

## Case Report

# Sporadic renal hemangioblastoma in a boy: a rare case report and review of literature

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**Abstract:** Hemangioblastoma is a slowly growing benign tumor which generally involves the central nervous system (CNS) in the majority of the cases. Hemangioblastoma of the kidney is exceedingly rare. To date, only 16 cases of renal hemangioblastoma (RH) have been described in detail in the English literature. Herein, we reported a case of RH in a boy and analyzed its clinicopathological features and also review the literature.

**Keywords:** Hemangioblastoma, kidney, diagnosis, differential diagnosis

### Introduction

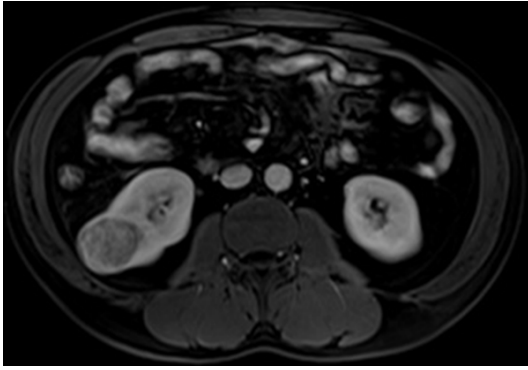
Hemangioblastoma, also referred to as capillary hemangioblastoma, is a benign tumor of uncertain histogenesis composed of stromal cells and a rich vascular network. Hemangioblastoma may be associated with Von Hippel-Lindau (VHL) disease in approximately one-quarter of the cases [1]. The tumor typically occurs within central nervous system (CNS), but occasionally occurs in the other sites, such as peripheral nerve, soft tissue, retroperitoneum, pelvic cavity, urinary bladder, bone, skin, lung, pancreas, liver, adrenal gland, and extremities [2-5]. The kidney is another rare site for the development of sporadic hemangioblastoma, and only a few cases have been reported in the English literature so far. In this study, we describe one additional case of RH in a boy without clinical evidence of VHL disease and compare it with the previous cases reported in the literature.

### Case report

A 14-year-old boy was admitted to our hospital with 3 days history of gross hematuria in February 11, 2014. The boy denied weight loss and had no decreased appetite, abdominal pain, respiratory, cardiovascular, and neurologi-

cal symptoms and signs. Furthermore, patient had not previously undergone surgery. Physical examination showed a well-developed and well-nourished boy. The boy had a pulse of 80 beats per min, temperature 36.8°C, blood pressure 120/62 mmHg and respiration 21 per min. Abdominal sonography revealed a mass in his right kidney. Magnetic resonance imaging (MRI) of the abdomen demonstrated a 3.5 cm round solid mass in the lower pole of the right kidney with heterogeneous density (**Figure 1**). No other tumor was detected by radiological examination including MRI of the brain, neck, thorax and abdomen. Laboratory examination showed no abnormalities. Laboratory examination revealed hemoglobine (Hb) of 124 g/L, red blood cell (RBC) count of  $4.73 \times 10^{12}/L$ , platelet count of  $195 \times 10^9/L$ , white blood cell (WBC) count of  $7.15 \times 10^9/L$  with 58% neutrophile granulocytes and 26% lymphocytes. Fasting blood-glucose was 4.89 mmol/L, blood urea nitrogen was 6.08 mmol/L and serum creatinine was 71.33  $\mu\text{mol}/L$ . Serum electrolytes and liver function tests were within normal limits. In addition, there was no remarkable family history and clinical evidences of VHL disease. A right radical nephrectomy was performed as a malignant tumor was suspected in February 16, 2014.

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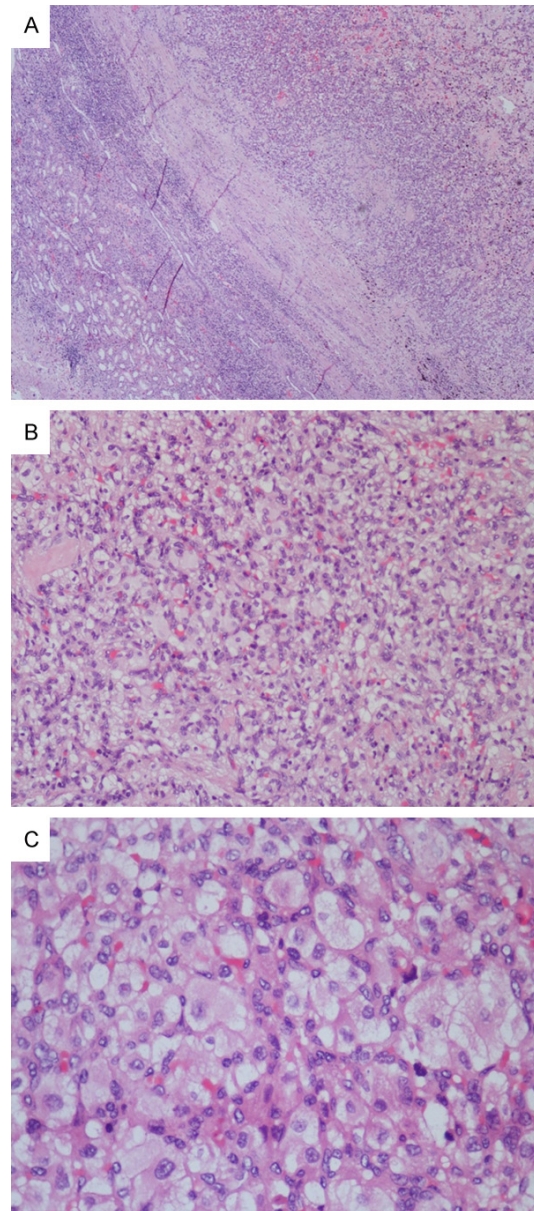


**Figure 1.** MRI showed a heterogeneous solid mass with well-defined border in the lower pole of the right kidney.

Grossly, the mass measured 3.5 cm × 3.5 cm × 3.2 cm with well-defined margin. The cut surface was grey to brownish in color. Microscopically, the tumor was encapsulated by a thick fibrous capsule and well-demarcated from the surrounding renal parenchyma. The tumor was consisted of nests of polygonal to oval cells with a rich vascular network. The tumor cells showed pale, eosinophilic cytoplasm exhibiting occasional lipid droplets and contained oval to round nuclei, delicate chromatin, and inconspicuous nucleoli. Occasionally, pleomorphic or bizarre tumor cells were found, and mitoses and necrosis were not observed in the tumor (**Figure 2**). Immunohistochemically, the tumor cells were diffusely positive for neuron-specific enolase (NSE), Vimentin,  $\alpha$ -Inhibin and S-100, whereas negative for CD10, CAM5.2, EMA, AE1/AE3, HMB45, Melan-A, PAX2, PAX8, SMA, CD31, CD34 and CD68. The Ki-67 proliferation indices were approximately 1% of tumor cells. The delicate capillary network of the tumor was highlighted by immunostaining of CD34 and CD31 (**Figure 3**). Pathological diagnosis of renal hemangioblastoma (RH) was established based on the histological features and immunophenotypic findings. The boy was well without any evidence of recurrence or metastasis at 27 months of follow-up after surgery.

### Discussion

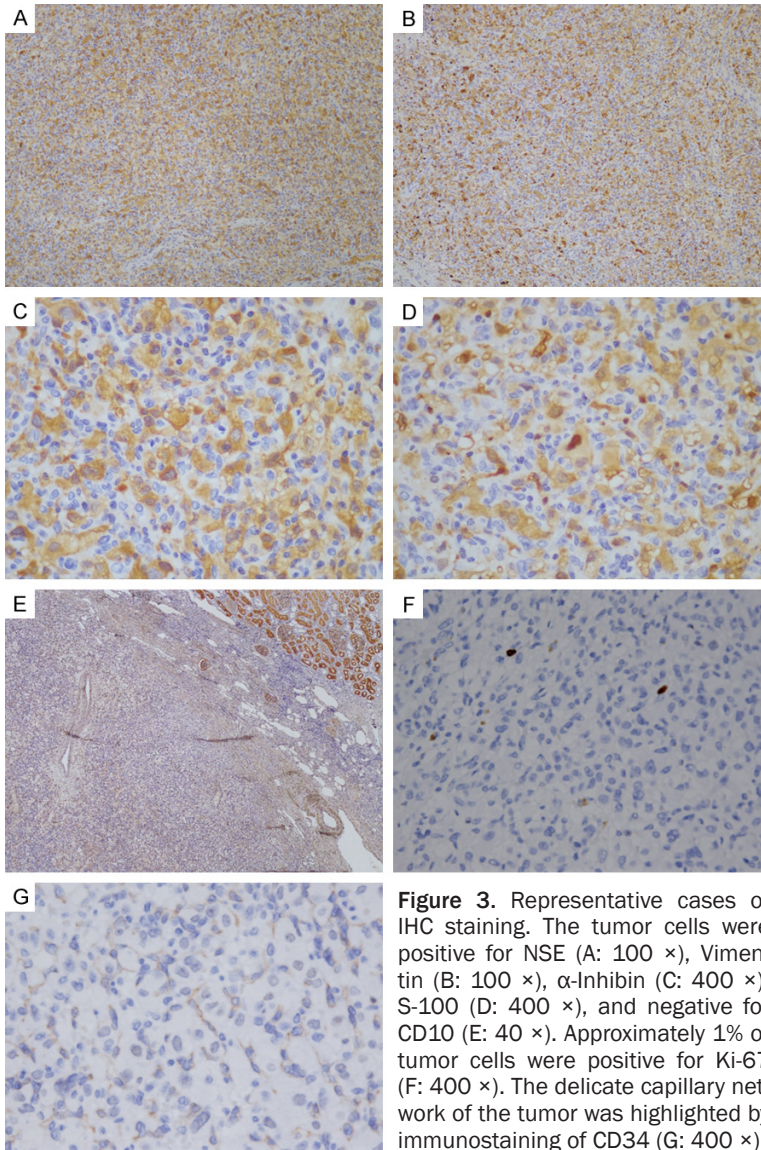
Hemangioblastoma is an uncommon benign neoplasm that typically involves the central nervous system, and can occur sporadically in majority cases or in association with VHL disease in about 25% cases. VHL disease is an autosomal dominant hereditary neoplastic



**Figure 2.** Histopathological analysis. A: The tumor was surrounded by a fibrous capsule and well-demarcated from the adjacent renal tissue (40 ×). B: The tumor was composed of polygonal and oval cells with a rich vascular network (100 ×). C: The tumor cells showed a pale or eosinophilic cytoplasm exhibiting occasional lipid droplets and contained oval nuclei, delicate chromatin, and inconspicuous nucleoli. Occasionally, pleomorphic or bizarre tumor cells were seen (400 ×).

syndrome associated with germline mutations of the *VHL* tumor suppressor at chromosome 3p25. Patients with VHL disease can develop a variety of neoplasms including hemangioblastoma in CNS, clear cell renal carcinoma, pancreatic neuroendocrine tumors, pheochrom-

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**Figure 3.** Representative cases of IHC staining. The tumor cells were positive for NSE (A: 100 ×), Vimentin (B: 100 ×),  $\alpha$ -Inhibin (C: 400 ×), S-100 (D: 400 ×), and negative for CD10 (E: 40 ×). Approximately 1% of tumor cells were positive for Ki-67 (F: 400 ×). The delicate capillary network of the tumor was highlighted by immunostaining of CD34 (G: 400 ×).

cytoma/paraganglioma, cystadenoma of the epididymis and broad ligament, and endolymphatic sac tumor of the inner ear [6].

There are only a few reports concerning sporadic hemangioblastoma occurring outside the CNS. Moreover, primary hemangioblastoma of kidney is extremely rare which first described by Nonaka and colleagues in 2007 [7]. To date, only 16 cases of RH have been described in detail in the English literature [5-15]. The clinicopathological features of the 17 cases including our case were summarized in **Table 1**, including 10 male and 7 female patients, with the mean age of 45.3 years old and median age of 51 years old (range 14~71 years). As shown in **Table 1**, the overwhelming majority

of renal hemangioblastomas appeared to occur in adults, and only two cases occur in children including a 16-year-old girl and a 14-year-old boy (our case). None of 17 cases were associated with VHL disease. All lesions of 17 cases have been unilateral and solitary with a slight predilection for the right kidney. Tumor size was reported in 15 patients, ranging in maximum diameter from 1.2 to 6.8 cm with mean size 4.0 cm and median size 3.5 cm. Twelve patients without any obvious symptoms were discovered incidentally during radiologic examination for unrelated reasons, and five patients were identified due to related symptoms including gross hematuria, lower back pain, or polycythemia. In addition, sixteen patients received resection of one side kidney and only one patient underwent a partial nephrectomy [8]. Accordingly, there was no evidence of local recurrence or metastasis during 3 to 108 months follow-up. In 15 cases, and follow-up data were not reported in 2 cases. The present patient underwent a right radical nephrectomy. After 27 months of follow-up, there is

no clinical evidence of recurrence or metastasis and the patient is still in follow-up currently.

Due to the rarity, RH is usually not considered in the differential diagnosis and easily misdiagnosed as other morphologically similar neoplasms, in particular clear cell renal cell carcinoma (RCC). It is very important for the correct diagnosis of RH because it is a benign tumor with much better prognosis than that of malignant RCC. RH is characterized by the presence of vacuolated tumor cells with a prominent capillary network, and occasionally exhibit nuclear pleomorphism and even highly atypical tumor cells mimicking malignancy. Though similar morphological features, some features such as clear cytoplasm and prominent reticular vasculature

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**Table 1.** Clinicopathological features of 17 cases of renal hemangioblastoma

Reference	Age (y)/Sex	Clinical features	Site	Size (cm)	IHC		Presence of VHL	Follow-up
					Positive	Negative		
[7]	71/F	No obvious symptoms	Superior pole of right kidney	6.8 × 6.0 × 2.5	SMA (F), MSA (F), Calponin (F), S-100, Vimentin (F), α-Inhibin	AE1/E3, CAM5.2, EMA, Desmin, CD31, CD34, Factor VIII, HMB-45, GFAP, Calretinin, WT, Chromogranin	Not reported	No recurrence 9 years after nephrectomy
[10]	58/M	Gross hematuria and polycythemia	Anterior inter-polar of right kidney	5.5	α-Inhibin, NSE, S-100, GLUT1 (weak)	AE1/AE3, CAM5.2, Synaptophysin, Chromogranin, HMB-45, Melan-A, Calretinin, MSA, Desmin, CD34	No	No recurrence 2 years after nephrectomy
[10]	55/F	Low back pain for 4 years	Lower pole of right kidney	3.5 × 3.0 × 3.0	α-Inhibin, NSE, S-100, GLUT1	AE1/AE3, CAM5.2, Synaptophysin, Chromogranin, HMB-45, Melan-A, Calretinin, MSA, Desmin, CD34	No	Well 5 months after nephrectomy
[8]	64/M	No obvious symptoms	Upper pole of left kidney	3.2	NSE, S-100, Vimentin, α-Inhibin (F), Carbonic anhydrase IX (F), EMA (F)	AE1/AE3, CK903, CD10, HMB45, Melan-A, CD56, Chromogranin, Synaptophysin, Calretinin, SMA, MSA, Desmin, CD34	No	No recurrence 1 year after partial nephrectomy
[11]	29/M	No obvious symptoms	Lower portion of right kidney	2.7 × 2.5 × 2.5	α-Inhibin, NSE, S-100	AE1/AE3, EMA, CD10, CD56, HMB45, Melan-A, SMA, CD34	No	No recurrence 20 months after nephrectomy
[12]	61/M	No obvious symptoms	Superior pole of right kidney	5.3 × 5.0 × 5.0	α-Inhibin, NSE, S-100, Vimentin, EGFR, EMA (F), CD10 (F), Ki-67 (1%)	AE1/AE3, CK8/18, CK19, gp200, Calretinin, HMB45, Melan-A, Chromogranin, Desmin, Actin, Myoglobin, CD68	No	No recurrence 12 months after nephrectomy
[13]	16/F	Gross hematuria and low back pain for 18 months	Upper pole of left kidney	1.2	NSE, S-100, Vimentin, α-Inhibin (F)	EMA, AE1/AE3, CD10, HMB45, Melan-A, CD56, Chromogranin, Synaptophysin, Calretinin, SMA, CD34, CD31	No	No recurrence 18 months after nephrectomy
[14]	61/M	No obvious symptoms	Upper pole of right kidney	6.5	α-Inhibin, NSE, S-100	Not reported	No	No recurrence 1 year after nephrectomy
[3]	51/F	Recurrent right-sided lumbar abdominal pain for 1 year	Lower pole of right kidney	5.5 × 4.5	PAX8, CD10, α-Inhibin, NSE, S-100, Vimentin, EMA (F), AE1/AE3 (F)	CK7, CK8/18, gp200, Synaptophysin, Chromogranin-A, c-kit, D2-40, HMB45, Melan-A, SMA, cathepsin K, Desmin, ER, PR, CD34, CD31, Ki-67 (< 3%)	No	No recurrence 12 months after nephrectomy
[9]	57/F	No obvious symptoms	Upper pole of right kidney	3.0 × 2.5 × 2.0	α-Inhibin, NSE, S-100, EGFR, CA9, HIF-1α, PAX2, CD10 (F), Ki-67 (few)	CKpan, HMB45, Melan-A, SMA, CD68, D2-40, TFE3, TFB	No	No recurrence 6 months after nephrectomy
[5]	30/M	No obvious symptoms	right kidney	3.2 × 2.5 × 1.4	Vimentin, α-Inhibin, NSE, S-100, EMA	CK7, CK8, CD10, AE1/AE3, PAX8, CD34	No	Died after nephrectomy for an accident
[5]	57/F	No obvious symptoms	right kidney	Not reported	Vimentin, S-100	α-Inhibin, EMA, CK7, CK8, CD10, AE1/AE3, PAX8, CD31, CD34	No	No recurrence 5 months after nephrectomy
[5]	48/M	No obvious symptoms	Low portion of right kidney	2.3	α-Inhibin, NSE, S-100	Vimentin, EMA, CK7, CK8, CK, CD10, AE1/AE3, HMB45, PAX8, CD34	No	No recurrence 42 months after nephrectomy
[5]	25/M	No obvious symptoms	Left kidney	4.1	NSE, S-100	Vimentin, α-Inhibin, CK7, CK8, CD10, AE1/AE3, HMB45, PAX8, CD34	No	No recurrence 27 months after nephrectomy
[5]	36/F	No obvious symptoms	Left kidney	Not reported	Vimentin, α-Inhibin, NSE, S-100, EMA, CD10	CK7, CK8, AE1/AE3, HMB45, PAX8, CD34	No	Well 3 months after nephrectomy
[15]	37/M	No obvious symptoms	Upper pole of left kidney	3.6 × 3.5 × 1.7	α-Inhibin, S-100, CA9, PAX2, PAX8, Vimentin	CAM5.2, CD10, gp200, Melanosome, Melan-A, TFE3, Cathepsin K, ALK, α-SMA, Brachyury	No	Not reported follow-up after nephrectomy
Our case	14/M	Gross hematuria for 3 days	Lower pole of right kidney	3.5 × 3.5 × 3.2	NSE, Vimentin, α-Inhibin, S-100	CAM5.2, CD10, EMA, AE1/AE3, HMB45, Melan-A, PAX2, PAX8, SMA, CD34, CD31, CD68	No	No recurrence 27 months after nephrectomy

F, Indicates focal; GFAP, Glial fibrillary acidic protein; GLUT1, Glucose transporter 1.

lar network are found in many types of tumors including RH and clear cell RCC. The presence of pericytomatous growth pattern and intracytoplasmic lipid vacuoles are closely related to RH. In contrary, hyaline globules, rhabdoid appearance tumor cells, and sclerosis zones are commonly associated with clear cell RCC. In addition, immunohistochemistry (IHC) is highly useful for the differential diagnosis. RH usually shows strong positivity for S-100, NSE,  $\alpha$ -Inhibin, and Vimentin, which are commonly negative in clear cell RCC. While clear cell RCC always demonstrates positive for CD10, AE1/AE3, CAM5.2, PAX2, and PAX8, which are routinely negative in RH. Other differential diagnoses include epithelioid angiomyolipoma, capillary hemangioma, paraganglioma, and adrenal cortical carcinoma. It is generally not difficult to distinguish RH from these lesions based on characteristic morphology and immunophenotype.

It is noteworthy that IHC is essentially helpful for the correct diagnosis of renal hemangioblastoma. All 17 cases demonstrated similar immunophenotype to those of the CNS, with tumor cells usually positive for S-100, NSE,  $\alpha$ -Inhibin and Vimentin, nevertheless negative for CD10, PAX2, PAX8, CD68, epithelial markers (e.g., AE1/AE3, CK7, CK8, CAM5.2 and EMA), muscle markers (e.g., desmin, SMA and calponin), neuroendocrine markers (e.g., chromogranin A and synaptophysin), melanocytic markers (e.g., HMB45 and melan-A), mesothelial markers (e.g., calretinin, D2-40 and WT-1), and endothelial markers (e.g., CD31 and CD34). As shown in **Table 1**, all 17 cases were positive for S-100, 15 cases were positive for  $\alpha$ -Inhibin, 14 cases were positive for NSE, and 10 cases were positive for Vimentin. These results indicate that S-100,  $\alpha$ -Inhibin, NSE and Vimentin appeared to be the most sensitive markers for the diagnosis of renal hemangioblastoma. However, aberrant immunohistochemical staining results might be occasionally observed in RH. In 2013, Zhao et al [3] reported a primary RH occurring in a 51-year-old woman, with tumor cells strongly and diffusely positive for PAX8, CD10,  $\alpha$ -Inhibin, S-100, NSE and Vimentin. Recently, Jiang et al [9] described a sporadic hemangioblastoma of the kidney in a 57-year-old female, in which tumor cells demonstrated unexpected positive staining of PAX2 and focal CD10 expres-

sion. CD10, PAX8 and PAX2 are ordinarily positive in normal kidney and in many renal epithelial neoplasms including clear cell RCC, whereas usually negative in CNS hemangioblastoma. Pathologist should pay attention to the unexpected positive expression of CD10, PAX8 and PAX2 in RH, which may lead to misdiagnosis. The appearance of abnormal immune phenotype in RH might be correlated with the earlier opinion that the hemangioblastoma has the capability to express site-specific antigens, perhaps as a result of derivation from organ-specific pluripotent cells or due to microenvironmental factors which influence antigen expression [7, 9]. Therefore, it is essential to select sufficient markers to carefully evaluate morphological features to avoid misdiagnosis.

In summary, RH is an extremely rare benign tumor of uncertain histogenesis with indolent clinical behavior. Nevertheless, characteristic imaging features of RH have not been discovered up to now, therefore it is likely to be misdiagnosed as malignant before operation which leads to patients receiving excessive treatment. So a correct diagnosis is extraordinary essential to avoid overdiagnosis and unnecessary clinical treatment. In this article, we presented an additional case of primary RH occurring in 14-year-old child, which indicated that RH occurred not only in adults but also in children. In our opinion, from the reported 16 cases and our case, we may draw a conclusion that there might be no relations between primary RH and VHL disease. However, more cases should be documented for further recognition of this peculiar rare type of renal neoplasm and developing new effective preoperative diagnosis methods for its precision therapy.

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### Disclosure of conflict of interest

None.

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