Primary Hemangioblastoma of Kidney with Molecular Analyses by Next Generation Sequencing: A Case Report and Review of the Literature

Xintong Wang  
Icahn School of Medicine at Mount Sinai  
https://orcid.org/0000-0003-3983-6414

George K Haines  
Icahn School of Medicine at Mount Sinai

Jane Houldsworth  
Icahn School of Medicine at Mount Sinai

Qiusheng Si (✉ qiusheng.si@mountsinai.org)  
Icahn School of Medicine at Mount Sinai

Case Report

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Abstract

**Background:** Hemangioblastoma is an indolent mesenchymal tumor most frequently occurring in the central nervous system (CNS), but can also arise extraneuraxially, as part of von Hippel-Lindau (VHL) disease or in sporadic cases. Extraneuraxial hemangioblastomas (EH) occur outside the central nervous system. It includes tumors arising from the nervous paraneuraxial structures and visceral organs. Sporadic hemangioblastoma of the kidney, a rare subset of EH, is an under-recognized renal neoplasm. There have been only 25 cases described to date in the English language literature. We report herein one additional case in a patient without VHL disease.

**Case presentation:** A 61 year old male presenting with gross hematuria was found to have a 3.5 cm renal mass at the lateral mid to lower pole of the left kidney on computed tomography urogram. Patient underwent a partial nephrectomy for the mass. The pathological examination showed a well-circumscribed non-encapsulated tumor composed of sheets of large polygonal cells traversed by a rich vascular network. The tumor cells showed clear to eosinophilic cytoplasm and overall bland nuclei. The diagnosis of hemangioblastoma was confirmed by positive immunostaining for alpha-inhibin, S100, neuron-specific enolase, PAX8, and negative staining for epithelial membrane antigen, HMB-45, and Melan-A. VHL gene mutation was not detected in this tumor. The diagnosis of sporadic renal hemangioblastoma was made.

**Conclusion:** Sporadic renal hemangioblastoma (RH) is a rare subset of EH. We report herein one such case in a patient without clinical or molecular evidence of VHL disease. We reviewed the literature to better understand the clinical, radiological and pathologic features of this neoplasm. From our review cases and the present case, we have found that the majority of RHs showed a positive immunostaining for PAX8, which supports the idea that the immunoproles of EH can vary depending on sites of origin. Diagnosis of renal hemangioblastoma is challenging because of its rarity and overlapping microscopic and immunophenotypic features with renal cell tumor, especially with clear cell renal cell carcinoma. However, accurate diagnosis is necessary, since RH is clinically benign and correct recognition of this pathological entity is important to avoid unnecessary over treatment.

**Background**

Hemangioblastoma is an indolent tumor of mesenchymal cell proliferation that most frequently occurs in the central nervous system (CNS), mainly in the cerebellum. Most cases are sporadic, and about 20–30% of patients have Von-Hippel-Lindau (VHL) disease (1). The extraneuraxial hemangioblastomas (EH), referred to the hemangioblastomas, occur outside the central nervous system, including tumors arising from the nervous paraneuraxial structures, soft tissue, bone, and visceral organs. Extraneural hemangioblastomas seem to be identical to the CNS hemangioblastomas morphologically and immunophenotypically, but there are certain differences. Renal hemangioblastoma (RH) is a rare subset of EH, which usually occurs in the setting of known von Hippel-Lindau disease. But, it can also occur sporadically. To date, only 25 cases of sporadic RH have been described in the English language literature.
We report herein one such case in a patient without clinical or molecular evidence of VHL disease, and reviewed the literature to better understand its clinical, radiological and pathologic features. Since RH is clinically benign, a correct recognition of this pathological entity is important to avoid unnecessary clinical treatment.

**Case Presentation**

A 61 year old gentleman presented with one episode of gross hematuria without fever, flank pain, pain with urination, weight loss, or neurological symptoms. Patient had a past medical history of coronary artery disease and well-controlled hypertension. A computed tomography (CT) urogram showed a 3.5 x 2.1 x 1.3 cm, arterially enhancing mass, at the lateral mid to lower pole of the left kidney, along with a branching calculus in left lower pole renal calyces. These findings were suspicious for a renal cell carcinoma. The patient was clinically doing well. The laboratory examination revealed normal creatinine. There was no family history of von-Hippel Lindau disease or neoplastic diseases. A cystoscopy was performed and revealed no tumor in the urethra, bladder or ureter. One month later, the patient underwent a laparoscopic left partial nephrectomy. Gross examination of the specimen revealed a well-circumscribed but non-encapsulated round mass, measuring 3.0 x 2.1 x 1.3 cm. On cutting surface, the tumor was tan-white in color, with partial fibrosis and mild hemorrhage. Histologically, under low power, the tumor was slightly lobulated, traversed by a prominent vascular network with thin-walled blood vessels (Fig. 1B), in a background of hyalinized and sclerotic stroma (Fig. 1A). On high power, the tumor cells were slightly variable in size, oval to polygonal in shape, and with abundant clear to eosinophilic cytoplasm (Fig. 1C and 1D) that sometimes contained fine vacuoles (Fig. 1E) and eosinophilic hyaline globules (Fig. 1F). Most tumor cell nuclei were bland with inconspicuous nucleoli, although focal mild pleomorphism was present. There was no tumor necrosis or atypical mitotic activity.

Immunohistochemically, the tumor cells diffusely expressed S100 (Fig. 1G), alpha-inhibin (Fig. 1H), neuron-specific enolase (NSE), Vimentin and PAX8 (Fig. 1I). AE1/AE3 showed only weak, focal cytoplasmic staining. The tumor cells were negative for Epithelial membrane antigen (EMA), Carbonic anhydrase IX (CAIX), CD10, CK7, CD117, p504s, synaptophysin, chromogranin, melanin A, HMB45 and Steroid factor 1. Ki-67 stain showed very low proliferative index in this tumor (<1%). The molecular analysis of the tumor was performed by next generation sequencing which indicated no genetic mutations, including VHL gene or copy number changes. Overall, the histological, immunohistochemical, and molecular findings supported the diagnosis of sporadic hemangioblastoma of the kidney. The postoperative course of the patient was uncomplicated, and there was no evidence of tumor recurrence or metastasis on follow-up CT 6 months after the surgery.

**Discussion**

Hemangioblastoma is an uncommon, benign neoplasm that mainly occurs in the CNS, especially in the cerebellum. EHs, also referred to as peripheral hemangioblastomas, are rare subsets of hemangioblastoma arising outside of CNS, but still within the nervous paraneuraxial structures, somatic
tissues, and visceral organs. There have been about 200 cases of EH reported to date in the world literature, as part of VHL disease or in sporadic cases, and up to 140 cases were from nervous paraneuraxial structures (14). The sporadic primary hemangioblastomas of the kidney is an even rarer neoplasm. We have reviewed the English literature and found 25 cases of primary RH (Table 1) (2–17). Clinically, sporadic RH is found to be identical to other subtypes of EHs and the sporadic CNS hemangioblastoma, and has a benign outcome.

As detailed in Table 1, 25 patients with sporadic RH were adults and only one was a child (diagnosed with RH at age of 16 years) (5), with the median age at diagnosis of 47.5 years, ranging from 16 to 71 years. Fourteen patients were male and 12 patients were female, with male-to-female ratio of 1.17/1.0. In 15 of 26 cases, tumors were located in the right kidney, and the upper pole was the most common site of tumor. The average tumor size was 4.22 cm in the greatest dimension, ranging from 1.2 to 15 cm (5, 11). Overall, 60% of patients were asymptomatic, 24% had hematuria, 12% experienced lower back or abdominal pain, while only one patient presented with systemic symptoms, such as fever and weight loss (11). None of the patients included in this study had VHL disease (One RH case with possible VHL disease (13) was excluded from review.

Since this tumor is so rare, there were minimal descriptions of its characteristic radiological features. He et al. have described peripheral nodular enhancement in the corticomedullary phase, progressive centripetal enhancement in the nephrographic and delayed phases, and sometimes complete “filling in” in the delayed phase in 2 RH cases, which may be unique only to RH compared to other renal neoplasms (16).

All reported tumors were removed surgically. Almost all RH cases (25/26) showed unilateral, unifocal distribution, with the exception of one case (11) in which the patient had 3 lesions in the left kidney (right kidney uninvolved), and all lesions were confirmed as RH histologically. Macroscopically, RH displayed a solid, occasionally cystic cut surface (7). Microscopically, similarly to CNS hemangioblastoma, RH was composed of well-demarcated, large sheets of polygonal cells, with a prominent, arborizing vascular network. The tumor cells were varied in size with clear to eosinophilic cytoplasm, which commonly contained sharply delineated fine lipid vacuoles. The rhabdoid feature was rare, but was reported in one case (7). In majority of the cases, the tumor cells were bland looking (2), but some cases showed cells with mild to moderate nuclear pleomorphism (3). Mitotic figures were rare in the reported cases.

Immunohistochemically, as detailed in Table 2, almost all of the RH cases demonstrated diffuse positivity for alpha-inhibin (24/26), NSE (23/23), S100 protein (25/25), and vimentin (19/21), and negativity for neuroendocrine markers (synaptophysin, chromogranin A), melanocytic markers (HMB45, melan-A), endothelial markers (CD31, CD34), and mesothelial markers (calretinin, WT-1).

In 3/21 RH cases, tumor cells expressed focal, patchy positivity for AE1/AE3 (10, 16), including the present case. The majority of RH cases exhibited no immunoreaction for muscle, such as desmin (2–4), but two cases were noted to have focal expression of smooth muscle actin (2, 15). CD10 was reported
positive in 7/16 cases (7, 8, 10, 14, 15). EMA was positive in 5/15 cases (4, 7, 8, 14, 15) and CAIX was positive in 3/4 cases (4, 8, 12).

Including the present case, the diffuse and strong nuclear positivity of PAX8 was observed in 8/14 cases (10–12, 14–16), and PAX2 was positive in 2 reported cases (8, 12). PAX8 and PAX2 are cell lineage specific transcription factors that play a crucial role in the organogenesis of the kidney (17). Both factors are expressed in normal kidneys as well as in many renal epithelial neoplasms such as renal cell carcinoma (RCC), although PAX8 is usually more sensitive. Zhao et al, has put forward a hypothesis suggesting that the immunoprofile of EH can vary with different sites of origin (10). With the findings of positivity for PAX8 and/or PAX2 in the above-mentioned 9 cases, we agree with the idea that RH is capable of expressing kidney-specific antigens.

RH is likely to be an underrecognized tumor of kidney due to its rarity. This indolent neoplasm can be mistaken for various malignancies, including clear cell RCC or epithelioid angiomyolipoma. Clear cell RCC share similar morphological characteristics with RH, such as a clear cytoplasm and prominent vascular network. The most useful feature to differentiate clear cell RCC from RH is the absence of fine cytoplasmic lipid vacuoles, which is predominantly present in RH. Immunohistochemically, clear cell RCC is usually positive for AE1/AE3, EMA, CAIX and CD10, but negative for alpha-inhibin, S100, and NSE. However, to add to the confusion, Montironi et al (18) have reported 2 cases of clear cell RCC with 60-70% of tumors showing hemangioblastoma-like features. In his reported cases, the tumor cells expressed alpha-inhibin and S100 in the hemangioblastoma-like part only (not in the clear cell RCC part), but PAX8, CD10, and RCC were positive in both components of the tumor. After carefully reviewing the histologic morphology in our present case, we have found ~10% of tumor cells showing clear cytoplasm, but all tumor cells stained consistently for S100, alpha-inhibin, NSE, Vimentin, and negative for CD10 and CAIX. These findings supported a diagnosis of RH. Another major mimicker of RH is epithelioid angiomyolipoma, which presents with a tumor that also possesses sheets of polygonal cells with an abundant cytoplasm and rich vascular network. The key feature to differentiate RH from epithelioid angiomyolipomas is that epithelioid angiomyolipomas usually show reticulated cytoplasm instead of a lipid containing vacuolated cytoplasm. Immunohistochemically, epithelioid angiomyolipomas are usually HMB45 positive, melan-A positive, but alpha-inhibin negative.

Molecular analysis of sporadic RH has been reported in two studies (five patients) (12, 14). No VHL gene mutation, hypermethylation or loss of heterozygosity (LOH) of chromosome 3p were detected. We agree with the hypothesis put forward by Muscarella et al. that (1) the genetic changes may be localized to the intronic or regulatory regions of VHL gene; (2) the genetic anomaly may involve other genes, which interplay with VHL gene expression; (3) alternative tumor genetic mechanisms (14). To possibly answer these questions, we performed molecular analysis of our case using next generation sequencing including (xxxx genes). No significant gene mutations, including VHL gene and copy number changes were detected. Therefore, the tumor genetic mechanism of RH, at least in our case, remained unclear.

**Conclusion**
Sporadic RH is a rare subset of EH. We report herein one such case in a patient without clinical or molecular evidence of VHL disease, and reviewed the literature to better understand the clinical, radiological and pathologic features of this neoplasm. From our review cases and the present case, we have found that the majority of RHs showed a positive immunostaining for PAX8, which supports the idea that the immunoprofile of EH can vary depending on sites of origin. Diagnosis of RH is challenging because of its rarity and overlapping microscopic and immunophenotypical (PAX8+, CD10+, CAIX+) features with renal cell tumor, especially clear cell renal cell carcinoma. However, accurate diagnosis is necessary, since RH is clinically benign and a correct recognition of this pathological entity is important to avoid unnecessary over treatment.

**Abbreviations**

CAIX: Carbonic anhydrase IX, CNS: Central nervous system, CT: computed tomography, EH: Extraneuraxial hemangioblastomas, EMA: Epithelial membrane antigen, NSE: neuron-specific enolase, RH: renal hemangioblastoma, VHL: von Hippel-Lindau

**Declarations**

**Ethics approval and consent to participate**

All ethical approval and consent procedures were approved by the Medical Ethical Committee of Icahn School of Medicine at Mount Sinai. According to the institutional guidelines, the patient’s signed privacy consent is not necessary for a single case report with de-identified patient specific information.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The dataset supporting the conclusions of this article is included within the article.

**Competing interests**

The authors declare no conflict of interest/competing interests in publishing the present manuscript.

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**Authors’ Contributions**
Xintong Wang; Data Collection, Manuscript writing

G. Kenneth Haines III; Jane Houldsworth; Qiusheng Si: Manuscript editing.

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Corresponding author: Correspondence to Qiusheng Si

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Author information

Affiliations

Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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**Tables**

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

**Figures**

![Figure 1](image)

**Figure 1**

Microscopic features and Immunohistochemical findings of renal hemangioblastoma. A (H&E, × 50), Low magnification demonstrates a solid mass divided into lobulated nodules by thick collagenous septa. B (H&E, × 200), the tumor is traversed by arborizing thin-walled vessels. C-D, the epithelioid tumor cells with eosinophilic (C, H&E, × 200) or clear cytoplasm (D, H&E, × 400). E-F (H&E, × 400), some tumor cells contain numerous well-delineated vacuoles (E) and eosinophilic hyaline globules (F). Tumor cells demonstrate diffuse reactivity for S100 (G), alpha-inhibin (H), and PAX8 (I).

**Supplementary Files**
This is a list of supplementary files associated with this preprint. Click to download.

- CAREChecklist.pdf
- Table1.xlsx
- Table2.xlsx