insurance. Families and practitioners who understand a lesion to be a “hemangioma” will have different expectations than they would have if the lesion is thought to be a vascular malformation. As our understanding of the biology and genetics of vascular malformations and tumors continue to grow[13], it is likely that it will become more essential to accurately label anomalies in order to provide the best and most targeted therapy.

We conclude that an understanding of vascular anomalies as tumors or malformations is not uniform in the community and even in a center with an interest in managing these disorders. Ongoing education will be needed to promote consensus terminology.

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Abbreviations key

AVM	Arteriovenous Malformation
CM	Capillary Malformation
CNS	Central Nervous System
CT	Computed Tomography
IH	Infantile Hemangioma
ISSVA	International Society for the Study of Vascular Anomalies
LM	Lymphatic Malformation
MRA	Magnetic Resonance Arteriogram
MRI	Magnetic Resonance Imaging
NCTracs	North Carolina Translational and Clinical Sciences
UNC	University of North Carolina at Chapel Hill
US	Ultrasound
VM	Venous Malformation
GLUT-1	Glucose transporter protein type-1
LYVE-1	Lymphatic vessel endothelial hyaluronan receptor-1
Prox-1	Prospero-related homeobox-1

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Table 1

Vascular Anomalies Classification

VASCULAR ANOMALIES				
Vascular Tumors			**Vascular Malformations**	
Benign	**Locally Aggressive**	**Malignant**	**Simple**	**Combined**
Infantile Hemangioma	Kaposiform hemangioendothelioma	Angiosarcoma	Capillary Malformation (C)	CVM, CLM
Congenital Hemangioma	Retiform hemangioendothelioma	Epitheloid hemangioendothelioma	Lymphatic Malformation (LM)	LVM, CLVM
Tufted Hemangioma	PILA, Dabska tumor		Venous Malformation (VM)	CAVM
Spindle-cell Hemangioma	Composite hemanigoendothioma		Arteriovenous Malformation (AVM)	CLAVM
Epithelioid Hemangioma	Kaposi Sarcoma		Arteriovenous Fistula	
Pyogenic Granuloma				

* ISSVA Classification of Vascular Anomalies ©2014 International Society for the Study of Vascular Anomalies Available at “issva.org/classification” (Accessed 3/20/2017)

Table 2

Clinical, Imaging, and Pathology Diagnosis by Discipline*

Diagnosis	Clinician 1: (n=35)	Clinician 2: (n=10)	Follow-up Diagnosis Clinician 1: (n=35)	Radiology: (n=35)	Pathology: (n=35)
LM	3	2	5	7	6
VM	2	0	4	3	4
AVM	2	1	8	3	9
VLM	3	1	5	6	3
Vascular Malformation	4	1	6	4	5
Hemangioma	3	2	2	5	2
Lymphangioma	4	0	5	1	3
Lymphangioma/Hemangioma	0	0	0	0	1
Mass	11	2	0	4	0
Cystic hygroma	1	1	0	1	1
VLM or VM	1	0	0	1	0
AV Fistula	1	0	0	0	0
Arteriovenous Hemangioma	0	0	0	0	1

* Number of patients assigned each diagnosis by each subspecialty