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CASE REPORT

Clinicopathological and Genetic Study of an Atypical Renal Hemangioblastoma[△]

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HEMANGIOBLASTOMA (HB), a kind of benign tumor with uncertain histogenesis, is characterized by the presence of stromal cells (SCs) and a rich vascular component.¹ It occurs sporadically, except for about 25% of the cases associated with von Hippel-Lindau (VHL) disease. HB typically occurs in the cerebellum, but it has been reported that HB occasionally occurs in extraneural tissues, such as kidney,² adrenal,³ gastrointestinal tract,⁴ soft tissue⁵, and so on. We reported an atypical case involving the kidney, which might be misdiagnosed for other renal tumors, especially clear cell renal cell carcinoma (RCC). We also reviewed previously published cases and literature, and made necessary molecular genetic study, in order to investigate its clinicopathological features and differential diagnosis, etc.

CASE DESCRIPTION

A 61-year-old male patient was found with a 3.0 cm×2.0 cm sized hypodense mass at the First Affiliated

Hospital of Wannan Medical College on May 27, 2015. The tumor was showed in the upper pole of the left kidney on the computed tomography (CT) scan (Fig. 1A, 1B). He had no significant past medical history except for hypertension for several years. The diagnosis of kidney tumor was initially made, but RCC remained to be ruled out. Then partial nephrectomy was performed, which showed, in the upper pole of the left kidney, a solid tumor measured 2.2 cm in diameter with unclear outline and homogeneous section. No other tumors were detected, especially in central nervous system (CNS), and there was no clinical evidence of VHL disease. No tumor recurrence or metastasis occurred within the half-year follow-up period.

Surgically resected renal tumor tissue was fixed in 10% buffered formalin and embedded in paraffin, cut into 5 µm-thick sections with microtome, and stained with hematoxylin and eosin or periodic acid-Schiff stain. SP immunohistochemical staining (IHS) was performed on additional sections for detecting vimentin, AE1/AE3, epithelial membrane antigen (EMA), CK7, CD10, melan-A, HMB45, S100, α-inhibin, neuronspecific endase (NSE), synaptophysin, chromogranin, CD56, CD34, CD31, FVIII, desmin, smooth muscle actin (SMA), and Ki-67 (Beijing Zhongshan Golden Bridge Biotechnology Co, Ltd). The analyses of VHL gene mutation and hypermethylation

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were performed according to the previously described method.⁶

Macroscopic features demonstrated that part of the left kidney with a size of 3.5 cm×3.2 cm×2.6 cm was cut off. A tumor of 2.2 cm in diameter was found, swelling up the kidney tissue. The cut surface of the tumor was brownish-white, solid and homogeneous (Fig. 1C), with an indefinite outline,

The tumor was ill-demarcated from the surrounding renal parenchyma (Fig. 2A), and in some area the tumor cells broke through the fibrous capsule (Fig. 2B). There was an alternation of cellular and paucicellular areas inside the tumor. The hypercellular areas were full of SCs with pale or eosinophilic cytoplasm (Fig. 2C), with an enriched capillary network enclosed inside (Fig. 2D). The SCs occa-

sionally exhibited lipid droplets, with oval nuclei, small nucleoli and delicate chromatin. Some cells showed pleomorphic, giant, bizarre nuclei, or took a rhabdoid shape (Fig. 2E), but no necrosis or mitoses. The paucicellular areas were composed of enriched capillaries and sparse tumor cells, or completely of fibrous stroma with hemosiderin pigment (Fig. 2F).

The IHS showed that SCs were diffusely positive for vimentin (Fig. 3A), NSE (Fig. 3B), S100 protein (Fig. 3C), α -inhibin (Fig. 3D), and focally positive for CD10 (Fig. 3E), AE1/AE3 and EMA. The tumor cells were strictly negative for CK7, HMB-45, melan-A, chromogranin, synaptophysin, and CD56. The rich and delicate capillary network was outlined well by CD34, CD31, and F VIII. Eosinophilic granula imparted a positive reaction to periodic acid-Schiff stain (Fig. 3F).

Figure 1. Computed tomography scan and macroscopic findings.

A round hypodense mass in the upper pole of the left kidney (A, B, arrows). The tumor with a diameter of 2.2 cm was ill-demarcated, and its cut surface showed brownish-white in color (C, arrow).

Figure 2. Microscopic findings of HE staining.

The tumor had an indefinite fibrous capsule (A, $\times 40$), and in some area it seemed that tumor cells broke through the capsule (B, $\times 40$, arrow). The tumor consisted of sheets or nests of large polygonal cells with pale or eosinophilic cytoplasm (C, $\times 400$) and abundant arborizing capillary network (D, $\times 400$). Lipoblast-like cells with multiple vacuolization (C), rhabdoid cells (E, $\times 400$, arrow), and hyalinization (F, $\times 100$) were focally seen.

VHL gene sequence analysis of all three exons and hypermethylation were performed. We found this tumor showed VHL

gene mutation in exon 2 (Fig. 4). Exon 1 and exon 3 had no gene mutation. Hypermethylation was also found in the sample.

Figure 3. Immunohistochemical and histochemical findings. SP ×100
Neoplastic cells were diffusely positive for vimentin (A), NSE (B), S100 protein (C), α-inhibin (D), and focally positive for CD10 (E). Eosinophilic globules imparted a positive reaction to periodic acid-Schiff stain with diastase treatment (F, arrow).

Figure 4. VHL gene molecular analysis.
A. All three exons of VHL gene were detected by using polymerase chain reaction, and a gene mutation was found in exon 2.
B. By gene sequencing analysis, we found a single base deletion (T).

DISCUSSION

Sporadic primary renal HB is a rare tumor, and to our

knowledge, there are about ten reports. It is a benign tumor in elderly people, and there is no sex predilection. Usually it is found by chance in the upper pole of the right kidney, and CT scan may revealed a hypodense mass like

our report (Fig.1 A, B), some with heterogeneous region in the centre. These patients may be clinically mistaken for other renal cell tumors, especially RCC.

Macroscopically, the tumor is commonly single and well-encapsulated, with an average diameter of 4.2 cm (from 1.2 cm to 6.8 cm).⁷ As far as our literature goes, there was only one case with some areas of poorly marginated growth.⁸ The cut surface of HB shows light brown to gray-tan in color, no necrosis or hemorrhage. Occasionally cystic changes are observed.

Microscopically, the tumor is enclosed within a thick fibrous capsule, which separates the tumor from the surrounding tissue. The tumor consists of two parts: ample arborizing capillary network, and sheets or nests of SCs. Based on the proportion of the clustering of SCs, HBs were classified into three subtypes—reticular (no clustering of SCs), cellular (predominant areas of clustering) and mixed (focal clustering of SCs). The SCs vary in size, from large polygonal to short spindle cells, and some may have clear or light eosinophilic cytoplasm, just like lipoblast cells. In our report there appear some giant cells with abundant eosinophilic cytoplasm, resembling the rhabdoid cells that have been reported by Yin *et al*⁹ in a HB case with the rhabdoid phenotype. Sometimes the tumor cells show eccentric nuclei, and eosinophilic globular intranuclear pseudoinclusions are occasionally seen. But neither mitotic activity nor necrosis is present. Sclerosis, haemosiderosis,¹⁰ and focal calcification of the fibrous stroma^{3, 11} have been documented in the paucicellular areas.

HB may morphologically mimic many renal neoplasms, including RCC, epithelioid angiomyolipoma, paraganglioma (pheochromocytoma), and so on. Sometimes, it is very difficult but necessary to make a differential diagnosis from clear cell RCC. Some clues to the diagnosis are: circumscribed borders, clear or light eosinophilic tumor cells, paucity of mitotic figures despite the existence of atypical cells and giant cells, no necrosis and rich capillary network. In this case we reported, all the features described above were observed except for the ill-demarcated borders, so the first diagnosis coming to our mind was clear cell RCC.

For such a particular case, IHS might be an important solution. Different from HB, clear cell RCC is usually negative for α -inhibin, S100, and NSE, but positive for AE1/AE3, EMA and CD10.¹¹⁻¹² This case was strongly positive for vimentin, NSE, S100 protein, and α -inhibin, but focally positive for CD10, AE1/AE3, and EMA. Expression of CD10 is thought to have substantial value in distinguishing CNS tumors from metastatic RCC.¹³ Focal positive immunoreaction for CD10 had been reported,⁹⁻¹⁰ and a potential explanation

was that the tumor was derived from pluripotent mesenchymal cells, but partially acquired some site-specific antigens during pathogenesis.^{3, 9, 14} IHS for EMA positive reaction had been found in some sporadic renal HB,^{7, 9, 11} and CNS hemangioblastomas.¹⁵⁻¹⁶ We also found focal expression of cytokeratin AE1/AE3 in a small percentage of tumor cells (about 5%). Cytokeratin AE1/AE3 positive reaction had been reported in CNS hemangioblastomas.¹⁶ In general, some authors recognized these tumors with the special phenotype as a subset of HB.^{14, 17}

The term 'hemangioblastoma' (HB) was introduced by Cushing and Bailey in 1928, typically consisting of capillary-sized blood vessels separated by intervacular SCs. HB is still regarded as 'neoplasms of uncertain histogenesis', and SCs have been shown to be the neoplastic cells. The histogenesis of SCs is still controversial,^{1, 18} and there are two main histological origins: blood vessels and neuroendocrine cells. The immunohistochemical phenotype seems to support the latter. SCs express vimentin, S100 protein, α -inhibin, or NSE, CgA,³ CKpan,⁷ EMA,^{7, 11, 15} and VEGF,⁵ but not CD34, F VIII, CD31. Immunohistochemical characteristics of HB were observed by Epari *et al*,¹⁹ which suggests that SCs are of "a possible precursor of neuroepithelial differentiation" or "an intermediate form between mesenchymal and epithelial cells".

Our report is an atypical HB of the kidney. Although it has an indefinite fibrous capsule, rhabdoid cells, and some markers (AE1/AE3, EMA, CD10) expressed focally, the tumor is composed of sheets of large, polygonal vacuolated stromal cells distributed in a rich capillary network, with rhabdoid cells spotted inside. IHS findings showed strong and diffuse immunoreactivity with antibodies to vimentin, NSE, α -inhibin, and S100 protein. And periodic acid-Schiff staining showed cytoplasmic glycogen particles. VHL gene mutation of sporadic primary renal HB mostly happened at exon 2 like our report. And hypermethylation was also found in the sample. All these features indicate the diagnosis of HB, instead of clear cell RCC. In addition, some immunophenotypes exclude the possibilities of epithelioid angiomyolipoma (for HMB-45-, melan-A-, etc.), paraganglioma (for chromogranin-, synaptophysin-, CD56-, etc.), and so on.

In this atypical case, the tumor was similar to the ordinary HB reported previously, except for the indefinite fibrous capsule, rhabdoid cells and expressing some markers. Though the progression and prognosis are still unclear, the circumscribed borders of HB show the sign of benign biological behavior. Even though it seems that the tumor cells in our case destroy and break through the fibrous capsule, just like in diagnosing follicular thyroid carcinoma,

whether or not it implies a kind of malignant feather is still unknown. The patient of our case is still alive without recurrence and metastasis at the 18-month follow-up.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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