

Sporadic Hemangioblastoma of the Kidney: A clinicopathologic study of 3 cases and review of the literature

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Case report

Keywords: Hemangioblastoma, Kidney, von Hippel-Lindau disease, immunohistochemistry

Posted Date: November 13th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-106987/v1>

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Abstract

Background: Hemangioblastoma is a benign tumor of unknown histogenesis that mainly occurs in the central nervous system (CNS) associated with von Hippel-Lindau (VHL) disease. Much attention has been paid to the renal hemangioblastoma, but there are still some challenges in the differential diagnosis.

Case presentation: Here, we describe three cases of sporadic renal hemangioblastoma with no clinical features of VHL diseases. All the three patients (male: 2; female: 1) were 40-56 years old. In all cases, the tumors were surrounded by a thick fibrous capsule and well-demarcated from the surrounding renal parenchyma. Tumors were composed of sheets or nests of polygonal to short spindle tumor cells and a rich capillary network. In case 1 and case 3, the large polygonal tumor cells contained abundant pale or eosinophilic cytoplasm, and some of the cells possessed intracytoplasmic lipid vacuoles. In case 2, tumor cells were characterized by uniform size, mild, clear or lightly stained cytoplasm and typical "clear cell" appearance. In the views of immunohistochemistry, the polygonal stromal cells were strongly and diffusely positive for α -inhibin, NSE, S100 protein, and vimentin. CD10 and PAX8 were positive, while EMA and CK showed focally positive in case 3. CK8/18, HMB45, MelanA, CgA, Syn, SMA, Desmin and CD56 were all negative. CD34 and CD31 outlined the contours and distribution of vascular networks in tumors.

Conclusions: Renal hemangioblastoma is rare and prone to be misdiagnosed. More attention should be paid to the morphological features and reasonable application of immunohistochemistry for the diagnosis of hemangioblastoma.

Background

Hemangioblastoma, a benign tumor of unknown histogenesis, mainly occurs in the central nervous system (CNS), such as cerebellum, brainstem and medulla oblongata. In a large number of cases, the pathogenesis of hemangioblastoma is associated with von Hippel-Lindau (VHL) disease that is an autosomal dominantly inherited neoplastic disorder with germline mutations in the *VHL* gene on chromosome 3p25. Whereas, in most of the other cases, the onset of hemangioblastoma is usually sporadic (1). It has been reported that hemangioblastoma may occur outside the CNS such as soft tissue, peripheral nerve, bone, skin, liver, lung, pancreas, kidney, retroperitoneum, bladder, adrenal gland, and gastrointestinal tract (2).

Differential diagnosis of sporadic renal hemangioblastoma is a huge challenge in clinical settings as it is similar to other malignancies such as renal cell carcinoma (RCC). In this case report, we presented three cases of sporadic renal hemangioblastoma without clinical evidence of VHL disease. Meanwhile, a literature review was performed to further understand the clinicopathologic features and differential diagnosis of this rare renal tumor.

Case Presentation

Material And Methods

The tumor samples were obtained from all cases after nephrectomy. Then the samples were fixed in 10% buffered formalin and embedded in paraffin. The sections (4 µm) were stained with hematoxylin and eosin. The histological features of the tumor mass were evaluated by two experienced pathologists. Immunohistochemistry stain was conducted with Ventana BenchMark XT automated IHC stainer (Roche, Basel, Switzerland). Sections treated with PBS served as negative control, and the positive control was using the specific tissues according to the manufacturer's instructions. Antibody information was given in Table 1.

Table 1
Antibody information

Antibody	Clon	Source	Dilution
CK	AE1/AE3	Dako	1:100
EMA	E29	Dako	1:500
CK8/18	Cam5.2	Dako	1:200
Vimentin	V9	Dako	1:200
CD10	56C6	Novocastra Laboratories	prediluted
Syn	polyclone	Dako	1:200
CgA	polyclone	Dako	1:100
NSE	polyclone	Dako	1:100
CD56	123C3	Dako	1:500
CD34	(QBEnd/10	Dako	1:50
CD31	JC/70A	Dako	1:50
PAX8	polyclone	Proteintech Group	1:800
α-inhibin	R1	Dako	1:50
HMB45	polyclone	Dako	1:50
MelanA	A103	Novocastra Laboratories	1:100
S100	polyclone	Dako	1:2000
Desmin	D33	Dako	1:50
SMA	1A4	Dako	1:200
Ki67	MIB-1	Dako	1:50

Results

Clinical history

Case 1

A 40-year-old male showed a hyperechoic mass in the middle pole of the right kidney after ultrasonography. Color doppler flow indicated shifted peripheral vessels around the mass and abundant blood flow signals. CT examination showed a heterogeneous soft tissue mass in the middle later pole of the right kidney, which showed obvious inhomogeneous enhancement after intensity (Fig. 1A). On this basis, RCC was suspected. The patient had no familial history or clinical evidence of VHL disease. An encapsulated tumor (3 × 3 × 3 cm) was seen to protrude outward from the kidney after nephrectomy. The cut surface was in a color of grayish-red or grayish-brown. The tumor mass was solid and tough, with no necrosis or cystic degeneration (Fig. 1B). The patient was followed up for at least 9 years with no tumor recurrence or metastasis.

Case 2

A healthy 45-year-old female was admitted to the hospital after trauma. CT scan displayed a round mass in the middle pole of the right kidney, with a diameter of about 3 cm. The tumor showed a clear boundary. CT scan showed equal and low confounding density, together with significant strengthening after enhancement (Fig. 1C). The clinical diagnosis was RCC and radical nephrectomy was carried out. For the macroscopic observation, there was a round tumor in the middle of the kidney (2 cm × 2 cm × 2 cm) and with complete capsule. The cut surface was in a grey-red or grey-brown color with a little grey-white at the center. The tumor was solid and tough, with no necrosis or cystic changes (Fig. 1D). She had no erythrocytosis, and no VHL-related tumors were detected. The patient was followed up for 6 years, and no tumor recurrence or metastasis was seen.

Case 3

A 56-year-old male was admitted to our hospital because of schizophrenia. CT scan indicated a round mass (8 cm) at the dorsal side of the right kidney. The lesion presented a clear boundary, which protruded to the extrarenal region. Meanwhile, low density necrosis was observed in it. There was a remarkable enhancement in arterial stage, but no enhancement was noticed in internal necrosis (Fig. 1E). Then the right kidney was removed by nephrectomy. A well circumscribed, soft gray-brown color tumor (8 cm × 7 cm × 5 cm) was observed in the middle of the kidney (Fig. 1F). The patient had no familial history or clinical evidence of VHL disease. The patient was still alive and was followed up for at least 5 years.

Microscopic features

In all cases, the tumors were surrounded by a thick fibrous capsule and well-demarcated from the surrounding renal parenchyma (Fig. 2A). Tumors were composed of sheets or nests of polygonal to short spindle tumor cells and a rich capillary network. In case 1 and case 3, the large polygonal tumor cells contained abundant pale or eosinophilic cytoplasm, and some of the cells possessed intracytoplasmic

lipid vacuoles. In case 1, there were diverse cell morphology, varying nuclear size and atypical of partial cells (Fig. 2B and 2C). However, tumor cells were characterized by uniform size, mild, clear or lightly stained cytoplasm and typical "clear cell" appearance in case 2 (Fig. 2D). No mitosis and necrosis were found in all cases. Significant hyaline degeneration of stromal cells could be seen in case 3 as well as psammoma-like calcification (Fig. 2E and 2F). In all 3 cases, there were edema and hemosiderin deposition in the interstitium.

Immunohistochemistry

The polygonal stromal cells demonstrated strong and diffuse positivity for α -inhibin (Fig. 3A), NSE (Fig. 3B), S100 protein (Fig. 3C), and vimentin. CD10 (Fig. 3D) and PAX8 (Fig. 3E) were positive in case 3. Additionally, EMA and CK were focally positive in case 3. The neoplastic cells uniformly showed negative reactivity with immunohistochemical antibodies to CK8/18, HMB45, MelanA, CgA, Syn, SMA, Desmin and CD56. CD34 and CD31 outlined the contours and distribution of vascular networks in tumors (Fig. 3F). Ki67 showed a proliferative index of less than 3%.

Discussion

Hemangioblastoma is often sporadic and partly related to VHL disease. Sporadic hemangioblastoma mainly occurs in the cerebellum and typically present as cystic masses. Multiple hemangioblastomas can also involve the brainstem, spinal cord, nerve roots and retina, which are closely connected with VHL disease. In recent years, raising attention has been paid on extraneural hemangioblastomas (2–4). To our knowledge, there have been 24 cases of sporadic renal hemangioblastomas in English literatures (3–16). Their clinical characteristics, along with three cases in current study, were summarized in Table 2. Twenty-one of 24 cases in the literature as well as our 3 cases have completely clinical data. The tumors in 19 cases (70.3%) were located in the right kidney and most of the patients were male (17/26, 65.4%). Among the male cases, 14 (53.8%) were aged < 50 yrs (ranged 16–71, mean age 45.19) and the tumor size was in a range of 1.2 cm-15 cm (mean size 4.2 cm). The sporadic renal hemangioblastomas was more likely to occur in the right kidney. It seemed that such disease was more prone to present in the young adults, but further patients are required in future to further confirm this phenomenon. There were no significant clinical symptoms, and occasional symptoms such as lumbar pain or hematuria were observed, in which only 1 case showed polycythemia. CT scan showed clear round or quasi-round low-density mass in the renal parenchyma, which presented uneven enhancement after enhanced scan. It would be easily misdiagnosed as clear cell RCC or angiomyolipoma. Interestingly, Michele et al found most of cases reported in the literature were from the Far East, and considered that there might be an unknown genetic feature common to members of a particular ethnic or racial group (2).

Table 2
Clinical characteristics of 27 cases of renal hemangioblastoma

Year	Reference	Site/size(cm)	Age	Gender	Clinical feature of VHL	VHL gene testing	Follow-up (months)
2007	Nonaka et al (14)	R/6.8	71	M	None	No	NED/108
2010	Ip et al (6)	R/5	58	M	None	Yes	NED/24
2010	Ip et al (6)	R/3.5	55	F	None	No	NED/5
2011	Verine et al (8)S	L/3.2	64	M	None	No	NED/12
2012	Wang et al (13)	R/2.7	29	M	None	Yes	NED/20
2012	Liu et al (7)	L/1.2	16	F	None	No	NED/6
2012	Yin et al (12)	R/5.3	61	M	None	No	NED/12
2013	Wang et al (9)	R/6.5	61	M	None	No	NED/12
2013	Jiang et al (15)	R/3	51	M	None	Yes	NED/6
2013	Zhao et al (11)	R/6	51	F	None	No	NED/12
2014	Doyle and Fletcher (4)	R/4.5	58	M	None	No	NED/19
2014	Doyle and Fletcher(4)	L/2–15(3tumors)	42	F	None	No	NED/5
2014	Doyle and Fletcher(4)	R/2.7	29	M	None	No	NED/32
2015	Kuroda et al (16)	L/3.6	37	M	None	No	NED/Not stated
2015	Wu et al (10)	R/3.2	30	M	None	No	Died
2015	Wu et al (10)	R/unkown	57	F	None	No	NED/Not stated
2015	Wu et al (10)	R/2.3	48	M	None	No	NED/42
2015	Wu et al (10)	L/4.1	25	M	None	No	NED/27

NED: no evidence of disease; VHL: von Hippel-Lindau disease.

Year	Reference	Site/size(cm)	Age	Gender	Clinical feature of VHL	VHL gene testing	Follow-up (months)
2015	Wu et al ⁽¹⁰⁾	L/unkown	36	F	None	No	NED/3
2017	Xu et al ⁽⁵⁾	L/2.2	61	M	None	Yes	NED/72
2018	Muscarella et al ⁽³⁾	L/3.5	19	F	None	Yes	NED/96
2018	Muscarella et al ⁽³⁾	R/3	28	F	None	Yes	NED/108
2018	Muscarella et al ⁽³⁾	R/3.1	47	M	None	Yes	NED/84
2018	Muscarella et al ⁽³⁾	R/unkown	Unkown	Unkown	None	Yes	Not available
	Current case 1	R/3	40	M	None	No	NED/108
	Current case 2	R/2	45	F	None	No	NED/72
	Current case 3	R/8	56	M	None	No	NED/60
NED: no evidence of disease; VHL: von Hippel-Lindau disease.							

Macroscopically, most tumors appear as well- defined masses surrounded by a thick fibrous capsule, only 2 cases presented areas of poorly marginated growth or the tumor broke through the fibrous capsule (**5, 10**). In contrast to CNS hemangioblastoma, renal tumors generally presented as a solid mass, occasionally with small focal cystic changes (**6, 14**). The cut surface often show grayish white, grayish yellow, grayish brown or red-brown to gray-yellow color, foci hemorrhage and necrosis were observed incidentally (**12**).

Histologically, renal hemangioblastomas had been well demarcated from the surrounding renal parenchyma, and some cases showed fibrous pseudocapsule. Similar to CNS hemangioblastoma, renal hemangioblastoma was composed of large, polygonal vacuolated stromal cells and a rich capillary network. According to the abundance of stromal cells, tumors were divided into cellular and reticular subtypes. Tumor cells were mild, presenting round nuclei with fine chromatin, microvacuoles within cytoplasm and rich in lipids. Eosinophilic hyaline globules were found both within tumor cell cytoplasm and within the stroma in 2 cases (**6, 11**). Atypical cells and cells with rhabdoid features presented in some cases, which may be mistaken for a malignant tumor (**12, 16**). In addition, a few mitotic activity and focal necrosis were also been documented (**10, 12**). Except classical rich capillary network, dilated thick-walled

vessels which similar to the thick-walled veins in angiomyolipoma could be observed in renal hemangioblastoma and stromal edema, fibrotic, hyalinization are also common findings. Focal calcification of the fibrous stroma and psammoma body-like calcifications were described by some studies (8, 11, 14). In this study, tumor cells distributed in sheets or lobular, with abundant eosinophilic cytoplasm and partly had lipid vacuoles (case1 and case 3). In some areas, atypical cells could be seen in case 1. In case 2, the stromal cells were scattered in small nests among the vascular networks and showed a transparent cytoplasm. Significant hyaline degeneration of stromal cells could be seen in case 3, together with psammoma-like calcification. Edema, hemosiderin deposition was observed in the interstitium in all 3 cases.

Based on the literature review, there were more than twenty antibodies utilized in the differential diagnosis of renal hemangioblastomas, including NSE, S100, α -inhibin, vimentin, AE1/AE3, EMA, PAX-8, PAX-2, CAIX, CD10, CK7, CK8/18, calretinin, HMB45, MelanA, CgA, Syn, SMA, Desmin, MSA, Calponin, GLUT-1, brachyury, CD34, and CD31. NSE, S100, vimentin and α -inhibin were strong positive in all reported renal hemangioblastomas, which showed similar expression pattern compared with that in CNS hemangioblastomas (7, 10). Whereas, the expression of CK7, CK8/18, calretinin, HMB45, MelanA, CgA, Syn, and Desmin was negative in all cases. CD34 and CD31 outlined the contours and distribution of vascular networks in tumors. However, renal hemangioblastomas showed distinct immuno-profiles from CNS tumors. RCC markers (i.e. PAX-8, PAX-2, CAIX and CD10) were observed to be diffuse or at least focally expressed in renal hemangioblastoms (5, 10–12, 15, 16). As for the abnormal immunohistochemical expression of renal hemangioblastomas, several authors speculated that the possible explanation was that these tumors were derived from pluripotent mesenchymal cells and acquired site-specific markers of their parental organs during tumorigenesis (11, 12, 14). Additionally, AE1/AE3 and EMA were also locally expressed in renal hemangioblastomas (6, 11, 12, 15). Similar to the cases in the literatures, all cases in our case were positive for NSE, S100, α -inhibin and vimentin. In addition, 1 case was positive for PAX8, CD10 and focal EMA positive. CK8/18, HMB45, MelanA, CgA, Syn, SMA, Desmin and CD56 were all negative. Expression of GLUT1 in CNS hemangioblastoma had been reported to be helpful for differential diagnosis with metastatic RCC. Unlike RCC staining, there was strongly endothelial staining in most hemangioblastomas (17). However, this finding was still controversial, as there were some doubts on the low specificity and tendency for high background staining (18). Recently, expression of brachyury has been described in cerebellar hemangioblastoma tumour cells (18, 19). Tirabosco et al (18) reported nuclear expression of brachyury in stromal cells in all 14 CNS cases. However, Doyle and Fletcher (4) reported no expression of brachyury in extraneural tumors.

VHL disease is an autosomal dominant hereditary disorder leading to clear cell tumors in various organs, such as CNS hemangioblastoma, pancreatic microcystadenoma, pheochromocytoma, epididymal papillary cystadenoma, endolymphatic sac tumor of the inner ear, and renal clear cell carcinoma. *VHL* gene is located at the short arm of chromosome 3 (3p26-P25). Its inactivation will lead to VHL protein synthesis disorder, which plays a key role in the regulation of the hypoxia response pathway. About 25% of CNS hemangioblastomas are associated with VHL disease and 75% are sporadic. Renal

hemangioblastoma were generally considered to be independent of VHL genetic mutations, as aberration *VHL* gene has been detected in none of the cases previously reported. However, Xu et al (8) reported that a tumor type showing *VHL* gene mutation and hypermethylation in exon 2. We consider that the relationship between renal hemangioblastoma and *VHL* gene remains uncertain and more studies are needed.

Renal hemangioblastoma is rare and is most likely to be misdiagnosed as clear cell RCC as it is characterized by a rich vascular network and epithelioid cells with clear or eosinophilic cytoplasm. In terms of organizational structure, sheet-like or compact architecture were common features of hemangioblastomas. In contrast, clear cell RCC is more likely to be characterized by tubular, alveolar, nests or papillary structures. In clinical settings, it might be a clue for the differential diagnosis of hemangioblastomas. Additionally, immunohistochemistry plays a key role in distinguishing clear cell RCC from hemangioblastoma. In the views of immunohistochemistry, NSE, S100 and α -inhibin were expressed in almost all hemangioblastomas, while there was no expression in clear cell RCC. Meanwhile, clear cell RCC is usually positive for AE1/AE3, PAX8, PAX2, CD10 and CA9.

However, there were two cases of clear cell RCC with hemangioblastoma-like features in the recent years (20, 21). Meanwhile, some RCC markers were positive in hemangioblastoma as above-mentioned. Therefore, a panel of antibodies were required for differential diagnosis. Another major confused tumor is epithelioid angiomyolipoma (AML), which could be based on the presence of large thick-walled veins, spindle smooth muscle bundles and various proportion of mature adipose tissue. Immunohistochemically, AML showed positive staining for HMB45, and MelanA while showed a negative reaction for α -inhibin, NSE, S100 in contradistinction to hemangioblastoma. Other differential diagnosis included adrenocortical adenocarcinoma and paraganglioma, which could be distinguished by careful morphological observation and adequate immunohistochemistry.

Conclusion

Renal hemangioblastoma is a rare tumor with benign nature. We reported 3 cases with renal hemangioblastoma and reviewed the literatures. Clinically, it occurs in middle-aged and younger population. In the micromorphological views, it shared similarities with clear cell RCC and AML. Genetically, renal hemangioblastoma appeared to have no related to VHL gene defects, but *VHL* gene mutations were found in limited cases. Recognition of this tumor and careful immunohistochemistry investigation are keys to a correct pathological diagnosis.

List Of Abbreviations

CNS: central nervous system; VHL: von Hippel-Lindau; AML: angiomyolipoma

Declarations

Ethics approval and consent to participate

The study protocols were approved by the Ethics Committee of the Tai'an Central Hospital. Each patient signed the informed consent.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

XYM wrote the manuscript. LXM revised the manuscript. MXH and MY did the data analysis. LJ and ZRY did the data collection. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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Figures

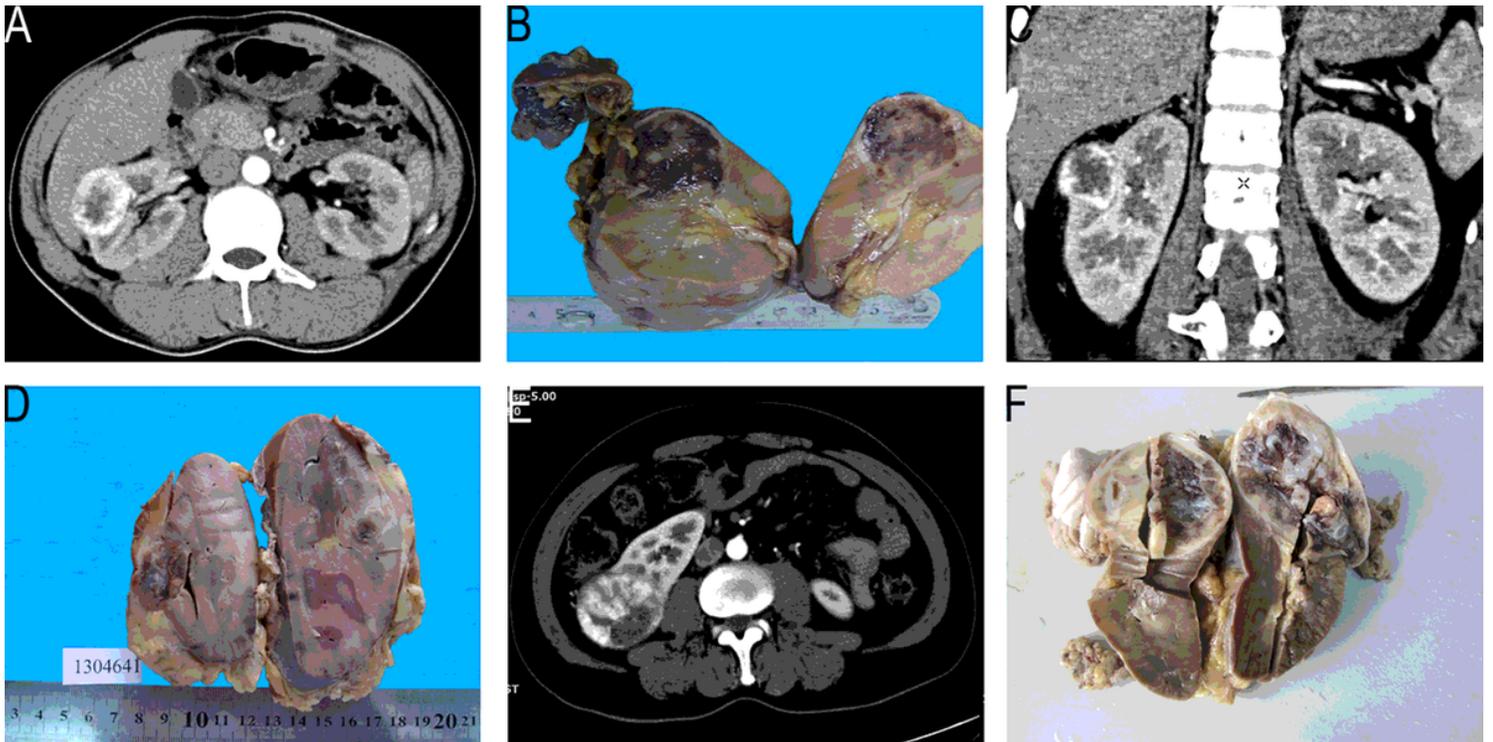


Figure 1

CT and macroscopic findings. (A). CT showed a heterogeneous soft tissue mass at the middle later pole of the right kidney in case 1. (B). The cut surface of the tumor was in a grayish-red to grayish-brown color. It was solid and tough, with no necrosis or cystic degeneration in case 1. (C). A round mass was seen at the middle pole of the right kidney of case 2 with a clear boundary and significant enhancement after contrasting enhanced scan. (D). The tumor was solid and tough, while the cut surface was in a color of grey-red and grey-brown with a little grey-white at the center. No necrosis or cystic changes were observed in case 2. (E). In case 3, there was a rounded mass at the dorsal side of the right kidney after CT scan. The lesion had a clear boundary, protruded to the extrarenal and pelvic parts, presenting low density necrosis. (F). A tumor in a soft gray-brown color at the middle of the kidney with well-circumscribed in case 3.

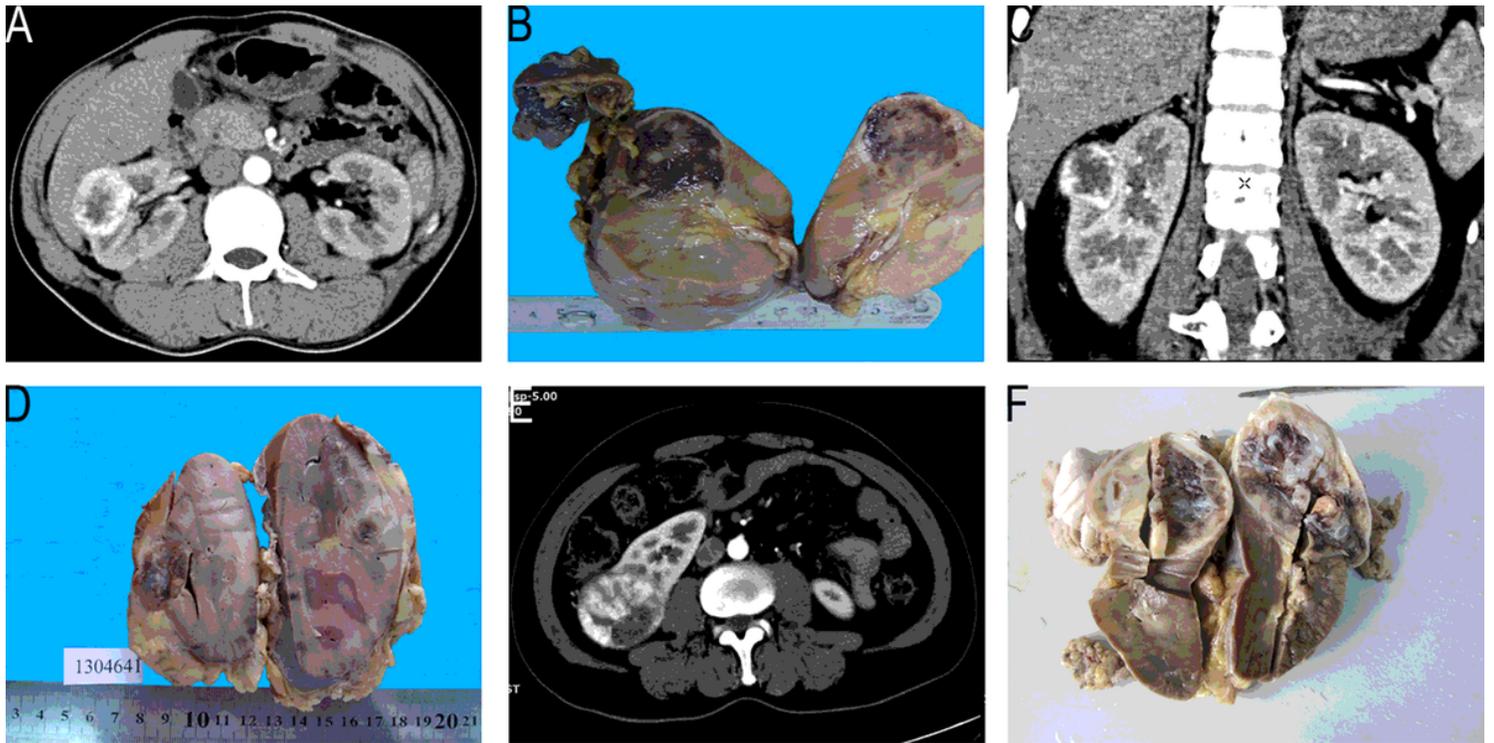


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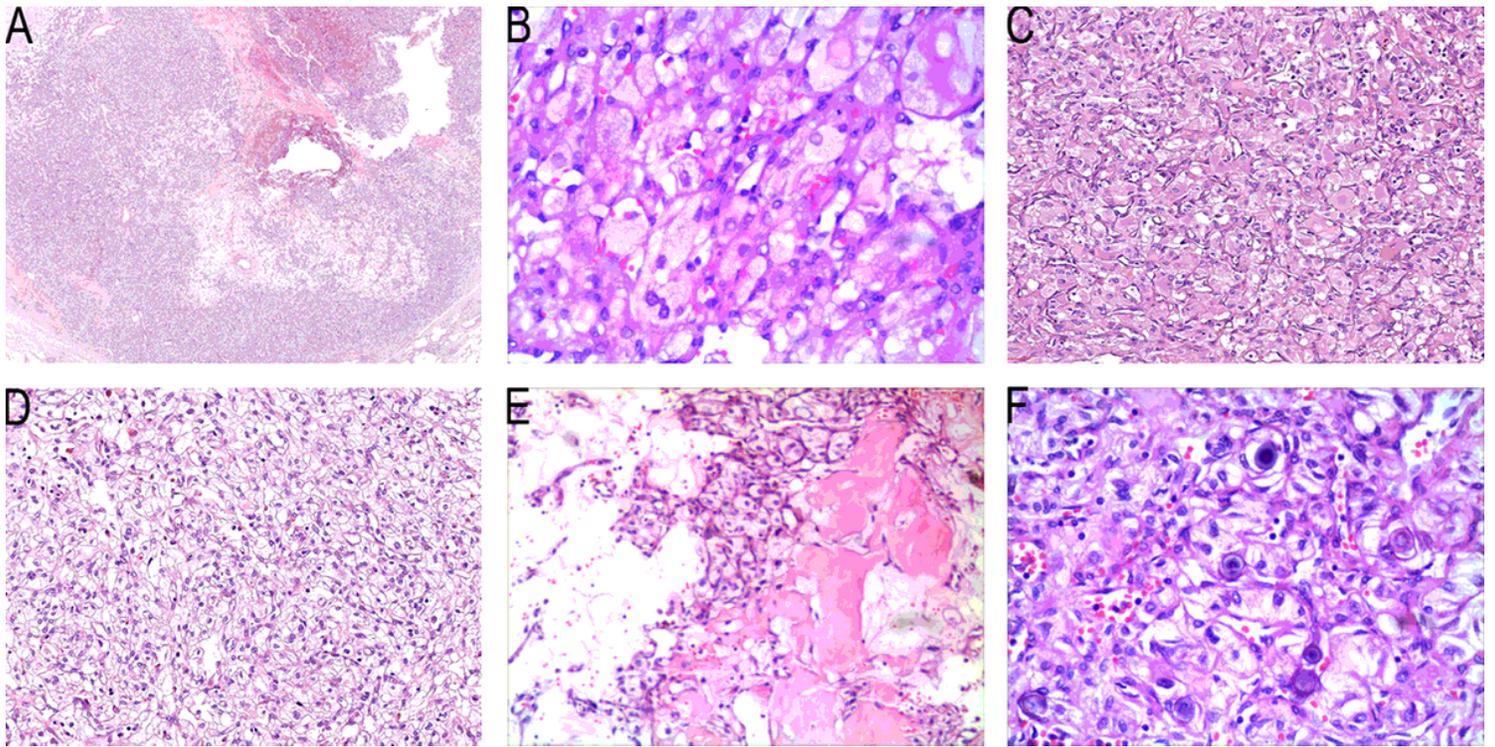


Figure 2

Histological features. (A). The tumors were surrounded by a thick fibrous capsule and well-demarcated from the surrounding renal parenchyma. (B). The large polygonal tumor cells contained abundant pale or eosinophilic cytoplasm. Some of the cells possessed intracytoplasmic lipid vacuoles. (C). Cell morphology, nuclear size and atypical of partial cells in case 1. (D). Tumor cells were characterized by uniform size, mild, clear or lightly stained cytoplasm and typical "clear cell" appearance in case 2. (E). Significant hyaline degeneration of stromal cells in case 3. (F). Psammoma-like calcification in case 3.

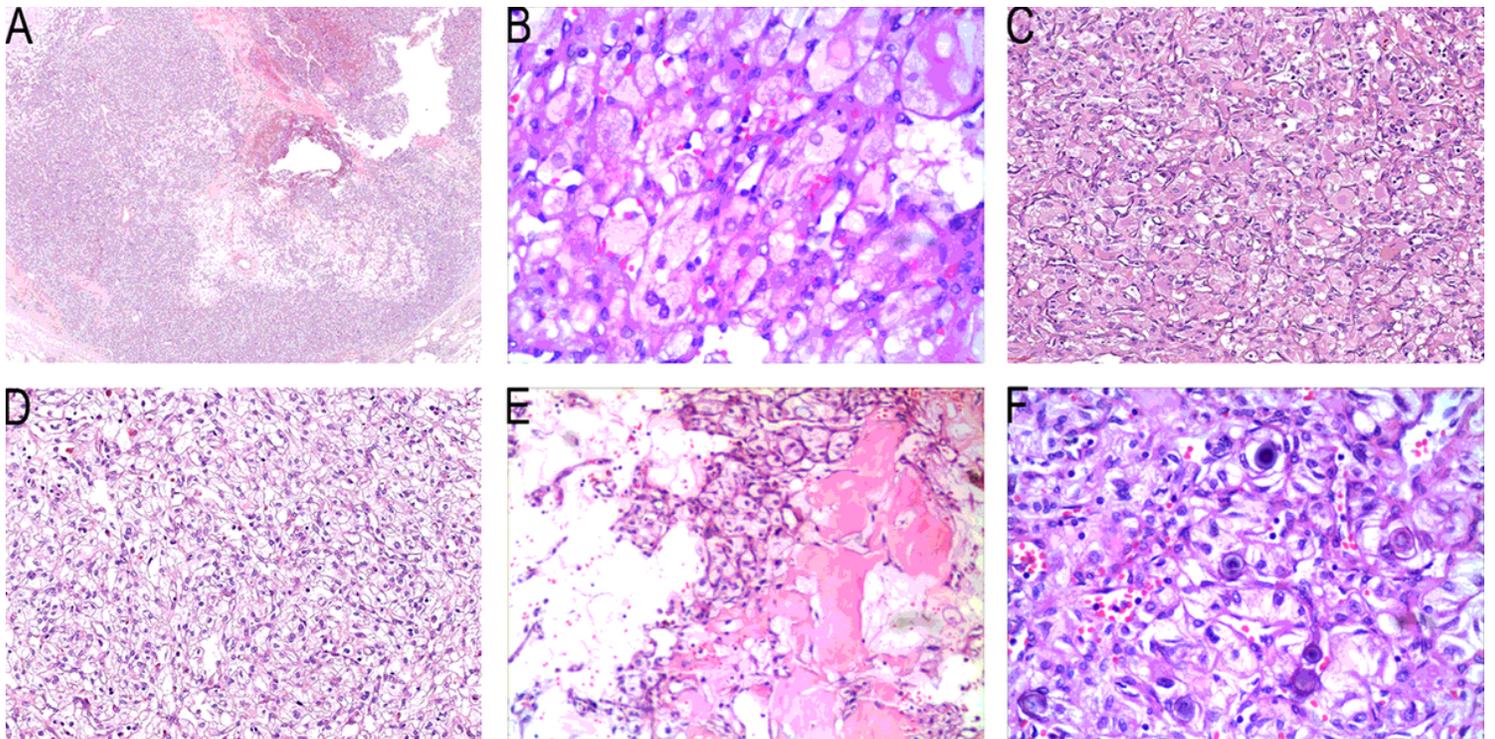


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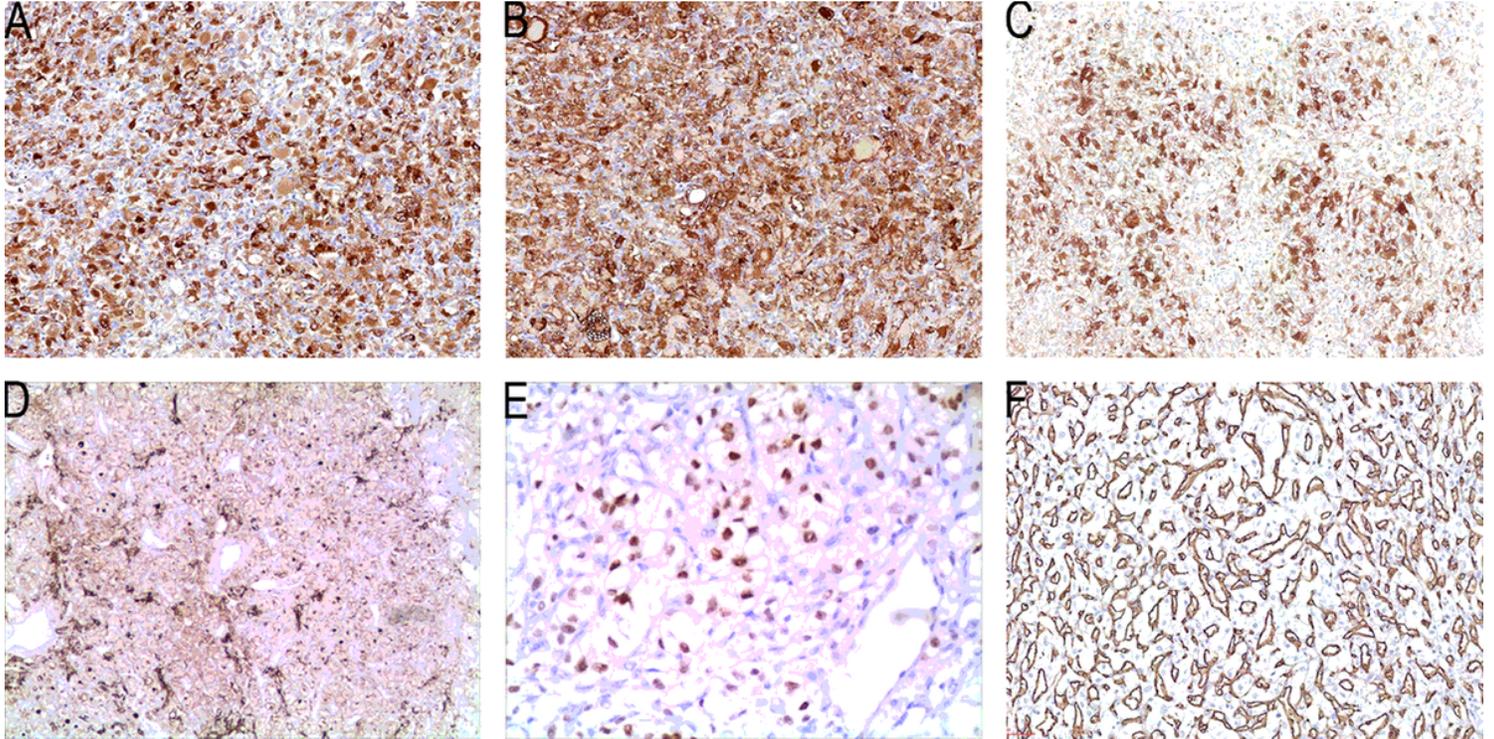


Figure 3

Immunohistochemical findings. (A), Tumor cells demonstrated diffuse and strong reactivity for α -inhibin. (B). NSE was diffuse and strongly positive. (C). S100 was positive in case 2. (D). CD10 showed diffuse positive in case 3. (E). Tumor cells were positive on PAX8. (F). CD34 highlighted the endothelial cells lining the rich vascular network.

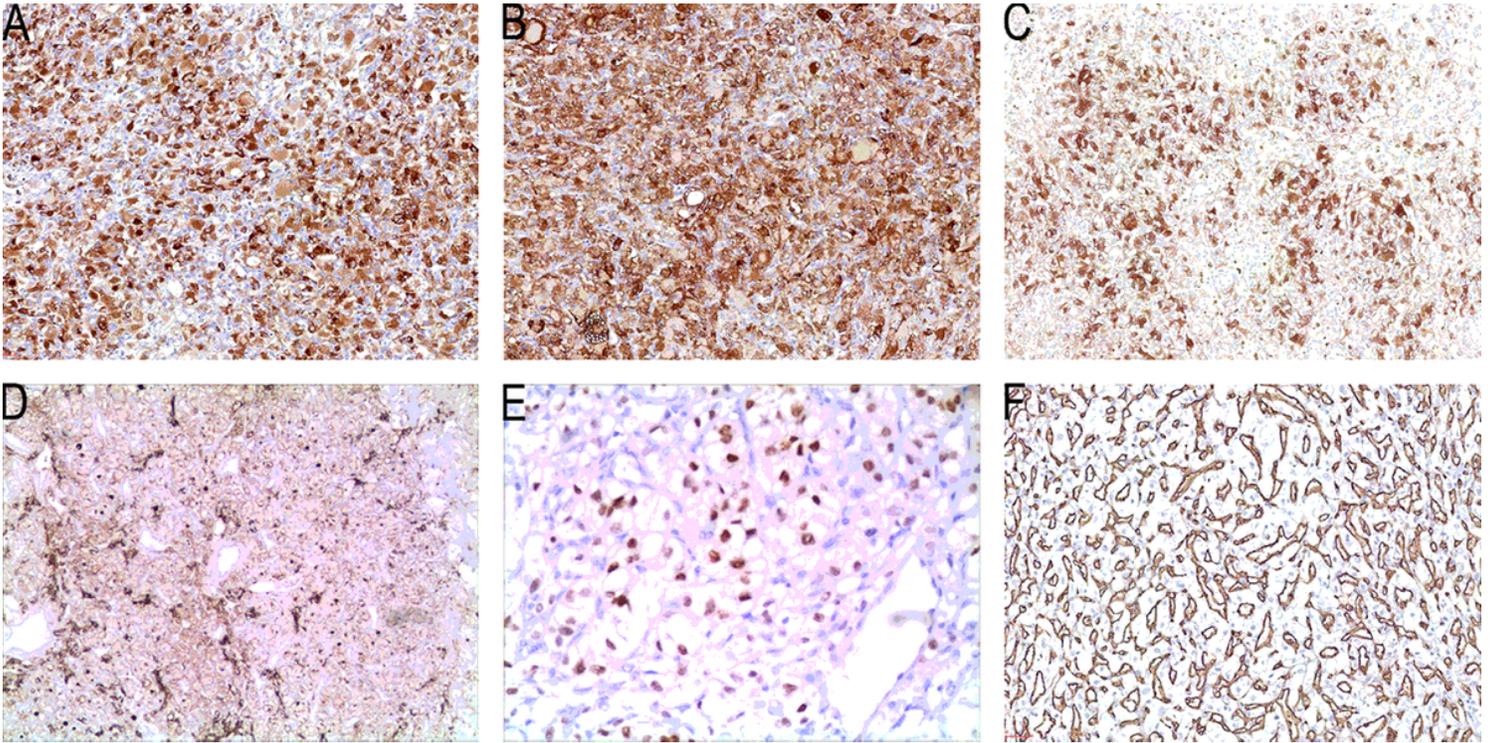


Figure 3

Immunohistochemical findings. (A), Tumor cells demonstrated diffuse and strong reactivity for α -inhibin. (B). NSE was diffuse and strongly positive. (C). S100 was positive in case 2. (D). CD10 showed diffuse positive in case 3. (E). Tumor cells were positive on PAX8. (F). CD34 highlighted the endothelial cells lining the rich vascular network.