Int J Clin Exp Pathol 2017;10(2):1792-1800
www.ijcep.com /ISSN:1936-2625/IJCEP0041392

Original Article

Clinicopathologic features of hemangioblastomas with emphases of unusual locations

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Received October 8, 2016; Accepted December 5, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: Hemangioblastoma (HB) is an unusual benign, of uncertain histogenesis neoplasm predominantly affect adulthood. It typically occurs in the central nervous system (CNS), predominantly in the cerebellum, occasionally in the meninges, spinal cord, corpus callosum, lateral ventricle and pituitary gland. Besides, it occurs in peripheral nerves and extraneural tissues such as soft tissue, retroperitoneum, skin, liver, pancreas, lung, adrenal, kidney, and urinary bladder. In most cases, HBs are sporadic, while approximately 25% are associated with von Hippel-Lindau (VHL) disease, an autosomal dominant hereditary neoplastic syndrome that results from a germline mutation in the VHL gene. Histologically, HB consists of networks of small blood vessels interspersed with lipid-laden stromal cells. Although the stromal cells are often bland-looking, they can exhibit significant nuclear pleomorphism, mimicking carcinoma or other malignancies. If this tumor occurs in a typical location and has a typical image, it is easy to be diagnosed. But if it occurs in unusual locations, it is a challenge for differential diagnosis. In this article, we report three cases of primary hemangioblastoma located in spinal cord, kidney and forearm without evidence of VHL disease. We review the literature to better delineate the clinicopathologic features and differential diagnosis of this rare tumor. At the same time, we collected 23 cases of hemangioblastoma in the central nervous system, and detected them by immunohistochemistry in order to investigate the histogenesis of this tumor.

Keywords: Hemangioblastoma, diagnosis, immunohistochemistry, histogenesis

Introduction

Hemangioblastoma (HB) is a benign, typically occurs in the central nervous system (CNS) either associated with VHL syndrome or more often sporadically. Rare occurrences of hemangioblastoma in peripheral nerves and extraneural tissues have been reported. HB is composed of lipid-containing stromal cells and a rich vascular network and is categorized as a WHO grade I tumor with good clinical outcome. VHL disease is an inherited multiple-neoplasia syndrome that is characterized by retinal and CNS HB, clear cell renal cell carcinoma (RCC), pheochromocytoma and paraganglioma, cysts and cystadenomas or pancreatic neuroendocrine tumors, endolymphatic sac tumors, epididymal cysts and cystadenomas, broad ligament and mesosalpinx cystadenoma [1]. According to the World Health Organization (WHO) in 2014, the clinical diagnosis of VHL disease is based on the presence of hemangioblastoma in the CNS or retina, the presence of one typical VHL-associated tumor (clear-cell RCC, pheochromocytoma, epididymal cystadenoma, neuroendocrine tumors, etc), or a previous family history. Because extraneural hemangioblastoma is rare and may mimic some malignant tumors, the correct diagnosis and differential diagnosis are necessary. By now, the histogenesis of HB remains uncertain. Various cell lineages such as vascular, glial, neural, fibrohistiocytic, and smooth muscle, myofibroblastic have been proposed for the so-called stromal cells [2]. In this series, the clinical, pathologic, and immunohistochemical features of 26 hemangioblastomas are reported.

Materials and methods

We collected 26 cases of Hemangioblastoma in the First Affiliated Hospital of Bengbu Medical

Table 1. Sources of the antibodies used in the immunohistochemistry analysis

Source	Antibodya
Vimentin	Monoclonal, clone V9
EMA	Monoclonal, clone E29
CK	Monoclonal, clone AE1/AE3
CD56	Monoclonal, clone 56C04
NSE	Monoclonal, clone E27
Syn	Monoclonal, clone SYP02
S-100	Monoclonal, clone 013
Calretinin	Monoclonal, clone SP13
a-inhibin	Monoclonal, clone R1
Ki-67	Monoclonal, clone MIB-1
GFAP	Monoclonal, clone GA-5
EGFR	Monoclonal, clone EP38Y
factor VIII	Monoclonal, clone F8/86
VEGF	Polyclonal
CD68	Monoclonal, clone KP1
CD31	Monoclonal, clone JC/70A
CD34	Monoclonal, clone QBEnd/10
calponin	Monoclonal, clone CALP
SMA	Monoclonal, clone 1A4
D2-40	Monoclonal, clone D2-40

All antibodies were obtained from Maixin Biotech, Inc. (Fuzhou, China), and were ready to use.

College from January 2009 to July 2016. Among 19 cerebellum cases, fourth ventricle 1 case, left temporal lobe 1 case, left cerebellopontine angle 1 case, dorsal medulla 1 case, 11 and 12 thoracic lumbar 1 case, left kidney 1 case, left forearm 1 case. All cases were sent to one of the authors for consultation. H&E-stained sections (4 um thickness) were re-examined to evaluate the tumour's histological features and immunohistochemistry was performed with Elivision technique. Antibody details are given in **Table 1**. Clinical demographics and follow-up data were obtained from medical records and referring physicians.

This study was approved by the Ethics Committees of the First Affiliated Hospital of Bengbu Medical College, and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Results

Clinical features

Case 1: A 24-year-old man felt paroxysmal pain in his lower back for half a year, accompanied by distending pain, numbness in the corresponding parts, paroxysmal appearance, especially in supine position. The symptom can relieve itself after a few minutes and occurs about once a month. There was no obvious discomfort in the interval between the onsets of the disease. In the past four months, there is urine waiting for pee and no frequent micturition, urgency, odynuria, or perineal sensory disturbance.

Magnetic resonance imaging (MRI) revealed that there was lumbar physiological curvature, clumps of abnormal signals can be seen in the T11-L1 spinal cord, long T1 and long T2, nodules were significantly enhanced and nodule length is 1.4 cm.

During the operation, it is found that the tumor located between 11 and 12 thoracic lumbar. The tumor was red, rich in blood vessels. After complete resection, below the tumor of the spinal cord cavity cerebrospinal fluid outflows, spinal cord beat well. The clinical diagnosis was considered as ependymoma.

Case 2: The patient was a 58-year-old man without documented systemic disease. When he visited the hospital for physical examination a week ago, abdominal sonography revealed a parenchyma mass in the left kidney accidentally. A computer tomography scan confirmed a 4.5 cm × 3.5 cm × 3.0 cm mass with heterogeneous density in the lower portion of the left kidney. The patient denied hematuria, weight loss, change in appetite, or neurological symptoms and signs. In addition, there was no family history of hereditary diseases. Under the suspicion of RCC, he underwent a left radical nephrectomy.

Case 3: A 55-year-old woman found painless mass in the left forearm for 2 months.

Gross and histological features

Case 1: The tumor was soft, about 1.4 cm long with a clear boundary. Pathology revealed that the tumor was composed of medium-sized cells, with partially eosinophilic and partially clear cytoplasm. This tumor is characterized by the presence of vacuolated tumor cells, referred to as stromal cells, closely associated with an elaborate network of capillary-sized blood vessels. In the local area large, deep and exotic nuclei can be seen (**Figure 1A**, **1B**).

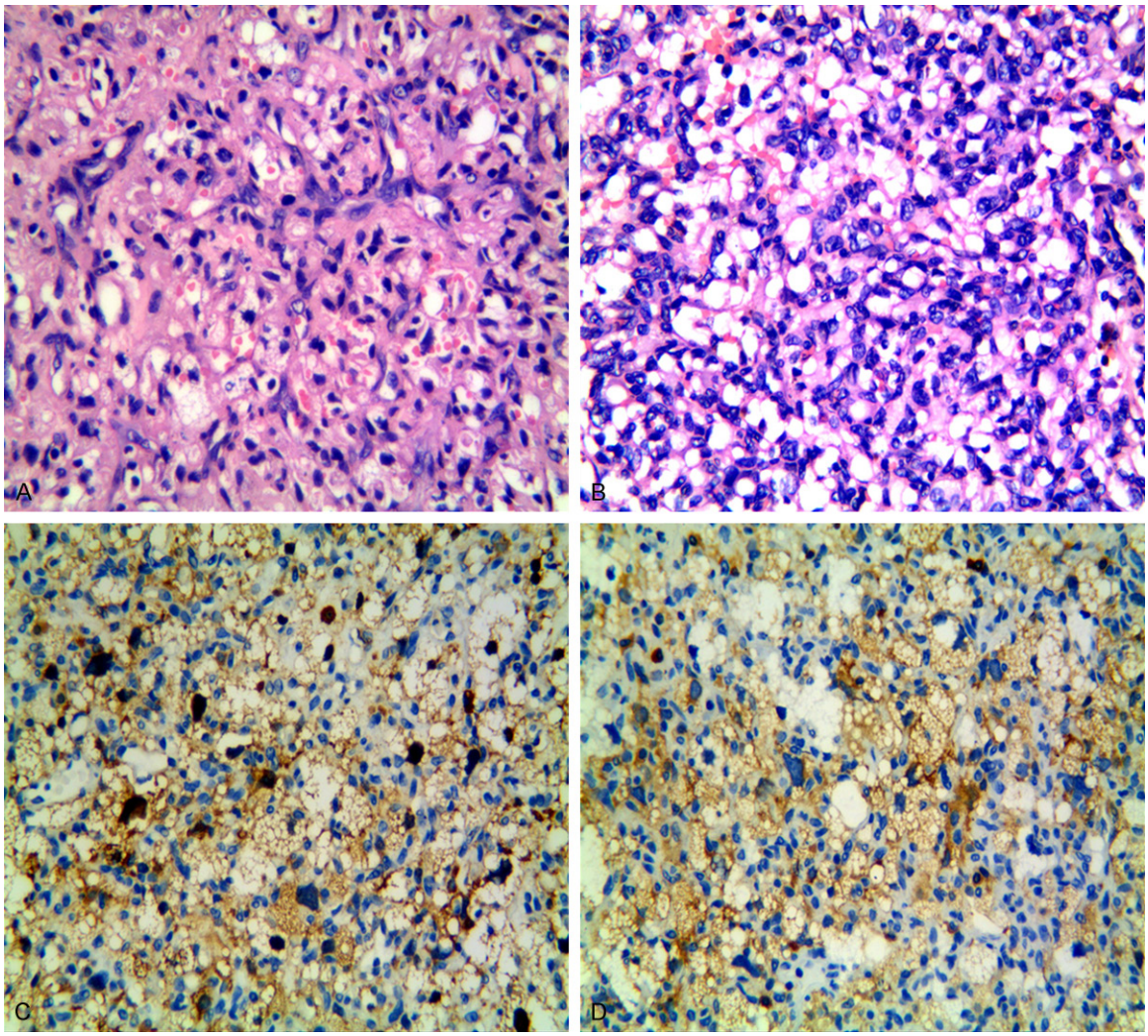

Figure 1. Histological and immunohistochemical features of the tumor from the patient described in case 1. A: At higher magnification, abundant anastomosing thin blood vessels surrounding small nests of bland appearing stromal cells (magnification, × 400). B: At higher magnification, in some areas, tumor cells were predominantly spindled, with only a hint of microvacuolation and a lack of palely eosinophilic cytoplasm and larger polygonal cells (magnification, × 400). C: Stromal cells positive for S-100 protein (magnification, × 400). D: Stromal cells positive for NSE (magnification, × 400).

Case 2: The renal specimen measured 14.0 cm × 8.0 cm × 7.0 cm in size. There was a well-defined, red to brown, soft tumor measuring 4.5 cm × 3.5 cm × 3.0 cm in size in the subcapsular renal parenchyma. Focal necrosis was seen in the tumor section. There was no evidence of invasion into the renal pelvis or the ureter, either.

Microscopically, the tumor tissue had relatively clear boundary and was consisted of polygonal to oval cells arranged in sheets with a rich vascular network. The tumor cells were slightly variable in size and shape, and their cytoplasm was mildly eosinophilic to clear with small lipid vacuoles. The blood vessels were mainly small and thin walled. Some areas were rich in cells while other areas were edematous and hyalinized with sparse stromal cells and abundant reticular vessels (**Figure 2A**). Extensive fresh hemorrhage was found in the tumor and there were also areas of myxoid change.

Case 3: After operation, the tissue was strip shape 9.0 cm × 3.5 cm × 2.0 cm. The tumor was around ulnar nerve and adhered the surrounding tissues. Microscopically, the resection specimen of the left forearm featured a lobular

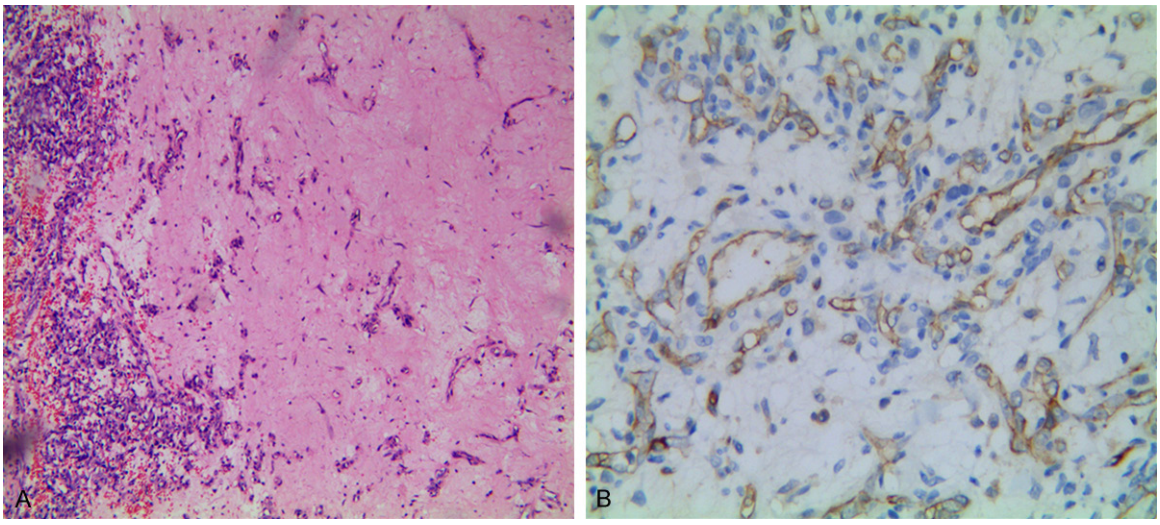

Figure 2. Histological and immunohistochemical features of the tumor from the patient described in case 2. A: Some areas were edematous and hyalinized with sparse stromal cells (magnification, × 100). B: Some areas were edematous and hyalinized with sparse stromal cells (magnification, × 400).

growth pattern (**Figure 3A**). It was composed of abundant anastomosing thin blood vessels surrounding small nests of bland appearing round to oval "stromal" cells exhibiting occasional cytoplasmic vacuolization (**Figure 3B**). There was no evidence of mitotic activity, cellular atypia, or necrosis.

Immunohistochemical features

Case 1: Tumor cells expressed Vim, S-100, a-inhibin, CD56 and neuron-specific enolase (**Figure 1C**, **1D**). CD31, CD34 highlighted tumor vasculature.

Case 2: The tumor cells reacted strongly and diffusely with antibodies to á-inhibin, S-100 protein, neuron-specific enolase, EGFR and vimentin, and they showed focal positivity with antibodies to epithelial membrane antigen and CK. Tumor cells were negative for RCC antigen, synaptophysin, D2-40, HMB45, melan-A, SMA, desmin. CD31, CD34 stain highlighted the vascular network but not the tumor cells per se (**Figure 2B**).

Case 3: The stromal cells were strongly positive for S-100 protein and vimentin, NSE, EGFR, CD56, a-inhibin (**Figure 3C**, **3D**) and negative for SMA, HMB45, Melan-A, CD68 and calretinin.

In order to further verify the origin of HB, we also performed immunohistochemical detection of 23 cases in which HB was found in central nervous system. Tumor cells expressed Vim in 87% (20/23) cases, expression of a-inhibin in 83% (15/18) cases, S-100 protein in 81% (17/21) and neuron-specific enolase (NSE) was present in 75% (15/20) cases, GFAP was present in 65% (11/17) cases. CD56 was positive in stromal cells in 6/7 cases and D2-40 in 5/8, EGFR in 4/6 cases. CD31, CD34 and factor VIII stains highlighted the capillary network of the tumor vasculature. The immunohistochemical profile of hemangioblastoma does not suggest a specific line of differentiation for this tumor. Expression of Vim, a-inhibin, S-100 and NSE is common, being present in 87%, 83%, 81% and 75% cases respectively. Although the immunohistochemical profile of hemangioblastoma is nonspecific, the combination of Vim, a-inhibin, NSE, and S-100 can give support in making diagnosis and may be extremely useful for those cases in which microvacuolated cells are scant. Immunostains may also be helpful in excluding other morphologic mimics tumors.

Diagnosis and differential diagnosis

Case 1: The final diagnosis was hemangioblastoma.

Single spinal cord hemangioblastoma need to distinguish from the following diseases: (1) ependymoma: mainly occurs among adults and comprises 60% of intramedullary spinal cord

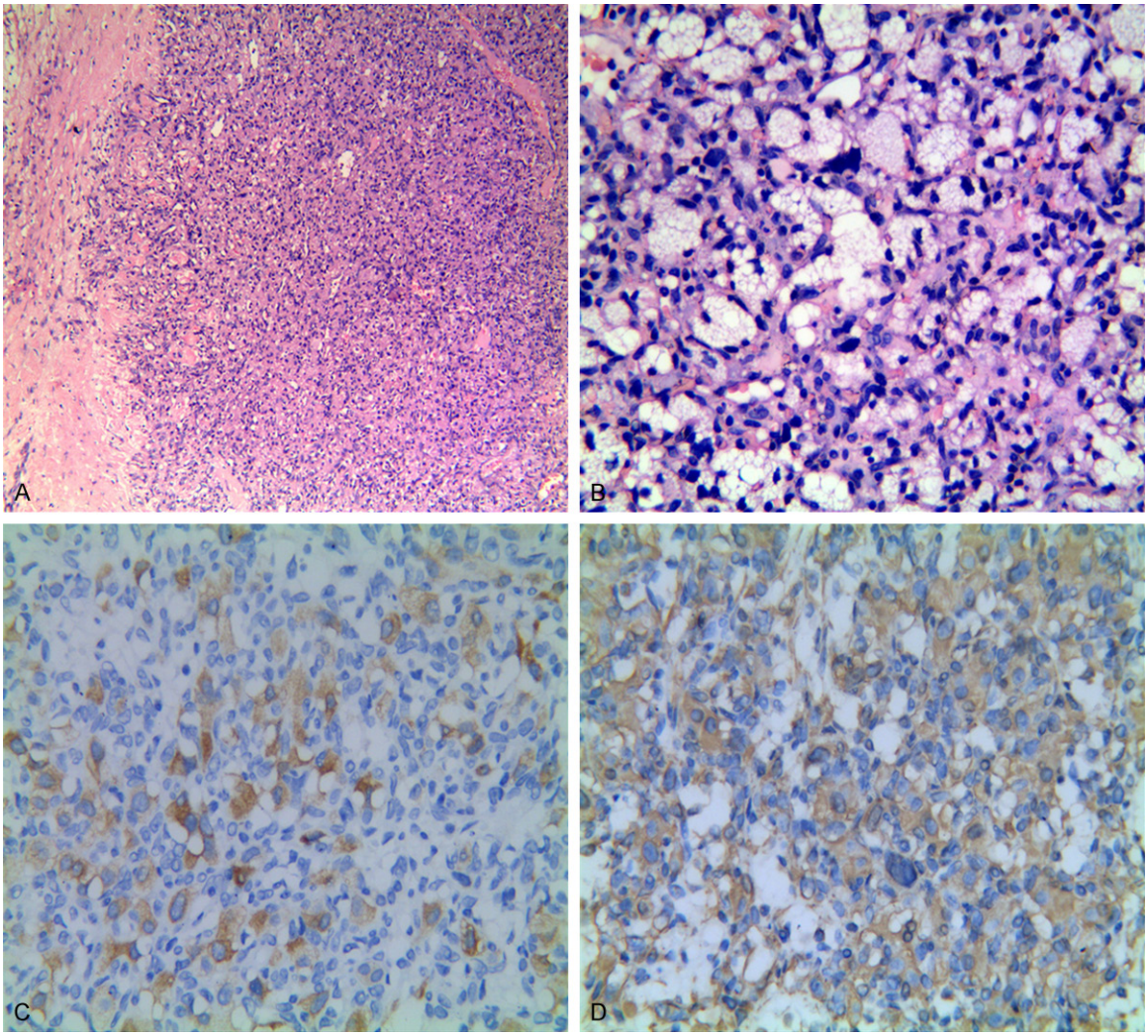

Figure 3. Histological and immunohistochemical features of the tumor from the patient described in case 3. A: Most tumors were solid and well circumscribed, often with a lobulated growth pattern. (magnification, × 100). B: Stromal cells showing moderate nuclear atypia, pleomorphism and pronounced cytoplasmic vacuolization (magnification, × 400). C: Stromal cells positive for a-inhinbin (magnification, × 400). D: Stromal cells positive for Vim (magnification, × 400).

tumors, occur in the cervical spinal cord and conus medullaris, tumor is in the center of the spinal cord, intratumoral often associated with cystic change and bleeding. secondary syringomyelia, but the occurrence probability and scope is smaller than hemangioblastoma. Microscopically, the tumor was clearly defined, false clusters around the blood vessels can be seen, positive in GFAP, most EMA is positive and also express S-100, Vim. (2) astrocytoma: younger age, male, lesions located in the thoracic, expansile or infiltrative growth pattern. The tumor's boundary was not clear, can secondary cysts, hemorrhage and cavity. (3) Vascular malformation (Cavernous hemangioma of the common): spinal cord involvement no swelling, often secondary hemorrhage, the smaller range of syringomyelia and atrophy and edema of the adjacent spinal cord can be seen. Hemangioma lacks cells with clear or microvacuolated cytoplasm, and careful examination for these cell types can aid in the diagnosis. Immunohistochemistry may also be helpful in such cases.

Case 2: The final diagnosis was renal hemangioblastoma.

Making the correct diagnosis of renal hemangioblastoma is challenging. The differential

diagnoses includes: (1) RCC, which is far more common and possesses a wide morphological variation. More common in the elderly, especially in male, there are clinical manifestations such as hematuria and renal pain. The most common histological subtype, clear-cell RCC, 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. RCC, which is usually more nested, typically expresses EMA and PAX8 and is negative for a-inhibin and S100. (2) Epithelioid angiomyolipoma: Microscopy, the tumor is composed of three main ingredients: fatty tissue, epithelioid smooth muscle cells and thick blood. The characteristic expression is HMB-45, S-100 protein and so on. (3) Paraganglioma: most of the patients had hypertension and other symptoms. The tumor cells were round or oval or epithelioid, abundant in cytoplasm, nuclear staining deep and round. A fibrous trabeculae vascular tumor cells will be divided into small lobes or nests, immunohistochemistry expression of CgA. (4) Adrenal cortical carcinoma: direct immersion or transfer to the kidney, the tumor cell atypia was obvious, easy to see vascular invasion, immunohistochemistry Syn, Melan-A positive and S-100 protein negative for identification.

Case 3: After consultation with a number of hospitals, the diagnosis is ulnar nerve hemangioblastoma. This case should be identified with granular cell tumor of soft tissue. Microscopically, granular cell tumor was not clearly defined. The cellular areas were composed of a nested, patchy, round or polymorphic cell. Among tumor cells, fibrous tissue can be seen. Tumor cell cytoplasm is rich, eosinophilic red, fine granular. According to the condition of tumor necrosis, vacuole nucleus and large nucleus, nuclear division, cell polymorphism and so on, the tumor can be divided into three groups, benign, atypical and malignant.

It is worth mentioning that the tumor boundary is unclear, involvement of adjacent structures and nerve invasion, If placed in other types of tumor these indicators often prompt malignant, but in the granular cell tumor, it is not suitable, because these forms are also seen in benign granular cell tumor. Immunohistochemically, the tumor cells is positive for S-100 protein, calretinin, a-inhibin and NSE. The immunohistochemical expression of this tumor cells was overlapped with hemangioblastoma. But there was no CD31, CD34 positive vascular component. In addition, the tumor in the forearm should be identified with granular leiomyoma and rhabdomyoma.

Follow-up

These 26 patients are currently all alive and well without evidence of recurrence and metastasis.

Discussion

Hemangioblastoma is an uncommon neoplasm, composed of lipid-containing stromal cells and a rich vascular network. It typically occurs in the CNS, mostly in the cerebellum, either in the setting of von Hippel-Lindau disease or more often sporadically [3]. Sporadic hemangioblastoma is a tumor of adulthood, generally occurring between 30 and 65 years, whereas VHL-associated tumors affect significantly younger patients [4]. A VHL diagnosis is established in an individual with a family history of VHL when he or she presents a single characteristic VHL-related tumor [5]. In the absence of a family history of VHL, a diagnosis requires two or more retinal or cerebellar HB, or one HB and a visceral tumor, excluding epididymal and renal cysts which are common in the general population [6]. Examples of HB developing in sites outside the CNS are exceptional and have been reported in small series and case reports, including liver [7], lung [8], pancreas [9], adrenal gland [10], urinary bladder [9], kidney [11-13], skin [14], retroperitoneum [15], soft tissue [16, 17] and bone [18], many of which are associated with one or more stigmata of VHL disease. Sporadic hemangioblastoma occurring outside the CNS is much rarer.

We report on 3 cases of HB arising in unusual locations, one in spinal cord, the other in kidney and the third in left forearm. The three patients do not meet any of VHL diagnosis criteria. Therefore, the three cases are considered sporadic. In our series, tumors were morphologically similar to those arising at CNS locations. However, in contrast to CNS HBs, which are usually cystic, the tumors in our study were

solid and have the common IHC profile (reactivity to Vim, S100, α-inhibin, and neuron-specific enolase). Histologically, based on the prominence of the stromal cell component, HB has been subdivided into two variants: reticular and cellular. Cytological features of the stromal cells are characteristically bland; however, they can occasionally exhibit nuclear pleomorphism mimicking malignancy, particularly in the cellular variant.

Extraneural HB is exceptional and raises a challenging differential diagnosis. Spinal cord HBs account for about 1-7% of all intramedullary tumors [19]. They are more common in the age below 40 years old, almost in the cervical and thoracic spinal cord, accompanied by various degrees of spinal cord edema and dilation of the spinal cord's central canal [20]. Clinical features include sensory impairment, pain, motor dysfunction, anal and bladder dysfunction. Because the tumor is more often in the root of the spinal nerve in the spinal cord, sensory disorders are more common than motor disorders, and pain is the most common symptom. Patient in this particular case with lumbar pain and sensory abnormalities as the main performance, in accordance with the literature. MRI is the gold standard for the diagnosis and assessment of intradural tumors.

So far, only more than 10 cases of HB occurred in the kidney have been published in the literature, mostly sporadic cases. Renal HB was more common in the elderly, no gender differences. Many are incidentally found in the physical examination and have no obvious symptoms. This case we report was considered malignant tumor with preoperative ultrasound and CT examination before surgery, so the image examination has little help for the diagnosis. Different with the cystic changes of intracranial hemangioblastomas, HB in the kidney are mostly solid. The stromal cells of this case are relatively large, which belong to the cellular subtype, and the cells are mild, which might be mistaken for other renal tumors, in particular clear cell renal cell carcinoma.

The first report of HB arising in the soft tissues is credited to Brodkey et al [21], who, in 1995, chronicled a case of HB arising in the radial nerve of a 79-year-old woman. Fanburg-Smith et al [22] delineated the first example of a soft tissue CH not attached to a peripheral nerve that developed in the retroperitoneum in a 47-year-old man. The histogenesis of hemangioblastomas remains uncertain. Possible origins include glial cells, endothelial cells, spider cell membrane, embryo choroid from, neural endocrine cells, fibrous tissue cells, neuroectodermal derived cells or a heterogeneous population of cells [23]. Immunohistochemical studies done on hemangioblastoma in our study have demonstrated variable expressions of neural (S-100 protein, neuron specific enolase, CD56), glial (glial fibrillary acidic protein), and generic mesenchymal markers (vimentin). An inhibin has also been reported as being generally positive. Among these, relatively nonspecific markers such as EGFR, D2-40 and VEGF, CD68 are constantly expressed in the tumor. CD31, CD34, factor VIII stain highlighted the vascular network. Muscle derived markers (MSA, desmin, calponin) were not expressed. The expression of epithelial markers (CK, EMA) is only in the kidney case. The regularly strong expression of vimentin has led to favoring an undifferentiated mesenchymal origin.

In our study, GFAP had a positive rate (11/17), but it is not clear whether these scattered GFAP positive cells are reactive astrocytes, the stromal cells with the differentiation of glial cells or the interstitial cells with phagocytic activity and cytoplasmic expression of GFAP.

In conclusion, HB may arise at anatomic sites outside the CNS. Sometimes it exhibits significant nuclear pleomorphism, mimicking carcinoma or other malignant tumors. Correct diagnosis and differential diagnosis are necessary. The immunohistochemical profile can aid diagnosis. Vim, a-inhibin, S-100 and NSE appeared to be the most sensitive markers and expressed in most cases. However, by now the precise lineage of these distinctive neoplasms remains poorly understood.

Acknowledgements

We would like to thank to Editage for English language editing. Thanks to Di-chen Li and Qun Xie (Department of Pathology, the Frist Affiliated Hospital of Bengbu Medical College) for their assistance with the histopathological and immunohistochemical stain evaluations. This study was supported by the Natural Science

Foundation of Anhui Province (No. 1608085-QH207), Key Foundation of excellent young talents in colleges and universities in Anhui province (gxyqZD2016161), the Natural Science Foundation of the Education Department in Anhui Province (No. KJ2015B040BY, No. KJ2015B045BY), and the Natural Science Foundation of Bengbu Medical College (No. BYKY-1401ZD).

Disclosure of conflict of interest

None.

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