Renal Cell Carcinoma with Prominent Hemangioblastoma-Like Pattern, a Case Report with Review of Literature

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Abstract

Background
Renal cell carcinoma (RCC) usually has a prominent vasculature. Rarely, however, the vascular component in these tumors may be well developed, complex and predominant mimicking a hemangioma or hemangioblastoma.

Case presentation
We report the case of a 69-year-old woman who underwent right radical nephrectomy for a renal mass. Pathologic evaluation of the tumor showed that the mass was composed of an extensive and complex vascular component with large numbers of stromal-like cells usually seen in hemangioblastoma. A few focal areas with renal cell carcinoma component were also identified within the tumor. Immunohistochemistry revealed that the carcinoma cells were reactive for CAIX, PAX 8, and focally positive for CK7, and CD10 indicating clear cell carcinoma. The vascular component strongly reacted for CD31 and CD34 while stromal-like cells were positive for S100, inhibin, GLUT1, vimentin and CD10 (stromal-like cells) and were negative for cytokeratins.

Conclusions
This is a rare finding with only four previously reported cases.

Keywords: Renal cell carcinoma; Clear cell variant; Hemangioblastoma; Immunohistochemistry.

Introduction
Renal cell carcinomas often have a well-developed thin-walled vascular network thought to result from secretion of various angiogenic factors by tumor cells [1]. Rarely renal carcinomas may have an extensive and extremely prominent vascular component so that these tumors may mimic a vascular tumor such as hemangioma or hemangioblastoma. The diagnosis of renal carcinoma in these cases would depend on the recognition of the epithelial component which may on occasion be scanty requiring extensive sampling. In this article, we document a case of clear cell renal cell carcinoma with prominent hemangioblastoma-like pattern in which the carcinoma component was scanty and only recognized after thorough sampling. Review of the literature revealed that there are only 4 previously reported cases of renal cell carcinoma with a hemangioblastoma-like pattern.

Case presentation
A 69-year-old woman was seen in the urology clinic at Hamad general hospital with an incidentally discovered asymptomatic right renal mass. Computed tomography (CT) of abdomen and pelvis (shown in Fig. 1. A) Revealed a solid heterogeneously arterially enhancing mass measuring approximately (38 x 36 x 42 mm) in the right lower pole anterior cortex with central non-enhancing areas, blunting of the adjacent calyceal system and surrounding fat stranding. No intrallesional calcifications are seen. Invasion of the proximal third of the right ureter is noted. Patent renal arterial and venous vasculature. No significant perirenal retroperitoneal lymph nodes are seen. A right radical nephrectomy was performed.

The resected specimen consisted of 523-gram kidney measuring 15.5 x 10 x 7 cm surrounded by abundant adipose tissue and with a well-circumscribed 3.5, red-brown and hemorrhagic mass in the lower pole. The mass was confined to the kidney. The remainder of the renal cortex was unremarkable with a well-defined cortical medullary junction (shown in Fig. 1.B).

Microscopic examination (shown in Fig. 1. C-H) revealed that most of the mass was composed of extensive vascular component with extremely rich intricate thin-walled network of blood vessels which in some areas revealed a prominent sinusoidal pattern. In addition, scattered throughout the tumor there were loosely arranged cells with abundant pale to eosinophilic cytoplasm and relatively small nucleci. These cells were reminiscent of the stromal cells usually seen in hemangioblastoma. More than 95% of the tumor was composed of these two elements. In a few
Figure 1: A: CT abdomen and pelvis: Arterially enhancing right lower pole solid renal mass.
B: Nephrectomy specimen revealing kidney with abundant adipose tissue and a well-circumscribed mass. The mass reveals a hemorrhagic, light brown to dark red cut surface. The remaining kidney parenchyma appears unremarkable.
C: Microscopic appearance of the tumor with a prominent vascular pattern with numerous thin-walled vascular spaces.
D: Another area in the vascular component with a prominent sinusoidal pattern.
E: Tumor with prominent vascular architecture and large numbers of stromal cells.
F: Large numbers of stromal cells in a prominent vascular background.
G: Higher magnification photomicrograph revealing stromal cells with small nuclei and abundant eosinophilic cytoplasm.
H: An area in the tumor with a focus of clear cell carcinoma surrounded by prominent vascular component.
Figure 2: Immunohistochemical features.
A: The carcinoma component is positive for CAIX (membranous).
B: The carcinoma component is positive for CK AE1-AE3 (cytoplasmic), adjacent stromal cells are essentially negative.
C: CD31 highlight complex extremely rich vascular network in the hemangioblastoma-like component.
D: The stromal cells of hemangioblastoma-like component are positive for S100 (cytoplasmic).
E: The stromal cells of hemangioblastoma-like component are positive for GLUT1 (membranous).
F: The stromal cells of hemangioblastoma-like component are positive for inhibin A (cytoplasmic).
Table 1: Immunohistochemical Stain Results

<table>
<thead>
<tr>
<th></th>
<th>CCRCC Component</th>
<th>Vascular component</th>
<th>Stromal-like cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAIX</td>
<td>Diffuse +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PAX 8</td>
<td>Diffuse +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CKAE1/AE3</td>
<td>Diffuse +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CK7</td>
<td>Focally +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MNF 116</td>
<td>Diffuse +</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GLUT1</td>
<td>Diffuse +</td>
<td>Weak +</td>
<td>Diffuse +</td>
</tr>
<tr>
<td>EMA</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CK 8/18</td>
<td>+</td>
<td>-</td>
<td>Diffuse +</td>
</tr>
<tr>
<td>Inhibin</td>
<td>Focally +</td>
<td>-</td>
<td>Focally +</td>
</tr>
<tr>
<td>CD10</td>
<td>Focally +</td>
<td>+</td>
<td>Focally +</td>
</tr>
<tr>
<td>CD31</td>
<td>-</td>
<td>Diffuse +</td>
<td>-</td>
</tr>
<tr>
<td>CD34</td>
<td>-</td>
<td>Diffuse +</td>
<td>-</td>
</tr>
<tr>
<td>Vimentin</td>
<td>Diffuse +</td>
<td>Diffuse +</td>
<td>Diffuse +</td>
</tr>
<tr>
<td>S100</td>
<td>-</td>
<td>-</td>
<td>Diffuse +</td>
</tr>
</tbody>
</table>

Table 2: Summary of cases of renal cell carcinoma with hemangioblastoma-like pattern

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Sex</th>
<th>Gross Feature</th>
<th>Tumor size</th>
<th>Carcinoma type</th>
<th>WHO/ISUP Grade</th>
<th>AJCC Stage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>Male</td>
<td>well demarcated nodule, 3.5 white central area reddish at the periphery, with scattered yellow spots</td>
<td>3.5 cm</td>
<td>Clear Cell Renal Cell Carcinoma</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Female</td>
<td>well demarcated nodule, 3.5 white central area reddish at the periphery, with scattered yellow spots 3.2 cm</td>
<td></td>
<td>Clear Cell Renal Cell Carcinoma</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>Male</td>
<td>Well circumscribed 4 cm tumor, with a variegated yellow hemorrhagic cut surface</td>
<td>4 cm</td>
<td>Clear cell renal cell carcinoma</td>
<td>N/A</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>Female</td>
<td>well-defined 1.7 cm heterogeneous mass, the cut surface had a tan and reddish area with focal cystic change</td>
<td>1.7 cm</td>
<td>Clear cell papillary renal cell</td>
<td>3-Feb</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>Female</td>
<td>well-circumscribed encapsulated red-brown and hemorrhagic mass</td>
<td>3.5 cm</td>
<td>Clear renal cell carcinoma</td>
<td>2</td>
<td>1</td>
<td>Current</td>
</tr>
</tbody>
</table>

Abbreviations: WHO: World Health Organization, ISUP: International Society of Urologic Pathology, AJCC: American Joint Committee on Cancer, N/A: not applicable.
Table 3: Summary of cases of renal cell carcinoma with hemangioma-like pattern

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Gross Feature</th>
<th>Tumor size</th>
<th>Carcinoma type</th>
<th>WHO/ISUP Grade</th>
<th>AJCC Stage</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>Female</td>
<td>well-circumscribed encapsulated tan-brown hemorrhagic mass</td>
<td>2.6 cm</td>
<td>Unclassified hemangioma-like renal cell carcinoma</td>
<td>3</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>Female</td>
<td>Well demarcated soft red-brown tumor with thick capsule</td>
<td>4.4 cm</td>
<td>Low-Grade Clear Cell Renal Cell Carcinoma Mimicking Hemangioma of the Kidney</td>
<td>2-Jan</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>Male</td>
<td>Same as case 5</td>
<td>5.5 cm</td>
<td>Low-Grade Clear Cell Renal Cell Carcinoma Mimicking Hemangioma of the Kidney</td>
<td>2-Jan</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>Male</td>
<td>Same as case 5</td>
<td>2.5 cm</td>
<td>Low-Grade Clear Cell Renal Cell Carcinoma Mimicking Hemangioma of the Kidney</td>
<td>2-Jan</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>Male</td>
<td>Well demarcated soft red-brown tumor with scattered small yellow areas and thick capsule</td>
<td>3.5 cm</td>
<td>Low-Grade Clear Cell Renal Cell Carcinoma Mimicking Hemangioma of the Kidney</td>
<td>2-Jan</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>Male</td>
<td>well-demarcated, diffusely hemorrhagic neoplasm</td>
<td>3.5 cm</td>
<td>Multifocal Capillary Hemangioma-Like Vascular Proliferation of the Kidney Associated with Clear Cell Renal Cell Carcinoma</td>
<td>3-Feb</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>Male</td>
<td>well-capsulated dark brownish solid and cystic mass with extensive haemorrhage</td>
<td>5.7 cm</td>
<td>Clear cell renal cell carcinoma With Hemangioma-Like Features</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: WHO: World Health Organization, ISUP: International Society of Urologic Pathology, AJCC: American Joint Committee on Cancer.

sections, small clusters of epithelial cells were seen primarily at the periphery of the mass. Some of these cells revealed clear cell morphology. This component was only recognized after the entire tumor was submitted for histologic examination. Focally there was suggestion of transition between the carcinoma cells and the stromal cells. The renal cell carcinoma component had histologic nodular grade 2 according to world health organization (WHO) [2]/ International Society of Urologic Pathology (ISUP grade) [3]. No sarcomatoid or rhabdoid features, tumor necrosis or lymph-vascular invasion was identified. The tumor was limited to the kidney with clear margins and the stage was determined by the size (pT1a) according to pTNM, AJCC 8th Edition staging system [4]. The ureter and renal pelvis were uninvolved by the tumor.

Immunohistochemical studies (shown in Fig 2. A-F), showed that the carcinoma component positive for CAIX, PAX 8, CKA/E1/AE3, MNF 116, EMA, and CK 8/18, and focally positive for CK7 and CD10, while vascular component stained strongly for CD31 and CD34 highlighting copious, delicate capillary network. The stromal-like cells stained for S100, inhibin A, GLUT-1, and vimentin, and were negative for HMWCK, CK 5/6, CK 20, GATA3, TFE3, AMACR, Synaptophysin, Chromogranin A, CD117, HMB45 (shown in Table 1). All three cellular components were negative for HMCK, CK5/6. CK20, GATA3, TFE3, AMACR, synaptophysin, chromogranin A, CD117 and HMB45.

**Discussion**

Clear cell renal cell carcinoma is characterized by malignant epithelial cells with clear cytoplasm arranged in solid, alveolar or acinar/ tubular growth pattern interspersed with intricate, arborizing vasculature. Although these tumors are normally highly vascular, in rare cases vascular component may overgrow the carcinoma component. Some of these highly vascular tumors may have hemangioma like appearance while in others the vascular component may resemble hemangioblastoma. Review of the literature reveals that there were four previously reported cases of renal carcinoma with a dominant hemangioblastoma-like component while another seven were found to have a vascular component with hemangioma-like growth. Clinic pathologic details of these cases are summarized in (Table 2 and 3).

There are five cases including the current case, in which the vascular component had a hemangioblastoma-like pattern (shown...
in table 2). All tumors appeared grossly well-circumscribed with reddish, yellow and hemorrhagic cut surface. The tumor size varied from 1.7 to 3.5 cm and all tumors were confined to the kidney. The age of the patient varied from 32 to 75 years. Three of the patients were female while two were male. The carcinoma component in four cases revealed clear cell morphology while one tumor revealed features of clear cell papillary carcinoma. The details of another 7 cases with renal cell carcinoma associated with hemangioma component are given in (shown in table 3). The hemangioma-like component appeared in 2 forms: anastomosing sinusoid-like or delicate micro vascular proliferation. These previous cases were all clear cell renal cell carcinomas, except for one unclassified renal cell carcinoma.

Hemangioblastoma is a benign tumor that can occur sporadically or in association with von Hippel-Lindau disease in approximately one-quarter of the cases. Exceptionally, hemangioblastoma occurs in other sites, such as peripheral nerve, soft tissue, retroperitoneum, skin, liver, pancreas, lung, adrenal, kidney, and urinary bladder, usually in the setting of known von Hippel-Lindau disease. Hemangioblastoma of the kidney is an extremely rare tumor. Histologically, the tumors are circumscribed and composed of sheets of large polygonal cells traversed by an extensive network of arborizing thin-walled blood vessels. Many of the tumor cells may show pleomorphic nuclei, but the mitotic figures were rare. The cytoplasm is eosinophilic, and occasionally finely vacuolated indicating the presence of lipid. On immunohistochemical staining, stromal cells are diffusely positive for NSE, S-100 protein, vimentin and focally express a-inhibin [10]. It has also been suggested that the immunohistochemical staining profile may differ somewhat based on the organ in which tumor arises [11, 12]. This benign neoplasm which can be mistaken for various malignancies such as renal cell carcinoma, epithelioid angiomylipoma, adrenal cortical carcinoma, and paraganglioma. In the previously reported cases of renal carcinoma with hemangioblastoma-like pattern as well as in our case, similar morphologic features are seen, and immunohistochemical staining pattern of stromal cells is also similar. However, the presence of renal carcinoma component distinguishes these tumors from pure hemangioblastoma. Presence of stroma-like cell distinguishes hemangioblastoma from hemangioma [10].

The nature of stromal cells seen in hemangioblastoma is not known. In our case, in some areas, there was suggestion of transition between the carcinoma cells and the stromal-like cells. However, unlike the carcinoma cells, stromal-like cells were negative for epithelial markers but were positive for S-100, Vimentin and Inhibin A. This would suggest that the vascular pattern in our case represents a true hemangioblastoma-like differentiation in a clear cell renal cell carcinoma.

Association of clear cell carcinoma with a dominant vascular component is intriguing (shown in Fig 3). The tumor cells in clear cell carcinoma usually have a deletion of VHL gene located at 3p (p3.25). Normally, pVHL plays a crucial role in the proteasomal degradation of hypoxia-inducible factors HIF1 and HIF2. Lack of a functioning pVHL owing to genetic alterations results in stabilization and accumulation of these factors. Following stabilization, HIFα migrates to the nucleus, where it dimerizes with HIFβ and binds to the hypoxia response element in the nucleus, resulting in expression of a wide array of genes, which leads to a variety of changes in the cell behaviour, including increased cell survival and proliferation, angiogenesis and invasion [13]. Presumably, in some of the cases, angiogenesis becomes a prominent element in the gene expression profile of the carcinoma, giving rise to hemangioma or hemangioblastoma pattern.

Figure 3: Cartoons depicting the role of HIF-a in the metabolism of normal and neoplastic cells. A: In normal cells HIF-a is inactivated by normally functioning pVHL along with several enzymes (collectively known as Ubiquitin). B: In the absence of a normally functioning pVHL, HIF-a stabilizes and accumulates in the cytoplasm. C: HIF-a dimerizes with HIF-b and activates the genes in the hypoxia-inducible factor in the nucleus. This leads to activation of several genes resulting in cell proliferation, increased cell survival, angiogenesis and invasion.
Conclusion

In this case report, we document a case of renal cell carcinoma predominantly composed of hemangioblastoma-like component with minor foci of renal carcinoma. This is a rare finding with only 4 previously reported cases.

Declarations

Ethics approval and consent to participate

All persons gave their informed consent prior to their inclusion in the study.

Consent for publication

This study was approved by the ABHATH Research Committee (Protocol number MRC-04-20-588) at Hamad Medical Corporation, Doha, Qatar.

Availability of data and material (data transparency)

We are disclosing that strictest confidence was maintained for data collection as well as access and application in the study. Data were never shared at any level with any individuals not authorized to access research material. Data were only available upon request by the authors following permission from ABHATH Medical Research Center at Hamad Medical Corporation, Doha, Qatar. We fully understand that the use of confidential data for personal purposes is prohibited.

Competing of interest

The authors declare that they have no conflict of interest.

Authors' contributions:

R. M. A. S., N. M. T. M. and M. A designed the study and performed the experimental work. R. M. A. S., and M. A analysed and interpreted the data. R. M. A. S., D. M. A. S., N. M. T. M. and M. A prepared the manuscript. R. M. A. S., and D. M. A. S. were supporting funding of paper. All authors critically reviewed the manuscript. All authors read and approved the final manuscript. All authors agreed on submission.

References