International Journal of TROPICAL DISEASE & Health

25(1): 1-8, 2017; Article no.IJTDH.34925
ISSN: 2278–1005, NLM ID: 101632866

A Five Year Retrospective Study of Vascular Tumours at Federal Medical Center Makurdi and Benue State University Teaching Hospital

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Authors' contributions

This work was carried out in collaboration between all authors. Author PDA designed the study, wrote the proposal and the first draft of the manuscript. Authors RAV and EA collated the data. All authors were involved in the diagnosis and management of the patients at various stages, literature searches and analyses of the study. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2017/34925
Editor(s):
(1) Romulo Dias Novaes, Department of Structural Biology, Federal University of Alfenas, Institute of Biomedical Sciences, Ifenas, Minas Gerais, Brazil.
Reviewers:
(1) Michael J. Nathenson, Dana-Farber Cancer Institute, USA.
(2) Ramesh Parajuli, Chitwan Medical College, Nepal.
(3) Ihsan Yıldız, Suleyman Demirel University, Turkey.
Complete Peer review History: http://www.sciencedomain.org/review-history/20525

Original Research Article

Received 20th June 2017
Accepted 10th August 2017
Published 16th August 2017

ABSTRACT

Aim: To determine the prevalence of vascular tumours, and their morphology at Federal Medical Centre and Benue State University Teaching Hospital Makurdi.
Study Design: Retrospective study of vascular tumours at the two tertiary healthcare institutions.
Methodology: All the cases of vascular tumours seen, histopathologically diagnosed and managed between March 2012 and February 2017 at the two hospitals were studied. Data collected from the patient's files included age, sex, anatomical site, and the histopathological diagnosis.
Results: Fifty nine patients with vascular tumours that were histopathologically diagnosed during the 5 year period were studied. There were 23 (39%) males and 36 (61%) females giving a male

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female ratio of 1:1.6. The age group 21 – 30 years was mostly affected by various types of vascular tumours. Benign tumours were the commonest and occurred in 36 (61%) patients. Intermediate (locally aggressive/rarely metastasizing) tumours constituted 21 (35.6%) cases. Malignant tumours were 2 (3.4%) in numbers. Most of the tumours 36 (61%) occurred in the head and neck region.
Conclusion: Benign tumours are still the commonest vascular tumours. Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome (HIV/ AIDS) pandemic is increasing the number of cases and severity of Kaposi sarcoma, an intermediate rarely metastasizing vascular tumour. There is need for more health education and improved healthcare geared towards the prevention and treatment of the Kaposi disease.

Keywords: Angiosarcoma; classification; haemangioma; Kaposi sarcoma; thrombocytopenia.

1. INTRODUCTION

Vascular tumours are classified into benign, intermediate (locally aggressive/rarely metastasizing) and malignant [1-4]. Prototype of the benign tumours are haemangiomas, those of intermediate (locally aggressive/rarely metastasizing) are Kaposi sarcoma and malignant ones are angiosarcomas. Majority of the lesions are benign. The tumours arise from the endothelium of the blood vessels, lymphatic vessels and specialized perivascular cells comprising the glomus cells and pericytes.

Researches on vascular tumours have been done in other parts of the world and Nigeria and their prevalences documented. The characterization of the tumours has been difficult but as more is known about them, and new ones discovered, the classification will continue to be improved upon as well as the management. The recently reviewed "International Society for the Study of Vascular Anomalies (ISSVA)" classification in which vascular tumours are included is shown in Table 1.

The difference between the ISSVA and World Health Organization (WHO) classification of tumours of soft tissue and bone is that based on biological behaviour, the intermediate vascular tumours are subdivided into two distinct types, intermediate (locally aggressive) tumours whose

Table 1. International society for the study of vascular anomalies classification of vascular tumours (Approved at the 20th ISSVA Workshop, Melbourne, April 2014)

Benign vascular tumors
▪ Infantile hemangioma/hemangioma of infancy ▪ Congenital hemangioma: Rapidly involuting (RICH) Non-involuting (NICH) Partially involuting (PICH) ▪ Tufted angioma ▪ Spindle-cell hemangioma ▪ Epithelloid hemangioma ▪ Pyogenic granuloma (aka lobular capillary hemangioma) ▪ Others: Venous malformations/lymphatic venous malformation Lymphatic malformations, Reactive proliferative vascular lesions
Locally aggressive or borderline vascular tumors
▪ Kaposiform hemangioendothelioma, ▪ Retiform hemangioendothelioma, ▪ Papillary intralymphatic angioendothelioma (PILA), Dabska tumour ▪ Composite hemangioendothelioma ▪ Kaposi sarcoma ▪ Others
Malignant vascular tumors
▪ Angiosarcoma, ▪ Epithelloid hemangioendothelioma ▪ others.

prototype is kaposiform haemangioendothelioma and intermediate (rarely metastasizing) variety whose prototypes are retiform haemagioendothelioma papillary intralymphatic angioendothelioma, composite haemangioendothelioma and Kaposi sarcoma [4].

The behaviour of these tumours is characteristic. Intermediate locally aggressive tumours infiltrate the surrounding tissues, cause their local destruction and recur after surgical excision, but they do not metastasize. They therefore require wide excision with a margin of normal tissue to prevent recurrence. The intermediate rarely metastasizing tumours are locally aggressive, occasionally metastasize to distant sites like the lymph nodes or lungs. The potential to metastasize is low and less than 2%. The ISSVA classification lumped all these five together and called them locally aggressive (borderline) tumours.

1.1 Infantile Haemangiomas

They are not present at birth, but appear a few weeks later in infancy or early childhood [1,3,4]. They are the commonest tumours of infancy occurring in 4-10% of children. They are commoner in the head/neck region and in females. They may be focal, multifocal segmental or indeterminate. They appear as a patch on the skin which may be superficial, deep or mixed. Segmental lesions are the ones commonly associated with PHACE and LUMBAR syndrome. PHACE syndrome comprises posterior fossa abnormalities, hemangioma, arterial, cardiac and eye anomalies; while LUMBAR syndrome comprises lower body haemangioma, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal, arterial and renal anomalies. Histopathological examination of haemangioma shows proliferating endothelial cells and pericytes. Glucose transporter 1 [Glut-1], Lewis y antigen, FcrII receptor [FcyRII] and merosin immunohistochemical makers are elaborated by these endothelial cells and are detectable as compared to the normal arteries that do not elaborate them. Haemangioma natural history is enlargement over months and then gradual involution.

1.2 Congenital Haemangiomas

They are present at birth. Their natural history subdivides them into 3 types [1-4]. Rapidly involuting (RICH) type regress and disappear before one year of age, are associated with transient thrombocytopenia and consumption coagulopathy. Partially involuting (PICH) type regress partially. Non involuting (NICH) remains stable and dose not regress. Morphology shows capillary lobules with large extralobular arteries, veins and lymphatics. The endothelial cells do not elaborate glucose transporter.

1.3 Tufted Angiomas

They may be present as erythematous plaques/macules at birth and associated with hypertrichosis/hyperhidrosis and may regress spontaneously. Some appear later in childhood or early adulthood. Morphologically they are composed of small tufts of capillaries surrounded by slit like vessels scattered in a fibrous dermis and subcutaneous tissue [1]. Kaposiform haemangioendotheliomas resemble tufted angiomas and are thought to be a spectrum of each other and not separate diseases. Kaposiform haemangioendothelioma morphology is same as tufted angioma and they both elaborate lymphatic endothelial immune histochemical (IHC) markers podoplanin, prospero homeobox 1 [prox-1]. Both tumours exhibit kasabach-merritt phenomenon with severe thrombocytopenia and consumption coagulopathy with high mortality.

1.4 Vascular Malformations

These may be simple malformations, combined malformations, malformation of named major vessel or malformation associated with other anomalies. In simple malformation, it may be capillary as in port wine stain morphologically characterized by dilated capillaries or venules and associated with overgrowth of soft tissue or bone. Simple malformations may involve lymphatic channels which are dilated and lined by endothelia cells and may have microcysts, macrocysts or mixed. They involve the cervico-facial area, axilla, chest and abdominal viscera which could cause chylous effusions [1]. They can also involve the bone causing vanishing bone in Gorham – stout disease. Primary lymphoedema is a lymphatic malformation characterized by dysgenesis of lymphatic network and are genetic due to causal mutations. Venous malformations may be present at birth or appear later in life, are blue when present on the skin and caused by somatic mutations of Tie 2 gene so could be familial. Glomu venous malformations are venous malformation in which morphologically, rounded Glomus cells which are

modified smooth muscle cells are seen in the walls of the veins. They are caused by inactivating mutation in the glomulin gene.

Arteriovenous malformations are made up of malformed arteries, capillaries and veins having arteriovenous connections giving rise to shunting. They are characterized by a bright red appearance of the area involved, pulsatile, have a palpable bruit and cause cardiac failure. Combined vascular malformations can occur whereby two or more vascular malformations are in one lesion.

1.5 Spindle Cell Haemangioma

It clinically presents as painful red brown lesions of extremities and associated with maffucci syndrome (cutaneous spindle cell haemangioma occurring with contilagenous tumours) morphologically, are seen cavernous blood spaces inter-spaced with proliferation of spindle cells [5]. Treatment is surgical excision.

1.6 Epitheliod Haemangioma

It can occur on the skin and in bone with mixed lytic and sclerotic lesions which are painful, and thought to be a reactive lesion following trauma. Morphology shows small capillaries with plump endothelial cells and abundant cytoplasm [5]. Treatment is excision, sclerotherapy and curettage.

1.7 Pyogenic Granuloma

It is a benign reactive lesion affecting all ages and is a type of capillary haemangioma. Lesions are lobulated vascular nodules that grow rapidly and bleed easily. They may be solitary, or multiple and occur on the skin, gingiva or oral mucosa [1,3]. Morphologically seen as capillaries and venules with plump endothelial cells organized into lobules by fibromyxoid stroma. They may spontaneously regress. Treatment is excision, laser photocoagulation and curettage. Granuloma gravidarum is a pyogenic granuloma occurring in the gingiva of pregnant women [3].

1.8 Intermediate (Locally Aggressive) Vascular Tumours

Prototype is kaposiform haemangioendothelioma. It is a locally aggressive tumour that occurs mostly in children but can occur in adults too. It is not related to HIV or Human herpes virus-8 (HHV-8). It is also known as "Kaposi-like infantile haemangioendothelioma." It occurs predominantly in the retoperitoneum but can occur in the skin particularly of the head and neck. It locally spreads to involve the lymph nodes and bone and may be complicated with kassabach-merritt syndrome characterized by consumption coagulopathy. Cutaneous lesions appear as plaques. Histopathological examination shows lobules separated by fibrous septa, spindle cells interspersed with capillaries and slit-like vascular lumens containing fragmented red blood cells [4]. Capillaries are lined by plump endothelial cells. The spindle cells are positive for CD34 and CD31, but negative for Von Willebrand (factor VIII-related) antigen. Prognosis is poor in infancy especially with Kassabach-Merritt syndrome from intra-abdominal sites. Complete excision can lead to cure.

1.9 Intermediate (Rarely Metastasizing) Vascular Tumour

The prototype is Kaposi sarcoma. Its associated with HHV-8 [3,4] Different forms of the disease exist and are classic, lymphadenopathic, transplant induced and AIDS-associated (epidemic) Kaposi. The classic Kaposi is a local disease, that is slow growing, does not metastasize and is not associated with HIV [3].

The AIDS-associated Kaposi however is found in a 3rd of AIDS patients, very aggressive, rapidly progresses, metastasizes to lymph nodes and other organs and fatalities result from opportunistic infections [3]. Morphologically, dilated disorganised vascular channels are seen surrounded by sheets of plump proliferating spindle cells in the dermis and subcutaneous tissue. Slit-like spaces contain extravasated red blood cells. Immunohistochemistry shows spindle cells positive for CD34 and CD31 but factor VIII negative. Endothelial cells are positive for vascular markers. A nuclear transcription factor FLI1 is elaborated in Kaposi sarcoma as well as in all vascular tumours and is a marker of identification. Prognosis depends on the type of Kaposi sarcoma, classical being best and AIDS-associated being worst. Treatment is cytotoxic chemotherapy. Antiretroviral therapy is combined with cytotoxic chemotherapy in AIDS-associated Kaposi. Only solitary lesions causing functional impairment, for example on the palms or soles of the feet are surgically excised. Radiotherapy can also be given.

1.10 Angiosarcoma

It is a rare malignant neoplasm of the blood vessels [1,4]. Majority arise from the skin. Cutaneous angiosarcomas are sharply demarcated painless red nodules, usually involving the head and neck region, males being equally affected as the females. Central necrosis and haemorrhages occur when the masses enlarge and become fleshy [3]. They may develop from radiotherapy bed especially following breast carcinoma excision and adjuvant radiotherapy. They also arise from chronic lymphoedema either of primary origin or following radical mastectomy with axillary lymph node resection in which case the tumour is arising from the endothelium of the lymphatic vessels. Deep sited soft tissue angiosarcoma may arise from muscle and retroperitoneum in only 25% of the population. Hepatic angiosarcomas are induced by chemical carcinogens in agricultural workers exposed to arsenic containing pesticides; and plastic industry workers exposed to polyvinyl chloride with a long latent period spanning over several years.

The tumour affects the elderly 70 years and above and is rare in children [4]. They are not associated with HHV-8. Two distinct types exist, the low grade and highly malignant angiosarcoma. The low grade type consists of large rounded epithelioid endothelial cells with large nuclei and abundant eosinophilic cytoplasm, arranged in sheets, nests or rudimentary vascular channels. They express cytokeratin and other endothelial markers and resemble carcinomas. The vascular channels may be lined by a single neoplastic endothelium resembling haemangioma while in other areas the neoplastic endothelium forms intraluminal buds or projections. Extensive haemorrhages may occur and resemble a chronic haematoma. The highly malignant angiosarcoma shows poorly differentiated spindle cells of high nuclear grade with abundant mitotic figures. Vascular channels are difficult to identify but ultra-structure shows pericytes [1,4]. The cells elaborate vascular antigens including Von Willebrand factor, CD31 and CD34. CD31 is the most highly sensitive and moderately specific marker which is positive in 90% of all grades of angiosarcomas. Type IV collagen as well as actin in pericytes is identified around the vascular channels.

Prognosis of the highly malignant aggressive angiosarcoma is very poor. Recurrence occurs in 20% after surgery, and 50% with metastatic disease to lymph nodes and other parts of the body die within the first year of diagnosis. Poor outcomes are seen in the older age group, retroperitoneal location, large size tumours and high Ki-67 values.

1.11 Epitheliod Haemangioendothelioma

It occurs in adults and involves medium sized and large veins. Tumour cells are cuboidal and resemble epithelial cells [3]. Vascular channels are not well defined. 40% of the tumours recur after excision, 30% metastasize and mortality is up to 15%.

Vascular anomalies present in varying forms with associated complexes like PHACE syndrome in infantile hemangioma and thrombocytopenia/kasabach-merritt syndrome in tufted angioma and kaposiform hemangioendothelioma with severe sometimes fatal bleeding from coagulopathy. Lesions that were not well understood are being characterized based on new findings and added appropriately to the classification. The diagnosis and treatment of vascular tumors varies. History, physical examination, radiologic investigations comprising ultra sound scan and where in doubt computerized tomography (CT) diagnose the vascular tumours. Magnetic resonance imaging and contrast enhanced imaging are used for diagnosis of vascular malformations [6,7]. Diagnosis is confirmed with histopathological examination.

The study is aimed at reviewing the histopathological types, site, age, sex, behavior of vascular tumors and their management in the two tertiary hospitals.

2. MATERIALS AND METHODS

This was a retrospective study of all the cases of vascular tumours seen, histopathologically diagnosed and managed between March 2012 and February 2017 at Federal Medical Centre and Benue State University Teaching Hospital. The data was extracted from the patient's files and included age, sex, anatomical site, and the histopathological diagnosis. The tumours were classified as benign, (borderline) intermediate (locally aggressive/rarely metastasizing) and malignant based on the WHO classification and International Society for the Study of Vascular Anomalies guidelines.

2.1 Data Analysis

Data was analyzed using simple ratios and means presented with tables. SPSS version 23.0 was the statistical tool used.

3. RESULTS

Total number of histopathology examinations done at the two hospitals during the study period was 5,548. Fifty nine patients were histopathologically diagnosed with vascular tumours out of this number. Vascular tumours thus represented 1.1% of all lesions. Vascular tumours prevalence among soft tissue tumours was 3.7%. There were 23 (39%) males and 36 (61%) females giving a male female ratio of 1:1:6 (Table 2).

Table 2. Gender and age group distribution of vascular tumours

Sex	Frequency	Percentage
Male	23	39.0
Female	36	61.0
Total	**59**	**100.0**
Age group	**Frequency**	**Percentage**
1 – 10	7	11.9
11 – 20	11	18.6
21 – 30	13	22.0
31 – 40	12	20.3
41 – 50	9	15.3
51 – 60	5	8.5
61 – 70	2	3.4
Total	**59**	**100.0**

The ages of the patients range from two months to sixty five years with mean age of 30.4 ± 16.1 years

The age distribution of the tumours showed that thirteen (22%) patients in the age range 21 – 30 years were affected by various types of vascular tumours.

Benign tumours were 36 (61.0%), borderline 21 (35.6%) and malignant 2 (3.4%). Based on the histopathological type of tumour, Kaposi sarcoma constituted 20 (33.9%) cases closely followed by haemangioma with 18 (30.5%) cases. The anatomical distribution of vascular tumours showed that 36 (61.0%) occurred in the head and neck region (Table 3).

4. DISCUSSION

Our study has shown that benign tumours were the commonest vascular tumours seen at Federal Medical Centre and Benue State University Teaching Hospital, and haemangioma ranked first among them. Wójcicki [7] in his study documented a similar finding with 87.7% occurrence of infantile haemangioma with lesions occurring in the liver and respiratory track that had to be diagnosed with CT and magnetic resonance imaging in some of the patients. Dubois [6] demonstrated haemangiomas as the commonest tumours occurring in children in his study. Kaposi sarcoma was the commonest intermediate (rarely metastasizing) tumour among the vascular tumours in our study. Of the 20 patients with Kaposi, eight (40%) were HIV positive. Total HIV load in the two hospitals during the study period was 2386 patients. Kaposi sarcoma prevalence in HIV patients in the two hospitals was 0.3%. Several studies have documented an increase of new, unusual presentations of Kaposi sarcoma which hitherto was endemic and not aggressive [8-11]. But with the HIV pandemic, unusual aggressive forms of Kaposi sarcoma have emerged associated with rapid mortality and the number of cases have been increasing. In our study too these unusual presentations were noticed in the AIDS-associated Kaposi sarcoma patients usually with florid generalized lesions worse in the lower

Table 3. Type of tumours and anatomical location

Histopathological type	Head/Neck	Trunk	Limb	Total	Percentage
Benign					
Haemangioma	13	4	1	18	30.5
Pyogenic Granuloma	16	-	-	16	27.1
Lymphangiomas	2	-	-	2	3.4
Intermediate (rarely metastasizing)					
Kaposi Sarcoma	3	1	16	20	33.9
Kaposiform haemangioendothelioma	-	-	1	1	1.7
Malignant					
Angiosarcoma	2	-	-	2	3.4
Total	**36**	**5**	**18**	**59**	**100**

limbs, and this have been collaborated by Kagu in Maiduguri [12]. Constitutional symptoms of weight loss, respiratory distress and GIT symptoms were seen in our patients and this has also been documented by Bayley [8]. We did not have any child with Kaposi sarcoma in our study, and National Cancer Institute has collaborated this statistic that its rare in children [5]. This is a positive development and in addition, is probably due to the prevention of mother to child transmission of HIV which the federal government of Nigeria through the federal ministry of health is doing ensuring that all pregnant mothers compulsorily have HIV screening at the ante-natal clinic and if positive are commenced on free antiretroviral therapy. Ahmed [11] and co-workers have documented children with HIV induced Kaposi sarcoma in Nigeria. We had only one mortality (1.7%) from vascular tumour in our study and it was due to Kaposi sarcoma. Some patients were lost to follow-up. Ahmed and Bayley [8,11] have documented very high mortalities in their studies. Ahmed had a mortality of five out of fourteen (35.7%) patients while Bayley had a mortality of eight out of thirteen (61.5%) patients in Zambia. Albores-Saavedra [13] and co-workers study of cutaneous angiosarcoma documented a survival rate of 71.7% in patients younger than 50 years after 10 years while those above 50 only 36.8%. They found worse prognosis of 13.8% in patients with head/neck lesions and 6.2% in those with distant metastasis after 10 years.

Our study demonstrated that vascular tumours predominantly affected the head/neck region. However a shift was noticed whereby Kaposi lesions were seen predominantly in the lower limbs. Dubois, Antonescu and Obaseki [6,14,15] have also documented head and neck lesions as the commonest sites for vascular tumours. Dubois documented a prevalence of 60% of vascular tumours lesions in the head/neck and Obaseki 39.5% at Benin in their studies.

In our study malignant lesions were not common only two cases of angiosarcoma were seen. But we had no facilities to identify the markers like CD_{31}, Fli_1, ERG and epithelialantigens like EMA, Cam 5.2 and AE $^1/_3$ that are usually elaborated from these tumors to differentiate them from carcinomas. The history, physical examination and the histopathological examinations could to a large extent diagnose the patients type of vascular tumour.

5. CONCLUSION

Benign tumours are still the commonest vascular tumours. HIV/AIDS pandemic is increasing the number of cases and severity of Kaposi sarcoma an intermediate (rarely metastasizing) vascular tumour. There is need for education of the public and improvement on healthcare services for the prevention and treatment of Kaposi sarcoma.

6. LIMITATIONS OF STUDY

Many lesions in the borderline tumours were not seen during the study period. This may be due to poor documentation in the medical records and may affect true prevalence.

CONSENT

It is not applicable.

ETHICAL APROVAL

Ethical clearance to carry out the research was given by the hospital ethical committees of the Federal Medical Center Makurdi and Benue State University Teaching Hospital.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/20525