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Original Research Article.

Retrospective, Descriptive Study of Incidence of Hemangioblastoma Among Vascular Lesions in Tertiary Care Center, SMS Medical College and Hospital, Jaipur, Rajasthan

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ABSTRACT

Background: Hemangioblastoma is rare, benign slow growing, vascular neoplasm and histologically characterized by neoplastic stromal cells and abundant small vessels. According to the World Health Organization classification of tumors of the nervous system, hemangioblastomas are classified as Grade I neoplasm. Hemangioblastoma arises either associated with von Hippel–Lindau (VHL) disease or more often as solitary sporadic lesions. They account for 1–3% of primary central nervous system (CNS) tumors. Typically occurring in the cerebellum, spinal cord and brain stem. The occurrence of this tumor in other locations such as supratentorial compartment, optic nerve, ventricular system, peripheral nerves or soft tissues and other organs are extremely rare.

Aims: The aim was to study the prevalence and demographic analysis of hemangioblastoma.

Materials and Methods: A retrospective observational study of 10 years duration was carried out in the department of pathology in SMS Medical College, Jaipur, Rajasthan as tertiary referral center. We retrieved 66 cases of hemangioblastoma retrieved from the archives of department which was processed and diagnosed in the department. IHC applied when required. Data collected and analyzed.

Results: During the study, we reported total 66 cases of hemangioblastoma and percentage of hemangioblastoma was 4.08 % of total vascular lesions and 1.62 % of CNS neoplasm. Common age group were 21 – 40 years followed by 41 – 50 years. Male female ratio in our study was 1.64: 1, which indicate slight male preponderance. Common location of lesion was cerebellum (69.6 %), followed by spinal cord (16.6 %), brainstem (9 %), frontal lobe (3 %) and 1 at CP angle (1.5 %).

Conclusions: In our study, prevalence of hemangioblastoma was 4.08 of total vascular lesions and 1.62% out of CNS tumors, which is low as per literature. There was a male predominance with Male: Female ratio 1.64:1. Cerebellum was the most frequent site (69.6%). We did not find lesion at periphery other than CNS as published in other literatures, where hemangioblastomas were in differential and diagnosed by IHC marker which indicate key role of IHC to a correct pathological diagnosis.

Keywords: Central Nervous System Tumor, Hemangioblastoma, Cerebellum, IHC (Immunohistochemistry).

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INTRODUCTION

Hemagioblastoma is histologically characterized by neoplastic stromal cells along with abundant small vessels. It is a benign and slow growing tumour specially of adults, typically occurring in the brain stem, cerebellum, and spinal cord.[1] The term hemangioblastomas were introduced and classified In 1928 by Cushing and Bailey.[2]

Epidemiology Haemangioblastomas are uncommon tumours that occur as sporadic lesions and in familial forms associated with VHL. Haemangioblastomas usually occur in adults. The average patient age at presentation of VHL-associated tumours is approximately 20 years younger than that of sporadic tumours. The male-to female ratio is approximately 1:1.[1]

According to various series, hemangioblastomas are rare and account for approximately 1–3% of primary CNS tumors.[2] Sporadic tumours occur predominantly in the cerebellum, usually in the hemispheres (80% of cases). Haemangioblastomas associated with VHL are often multiple (in 65% of patients) and affect the brain stem, spinal cord, and nerve roots in addition to

the cerebellum.[1] The occurrence of this tumor in other locations such as supratentorial compartment, optic nerve, sella turcica, ventricular system, peripheral nerves or soft tissues of extremities are extremely rare.[2] Macroscopically most haemangioblastomas (60%) present as well- circumscribed, partly cystic, highly vascularized lesions; about 40% are completely solid. Occasionally, the tumour is yellow due to rich lipid content.[1]
Microscopically haemangioblastomas are characterized by two main components: Stromal cells that are characteristically large and vacuolated (but can show considerable cytological variation) and abundant vascular cells. In adjacent reactive tissues, particularly in cyst and syrinx walls, astrocytic gliosis and Rosenthal fibers are frequently observed. The tumour edge is generally well demarcated, and infiltration into surrounding neural tissues rarely occurs. Mitotic figures are rare.[1]

MATERIALS AND METHODS

This was a retrospective observational study of 10 years duration from 2011 to 2020, carried out in the Department of Pathology of SMS medical college, Jaipur. During this period, total 188515 biopsy specimen received among them 1616 vascular lesions, 4045 CNS neoplasm and 66 cases of hemangioblastoma were retrieved from the archives of department. The diagnosis in all the cases was made on histological examination of processed tissue. All the sections were processed by fixing, dehydration and clearing followed by impregnation with wax. The wax blocks were cut in 2-4 micron sections and stained by hematoxylin and eosin stain. Special stain and IHC is done as and when required.
The relative frequency of tumors and distribution of age and sex were analyzed. Following Data was collected: Path number, Name, Age, Sex, Site of lesion.

Table 1: Age wise distribution of hemangioblatomas cases.

S.N.	Age Group	Number of Hemangioblastoma case
1	11 -20 years	08
2	21 -30 years	17
3	31 -40 years	15
4	41 -50 years	11
5	51 -60 years	9
6	61 -70 years	5
7	71 -80 years	1

Table 2: Site wise distribution of hemangioblatomas.

S.N.	Site	Numbers of cases	%
1	Cerebellum	46	69.6 %
2	Spinal Cord	11	16.6 %
3	Medulla	06	9.0 %
4	Frontal Lobe	02	3.0 %
5	C P Angle	01	1.5 %

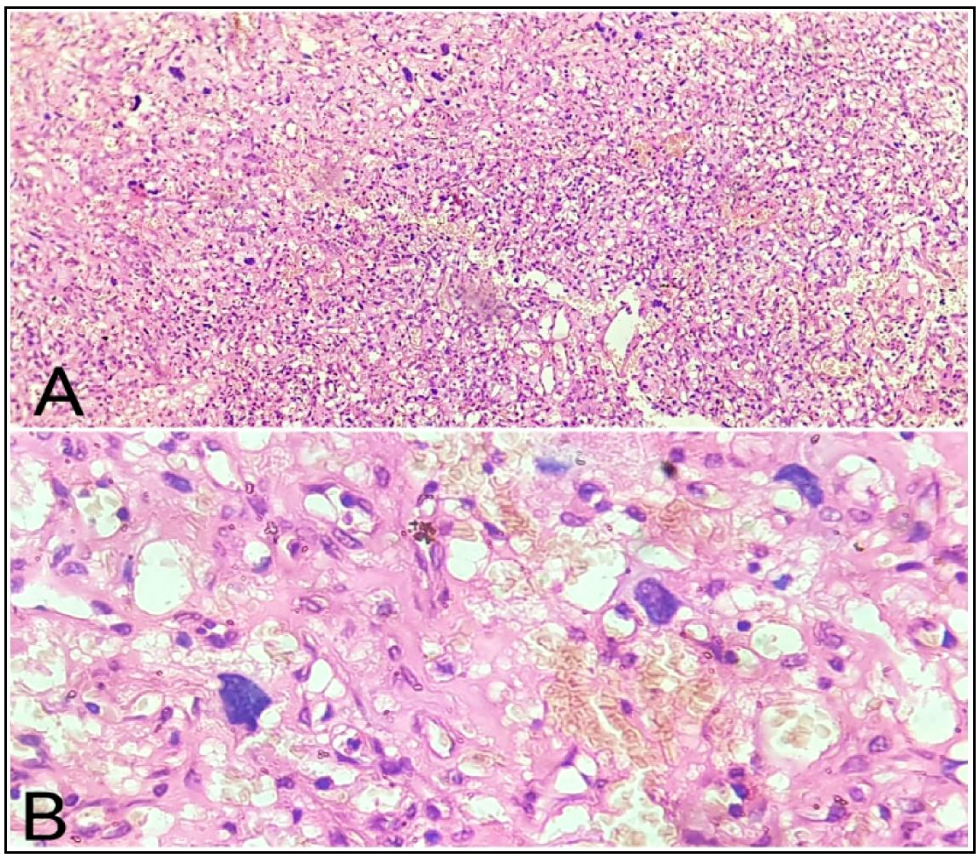

Figure 1. (A) Prominent vascular tumour comprised of anastomosing network of capillaries along with few large caliber feeder vessels. The stromal cells lying in between the vessels display a vacuolated cytoplasm (HE X 400). (B) Stromal cells show hyperchromatic ovoid nuclei with irregular nuclear membrane (HE X 400)

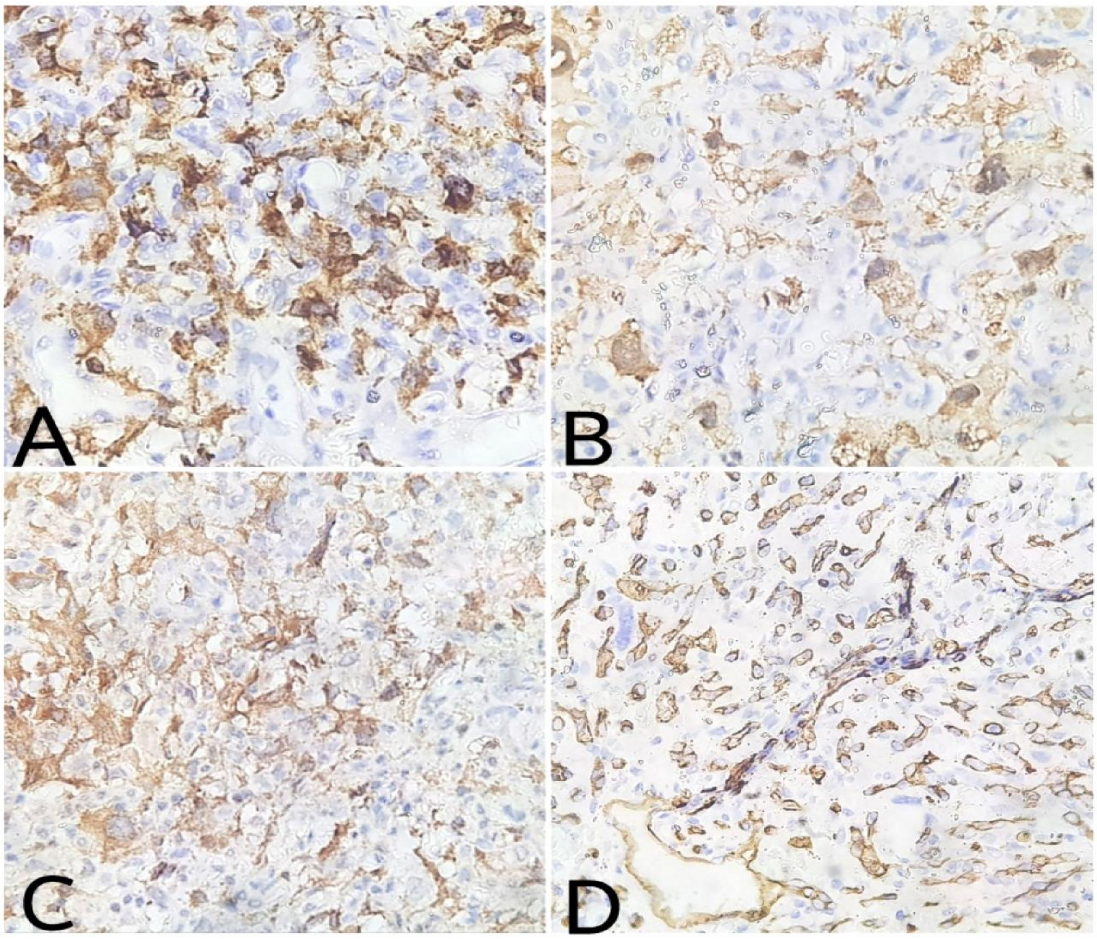

Figure 2. Immunohistochemistry (X 400) Stromal cells show positivity for (A) a- Inhibin, (B) NSE and (C) GFAP. Endothelial cells are positive for CD 34 while stromal cells are negative.

RESULTS

During a period of 10 years we received total 188515 biopsy specimen. We retrieved 1616 cases of vascular lesions and 4045 cases of CNS neoplasm. Among them we found total 66 cases of hemangioblstoma. We observed the percentage of hemangioblastoma which is 4.08 % of total vascular lesions and 1.62 % of CNS neoplasm. Among 66 cases of hemangioblstoma, there were 41 male and 25 female, which indicate male preponderance (M:F ratio 1.64: 1). In study age of the patient varies from 14 to 80 years. Age distribution in our study showed that tumors were more common in age group of 21 – 40 years followed by 41 – 50 years. Of 66 cases of hemangioblastoma 46 located in cerebellum (69.6 %), 11 in spinal cord (16.6 %), 6 in brainstem - medulla (9 %), 2 in frontal lobe (3 %) and 1 at CP angle (1.5 %).

Grossly, size varies from 0.8 × 0.5 × 0.4 cm to 4 × 2 × 1 cm. They were soft in consistency with reddish brown to yellow cut surface. Microscopically in most of cases show variable cellularity of stromal cells arranged in nests or lobule with intervening thin plexiform vasculature. Stromal cells were large polygonal with vacuolated or foamy cytoplasm with uniform round nuclei. At places, stromal cells showed large, pleomorphic, hyperchromatic nuclei but no mitotic activity. In few cased adjacent neuroparenchyma showing astrocytic gliosis and rosenthal fibres. Reticulin stain highlight the vascular network. On selected cased we applied IHC which revealed positivity of stromal cells to GFAP, inhibin, NSE and S-100. Stromal cells are negative for EMA and Pan CK. Vascular channels are positive for CD34.

DISCUSSION

After observation of data obtained during our study, Incidence of hemangioblastoma in our series was 4.08 % of vascular lesions which is higher than from others[5] and 1.62

% of CNS neoplasm which corresponds to the incidence observed in the literature.[4,6,7,10] Majority of cases were adults with age ranging from 20-50 years in our series which corresponds to the studies.[4,6-8] Like other studies, we found low incidence in younger patients of 0-19 years and older than 80 years.[7-9] We found male preponderance in our study. In other studies, there are equal risk in male and female [8] or moderate male preponderance[4,6,7,10] and slight female preponderance.[9] The most common location in our series was cerebellum in 46 (69.6 %) cases followed by spinal cord in 11 (16.6 %) case and brainstem-medulla in 06 (9.0 %) cases which correlates with following literatures.[4,7,10] At supratentorial location in frontal lobe we found 2 (3%) which is less common in our study, but is some other study this location is more common than spinal and brain stem.[6] No single case of peripheral hemangioblastoma seen like other studies.[11,13] Other small case series revealed unusual locations of hemangioblastoma, like liver[14,15], lung[15], pancreas[16], urinary bladder[6], adrenal gland[17], kidney[18-20], skin[21], retroperitoneum[22], soft tissue[23,24], and bone.[25]

Microscopically in most of cases show prominent dense network of vascular channels and numerous lipid laden stromal cells with uniform nuclei.[4,6,10-12] In some cases stromal cells showed large, pleomorphic, hyperchromatic nuclei.[4] No mitotic activity seen in any cases.[4,10-12] In few cases adjacent neuroparenchyma showed

astrocytic gliosis and rosenthal fibres which resembled pilocytic astrocytoma.[4,6] Reticulin stain highlighted the vascular network around tumours cells.[4,11,12] On selected cased we applied IHC which revealed positivity of stromal cells to GFAP, inhibin, NSE and S- 100.[4,6,10-12] Stromal cells are negative for EMA and Pan CK.[4,6,10-12] Vascular channels are positive for CD34.[4,10,12] MIB – 1 labelling Index is 2 -3 %.[4] F. P. Mcgrath et al reported hepatic and pulmonary hemangioblastoma in a 39-year-old female with previously resected cerebellar and spinal Haemangioblastomas. In this case initial diagnosis giant cavernous haemangioma was made.[15] Prabal Deb et al diagnosed a case of adrenal hemangioblastoma where clinical diagnosis was phaeochromocytoma. In microscopic examination using IHC markers, Tumour showed immunoreactivity for NSE, AQP-1, S-100 and vimentin with CD34- immunoexpression restricted to the vascular channels. Tumour was vimmuno negative for chromogranin, synaptophysin, HMB-45, Epithelial membrane antigen, cytokeratin (CK), muscle specific actin, α-smooth muscle actin.[17] Case series published by Yiu-Tung Ip et al, Yadong Wang et al and Chung- Chieh Wang et al reported sporadic renal hemangioblastoma where primary differential was renal cell carcinoma. They found positive immunostaining for α-inhibin, S100, and neuron-specific enolase and negative immunostaining for HMB-45, Melan-A, and epithelial markers cytokeratin and epithelial membrane antigen.[18-20] Making the correct diagnosis of renal hemangioblastoma is challenging. RCC (clear-cell variant), shares main morphological characteristics with hemangioblastomas, such as clear cytoplasm and a vascular network. The presence of a pericytomatous growth pattern and intracytoplasmic lipid vacuoles are major clues to the diagnosis of hemangioblastoma.[20] Other differential diagnoses include adrenal cortical carcinoma, epithelioid angiomyolipoma, and paraganglioma, which are also mimickers of RCC. An IHC panel is useful to differentiate these morphologically similar neoplasms.[20]

Alan S. Boyd reported a case of skin hemangioblastoma in 45-year-old man where he found proliferation of clear cells with vascular proliferation which replaced the dermis The nuclei of the clear cells were monomorphous without atypical nuclei, mitotic activity, or chromatin clumping. The clear cells stained positive for neuron-specific enolase NSE and faintly for CD68. Epithelial membrane antigen was negative. A CD34 stain was taken up by endothelial cells of the vasculature.[21] The differential diagnosis for hemangioblastomas arising in the skin is that of neoplasms with clear cell differentiation, particularly balloon cell nevus and melanoma, basal cell carcinoma, clear cell hidradenoma, and metastatic renal cell carcinoma. IHC investigation are keys to recognition of these entity.[21]

Julie c'. Fanburg-Smith et al reported a case of retroperitoneal peripheral hemangioblastoma in 47 year old male. In this case Immunohistochemical stains revealed that the stromal tumor cells were positive for vimentin, calponin , S-100 protein, NSE and Leu7 (CD57), and were negative for glial fibrillary acidic protein (GFAP), desmin, actins, HMB-45, CD34, epithelial membrane antigen and cytokeratins.[22] The morphologic differential diagnosis of hemangioblastoma in a retroperitoneal (nonvisceral) location includes metastatic renal cell carcinoma, extraorbital giant cell angiofibroma, hemangiopericytoma, angiomyolipoma, and cellular hemangioma. It can be distinguished from lesions in its differential diagnosis by its immunohistochemical features.[22]

Peripheral soft tissue hemangioblastoma reported by Michal Michal et al in a 74- year-old women at inner ankle[23] and Kurt T. Patton et al in 53-year-old woman at left popliteal fossa.[24] In both the cases tumour were positive for S-100 protein , NSE, vimentin, calponin and negative for GFAP, CD34, CD31, cytokeratins, actin, desmin, EMA, and HMB- 45.[23,24] Capillary hemangioblastoma in peripheral soft tissue should be distinguished especially from a well-differentiated liposarcoma[23], chondroid lipoma[24], lipomatous HPC[24], cellular capillary hemangioma[24] and metastatic clear cell carcinoma.[23,24] John Panelos et al reported Primary Capillary Hemangioblastoma of Bone in 72-year-old woman as lytic lesion of the sacrum not associated with VHL disease. This case showed same immunoreactivity as mentioned in previous case reports. In light of the histological findings and the site of involvement, the differential diagnosis included in this case were metastatic clear cell carcinoma of the kidney, hemangioma, hemangiopericytoma, schwannoma, and chordoma.[25] Markers of epithelial (cytokeratin and epithelial mem brane antigen), neuroendocrine (chromogranin and synaptophysin), and neuroectodermal (chromogranin, synaptophysin, neurofilament protein) differentiation are generally negative in these neoplasms, assisting in their differential diagnosis from other lesions.

CONCLUSIONS

As hemangioblastoma is rare neoplasm with low incidence, 4.08 % in vascular lesions and 1.64 % in CNS neoplasm. Predominance age group is 21 – 40 years followed by 41– 50 years. Male female ratio 1.64:1. Common site is cerebellum followed by spinal cord, brainstem - medulla, frontal lobe and CP angle. In published small case series, there are many examples of hemangioblastomas found in unusual locations other than CNS, that means we have to rule out hemangioblastoma from it's differentials with the help of IHC markers studies, as IHC are keys to a definite pathological diagnosis.

Final outcome is to keep hemangioblastomas in histopathological differentials, in tumours with vascular component, like different published studies in peripheral site other than CNS, which are still being underdiagnosed or over diagnosed.

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