Original Article

Morphological Spectrum Of Vascular Neoplasms: A Histopathological Study In A Tertiary Care Center In South India

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Abstract

Background

Vascular neoplasms can be benign asymptomatic, locally aggressive, or highly malignant. It is important to subclassify them as it strongly influences the treatment and prognosis. However, only a few case series are published now. Hence in this study, we aim to classify vascular neoplasms into various categories and to find their relationship with age, sex, and location.

Methods

A retrospective analysis of vascular neoplasms from 2013-2018 in the department of pathology at Amrita Institute of Medical Sciences (AIMS), Kochi was done.

Results

A total of 221 vascular neoplasms were identified and were subclassified into benign-186(84.2%), intermediate-4(1.8%), and malignant-31(14%) according to World Health Organization (WHO) classification. The majority of the benign tumors were various types of hemangiomas-153(82.2%) and were common in young adult females. The commonest site of occurrence was head and neck, followed by soft tissue. The majority of malignant neoplasms were angiosarcomas-26(84%) and were more common in elderly females. Skin and soft tissue, followed by breast were the frequently involved sites. The second malignant neoplasm was epithelioid hemangioendothelioma-5(16%) which was common in the head and neck. Other rare types of hemangioendothelioma were included in the intermediate category.

Conclusion

The commonest benign vascular tumor is hemangioma, which occurs mostly in adult females in the head and neck region. The commonest malignant vascular tumor is angiosarcoma which occurs in elderly females in the skin and soft tissue and has a poor prognosis

Keywords:

Vascular neoplasm, Hemangioma, Angiosarcoma, Hemangioendothelioma

Introduction

Vascular neoplasms include tumors arising from blood vessels. They have a broad variety of morphological appearances and

clinical behavior. They constitute a spectrum from benign hemangiomas, intermediate lesions which are locally aggressive to highly malignant angiosarcoma.

Classification of vascular neoplasm is difficult because of the grey zone between benign and malignant lesions. The vascular tumors of the intermediate category refer to neoplasms that have very low but definite metastatic potential. [1,2] There are so many similarities between clinical, radiological, and histological patterns of benign, malignant, and nonmalignant vascular lesions. So histopathology and supportive investigation like immunohistochemistry (IHC) and molecular study are essential in many cases.[3]

Among the vascular tumors, angiosarcoma is a highly aggressive malignant vascular neoplasm, exhibiting anastomosing vascular spaces lined by atypical endothelial cells, occurring in elderly men with a predilec¬tion for the scalp.[4] Kaposi sarcoma is a low-grade malignant vascular neoplasm associated with the HHV8 virus and shows slit-like vascular channels lined by spindled endothelial cells with extravasation of RBCs.[5] Epithelioid haemangioendothelioma (EHE) is a low-grade malignant vascular tumor with cells showing intracytoplasmic lumina and is seen in the background of myxo hyaline stro¬ma.[6] Retiform haemangioendothelioma (RHE), which is included in intermediate vascular neoplasm, displays a reti¬form pattern of blood vessels lined by hobnail endothelial cells.[7] Kaposiform haemangioendothelioma (KHE) is a locally aggressive vascular tumor, that displays nodules and sheets of spindled endothelial cells arranged in a slit-like vascular channel and is associated with Kasabach-Merritt phenomenon (KMP).[8] Pseudomyogenic haemangioendothelioma (PHE) is an intermediate vascular tumor with locally aggressive behavior and rarely metastasis.[9] Epithelioid haemangio¬ma (EH) is a benign vascular tumor with a predilection for the head and neck region, composed of well-formed, capillary-sized vessels lined by plump, epithelioid endothelial cells.[10] Papillary intralymphatic angioendothelioma (PILA, also known as Dabska tumor) is composed of hobnail-like endothelial cells exhibiting papillary hyperplasia and protruding into vascular lumens like glomeruloid formation.[11] A rare and new entity anastomosing haemangioma is a benign tumor, composed of monolayer endothelial cells with protuberant nuclei arranged in thin-walled anastomosing vessels.[12]

Endothelial cell markers such as CD31, CD34, FLI-1, and ERG are positive in the majority of vascular tumors except that PHE is negative for CD34.[13] Specific molecular findings are known in several vascular tumors. Recurrent fusion genes involving the FOS or FOSB gene are identified in about half of the cases of epithelioid haemangioma.[14,15] SERPINE-1-FOSB or ACTB-FOSB fusions are often seen in PHE. [16, 17] EHE harbors a t(1;3) (p36;q23-q25) resulting in a WWTR1-CAMTA1 fusion in more than 90% of cases. [18,19] YAP1-TFE3 fusion in a subset of cases characterizes EHE with distinct morphologic features. [20]

It is important to subclassify vascular neoplasm, as it strongly influences the treatment and prognosis. The present study includes the vascular tumors classified as per the recent edition of the classification of vascular tumors proposed by WHO. It is an endeavor to classify vascular tumors into benign, intermediate, and malignant categories based on morphology and immunohistochemistry.

Objectives: To classify the vascular neoplasms into various categories and to find their demographic profile and site predilection.

Materials and Methods

Study type: Retrospective descriptive study of vascular neoplasms diagnosed at the Department of Pathology at AIMS, Kochi over 5 years (January 2013- January 2018).

Inclusion Criteria: All patients with vascular neoplasms as per the WHO classification.

Medical records of these patients were reviewed and their demographic characteristics (age, sex); clinical history (presenting symptoms, location, size, treatment received, and follow-up); radiological findings; histopathological features - type, subtype, Ki 67 Index and Immunohistochemistry (IHC) markers were tabulated and analyzed for the results. Recent WHO guidelines were used for the sub-classification of tumors.

A detailed macroscopic examination was carried out. Formalin-fixed paraffin-embedded representative tissue sections were stained with hematoxylin and eosin for histopathological examination.

After a review of cases, a panel of further IHC studies (CD31, CD34, ERG, Ki67) was done on paraffin-embedded tissue sections. Sections were cut at 4-μm thickness. Immunostaining was performed by the recommended protocol of the HRP/DAB IHC detection kit. This protocol includes deparaffinization and hydration of tissue, unmasking of antigens by pretreatment solution, peroxide block, protein block, incubation of slides with primary antibody, addition of polymer HRP antibody, addition of DAB substrate solution, counterstaining with hematoxylin, dehydration of tissue and mounting.

All standard protocols were followed for the diagnosis and treatment. Approval for the present study was obtained from the Institutional Review Board and ethical committee.

Statistical Analysis: The percentage distribution of all tumors, their subtypes, and site predilection was assessed.

Results

A total of 221 cases of vascular neoplasms were identified during the study period of 5 years (2013-2018). These tumors were further sub-classified as per recent WHO guidelines. The majority of the tumors were benign 186 (84.2%) followed by malignant 31 (14%) and 4 (1.8%) were of intermediate type.

Among all the 186 benign tumors, hemangiomas 153 (82.2%) were the most common tumors followed by lymphangioma 33 (17.8%). Hemangiomas were more common among females (F: M-1.2:1). Majority of them (81/153, 53%) occurred in young and middle-aged patients. The commonest age group affected was 30-60 years. Hemangiomas were further sub-classified based on their morphological characteristics as shown in Table 1 and Figure 1.

Table 1 Sub classification of Hemangiomas.

Hemangioma Subtypes (n=153)	N (%)
Hemangioma (Broad Category)	51 (33.3)
Capillary	48 (31.3)
Cavernous	17 (11.1)
Venous	12 (7.8)
Sclerosing	6 (4)
Intramuscular	8 (5.3)
Verrucous	3 (2)
Epithelioid	3 (2)
Arteriovenous	3 (2)
Hobnail	1 (0.6)
Sinusoidal	1 (0.6)

Overall skin and soft tissue were the most common site of occurrence of hemangiomas (103/153, 67.2%). Skin and soft tissue of the head and neck region were most commonly affected 65 (63%), followed by extremities 28 (27%) and trunk 10 (10%). Central nervous system-brain and spinal cord was the next most common site of occurrence 28 (18%). The liver, lungs, lymph nodes, and bones were the rarely affected organs.

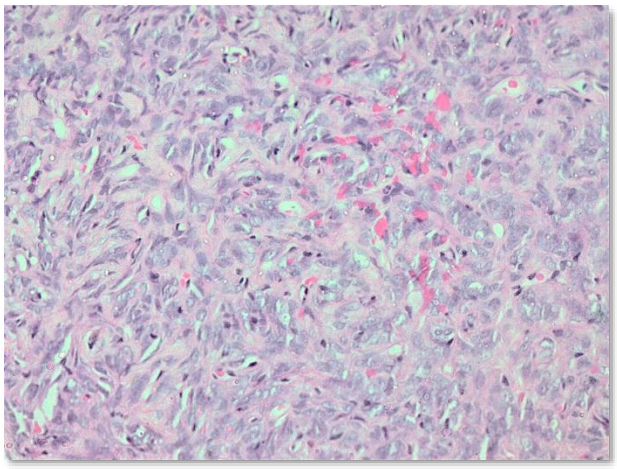

Figure 1: Epithelioid hemangioma, Proliferating blood vessels lined by epithelioid cells, Hematoxylin and eosin (HE), X200

Lymphangiomas were more common among males (M: F-1.2:1). Majority of them (21/33, 64%) occurred in young patients less than 30 years of age. Overall skin and soft tissue were the most common site of occurrence of lymphangiomas (26/33, 79%). Skin and soft tissue of the head and neck region were most commonly affected 18 (69%), followed by trunk 6 (23%) and extremities 2 (8%). Of the 7 other lymphangiomas, 3 were noted in the mesentery and 1 each in the liver, spleen, lung, and breast.

Intermediate tumors did not show any age or gender predilection. All of them occurred in the skin and soft tissue. All underwent wide local excision and no recurrence was noted. Their distribution and morphology are depicted in Table 2 and Figure 2.

Table 2 Distribution of Intermediate tumors

Type	Location	Number (n)
Spindle cell type (Spindle cell Hemangioma)	Tongue	1
Kaposiform type	Gluteal	1
	Retro aural	1
Retiform type	Face	1

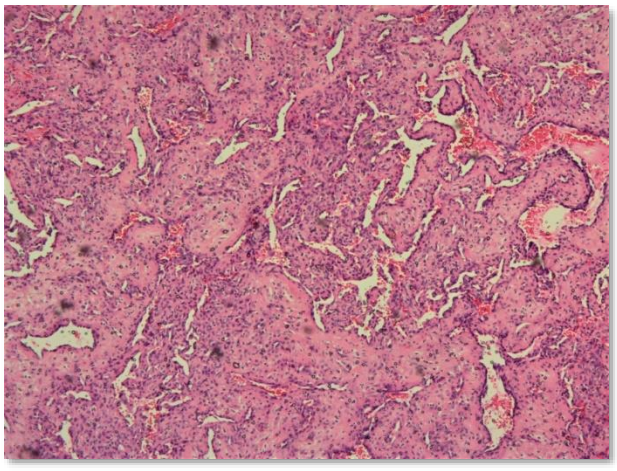

Figure 2 Retiform hemangioendothelioma Arborizing vascular channels, Hematoxylin and eosin (HE), X 100

Angiosarcoma was the most common 26/31 (84%) malignant neoplasm. The majority 18/26 (69%) of them occurred in elderly females. Five of them were post-radiation therapy angiosarcomas (3 - Breast; 1- Upper limb; 1 - Lung). Skin and soft tissue was the most commonly affected site (18/26, 69%), followed by bone and liver – 3(11.5%) each and 1(4%) each in heart and lung. Skin and soft tissue of the head and neck region were most commonly affected (7/18, 39%), followed by breast – 6 (33%) and extremities 5 (28%). Histomorphology and IHC of angiosarcoma are depicted in figure 3, figure 4, figure 5.

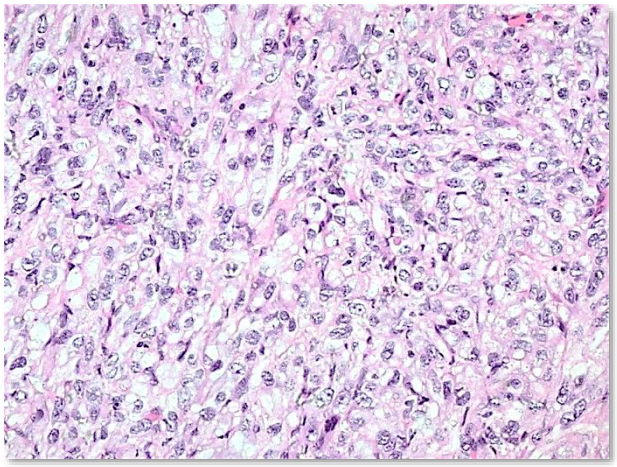

Figure 3 Epithelioid angiosarcoma The solid growth pattern of cells with mitoses, Hematoxylin, and eosin (HE), X200

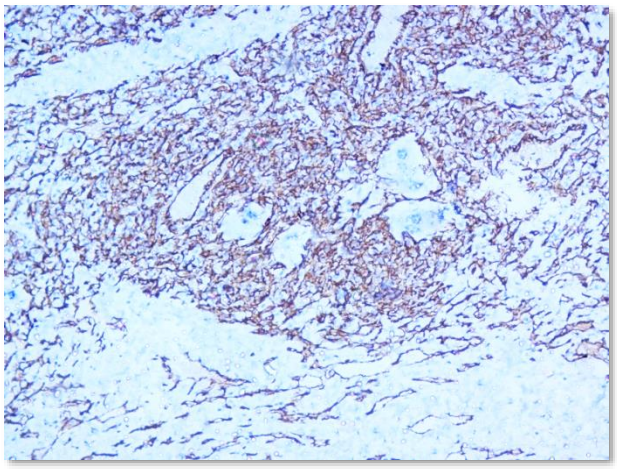

Figure 4 CD31 Immunohistochemistry (Angiosarcoma) Tumour cells showing diffuse strong cytoplasmic and membranous positivity for CD31, X 200

Among the total 26 angiosarcomas 16 (61.5%), developed progressive disease after resection and chemoradiotherapy (CTRT). 13 recurred at a different site and 3 had local recurrence.

Time of recurrence varied from 2 months to 5 years. 6/16 (37.5%) expired with a median survival of ~ 6 months after diagnosis. Three were doing well post-resection (2 months - 4 years) and 7 lost to follow-up. Patients with progressive disease had significantly larger tumor sizes and a high Ki 67 index.

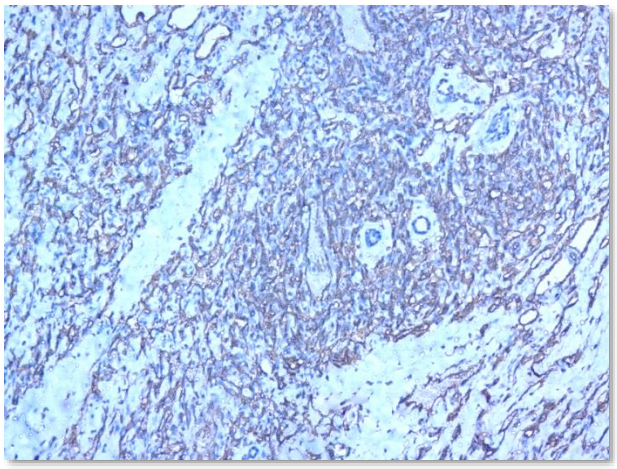

Figure 5 CD34 Immunohistochemistry (Angiosarcoma) Tumour cells showing diffuse strong cytoplasmic and membranous positivity for CD34, X200

Epithelioid hemangioendothelioma was the second most common malignant neoplasm 5(16%). Most cases occurred in elderly males and were in the brain and head-neck region. Among them, 2 lost to follow-up, 2 were doing fine for ~1-year post resection and CTRT and 1 patient expired who developed a local recurrence of tumor at the nape of neck 1 year after treatment which was of ~8cm size and had high Ki 67 Index - 60%. (Figure 6).

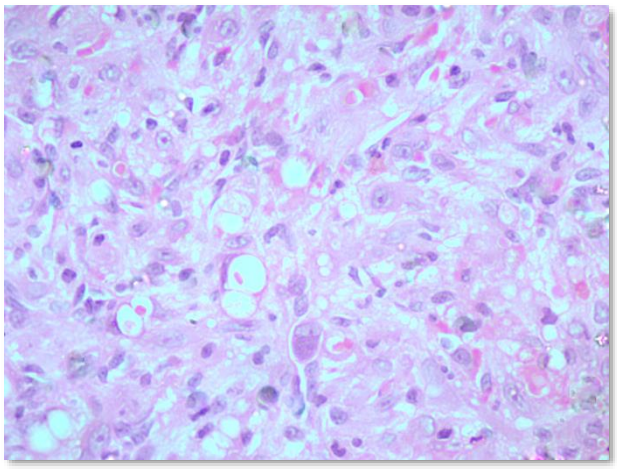

Figure 6 Epithelioid hemangioendothelioma Formation of intracytoplasmic lumina with luminal RBCs, Hematoxylin and eosin (HE), X200

Discussion

As an increasing number of vascular lesions with histologically distinct characteristics have been recognized, their sub-classification has become important to determine their behavior so that appropriate therapies may be studied and implemented in affected patients.

In the present study, we used the recent classification of vascular tumors proposed by WHO. [4] We have studied a total of 221 cases of vascular neoplasms over 5 years and noted a progressive increase in their incidence. The majority of the tumors were

benign 186 (84.2%) followed by malignant 31 (14%) and 4 (1.8%) were of intermediate type.

Among all the benign tumors, hemangiomas were the most common tumors (82.2%) followed by lymphangioma (17.8%). Hemangiomas were more common among females (F: M - 1.2:1). Majority of them occurred in young and middle-aged patients (30-60 years). A capillary subtype of hemangioma was the most common subtype (31.3%).

Most hemangiomas occurred in the skin and soft tissue of - the head and neck region (63%), followed by extremities (27%) and trunk (10%). Central nervous system - brain and spinal cord was the next most common site of occurrence. The liver, lungs, lymph nodes, and bones were the rarely affected organs. This data is in concordance with the literature. [1,21, 22]

Similarly, another study of 100 cases (Benign-97, Intermediate-2, and Malignant-1) by Dharmesh et al. [23] also reported capillary hemangioma as the most common vascular neoplasm (37%). In their study, head and neck was the most common site of occurrence (67%), followed by extremities (29%) and trunk (4%). They noted that these tumors occurred more commonly in females at younger ages, but as age increased proportion of male patients increased. This study did not provide any follow-up and prognosis data. Another study of 98 cases (Benign-90%, Intermediate-4%, and Malignant-6%) by Kalyani et al. [24] reported granuloma pyogenicum (48%) as the most common benign lesion and capillary hemangioma occurred in only (7%) of cases. The head and neck were the most common site of occurrence of vascular lesions (48%), followed by the trunk (27%) and extremities (24%). The incidence of benign tumors was higher in females, and malignant tumors showed equal gender distribution. This study also lacks follow-up and prognosis data. Inflammatory lesions were not included in the benign category in our study.

The present study also included 4 cases of Intermediate tumors, which did not show any age or gender predilection. All of them occurred in the skin and soft tissue. Similar findings were observed in other studies. [23,24] All 4 patients in our study underwent wide local excision and no recurrence was noted with follow-up, however, other studies have not mentioned their course.

In our study, Angiosarcoma was the most common 26/31 (84%) malignant neoplasm. The majority (69%) of them occurred in elderly females. 5 of them were post-radiation therapy angiosarcomas. Skin and soft tissue were the most affected site (69%), followed by bone and liver (11.5%), and rare in heart and lung(4%). Most angiosarcomas (61.5%), developed progressive disease after resection and CTRT. 13 recurred at different sites and 3 had local recurrence. Time of recurrence varied from 2 months - 5 years. Six of 16 (37.5%) expired with a median survival of ~ 6 months after diagnosis. 3 were doing well post-resection (2 months - 4 years) and 7 lost to follow up. Old age, retroperitoneal location, large size, and high Ki-67 values are predictors of poor prognosis.[3] In our study, patients with progressive disease had significantly larger tumor sizes (5-10cm) and high Ki 67 index (30%-60%).

Epithelioid hemangioendothelioma was the second most common malignant neoplasm 5/31 (16%) in our study. It occurred mostly in elderly males and the brain and head-neck region. One of the studies has identified size >3 cm, >3 mitoses/50 HPF as poor prognostic factors and mentioned 5-year disease-specific survival of 59%.[25] In our study, 2 patients lost to follow-up, 2 were doing fine for ~1-year post resection and adjuvant CTRT and 1 patient expired who developed local recurrence of tumor at the nape of neck 1 year after treatment which was of ~8cm size and had high Ki 67 Index - 60%.

Various molecular markers have been identified for vascular tumors with epithelioid morphology. Common gene fusion in epithelioid hemangioendothelioma is WWTR1- CAMTA1. The presence of TFE3 expression and or TFE3 gene rearrangement by FISH is identified in epithelioid hemangioendothelioma in the head and neck region and occurred in young adults of less than 35 years. Epithelioid hemangiomas are rare, carrying TEK (TIE2) mutations, particularly lacking CAMTA1, WWTR1, and TFE3

gene rearrangements. High-level MYC amplification on 8q24 is the hallmark of radiation-induced and lymphedema-associated angiosarcoma. FLT4 co-amplification on 5q35 (encodes VEGFR3) is noted in Secondary angiosarcoma. 10% of angiosarcomas show activating mutation in the KDR gene (encodes VEGFR2). [26,27] Further studies are required to assess the molecular genetics of our cases.

Conclusion

Accurate categorization of vascular tumors is validated and needs to be emphasized as it influences clinical outcomes. Most of the vascular neoplasms are benign and occur most commonly in young females, mainly in the skin and soft tissue. Intermediate tumors can be managed only with wide local excision, while malignant tumors usually need surgical excision and adjuvant CTRT. Angiosarcoma is the most aggressive vascular tumor and has a poor prognosis with a median survival of ~ 6 months. Grading of this tumor has no relevance to clinical outcomes.

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