Chromophobe renal cell carcinoma
(differential diagnosis with clear/ granular cell carcinoma and oncocytoma)

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Chromophobe carcinomas were first described in humans in 1985. Reports in the literature have described an incidence of 5-9% in surgical series. The late discovery is related to its close phenotypic similarity to conventional clear cell carcinoma on the one hand and to oncocytic adenoma on the other hand. Below is a description of the morphological findings.

Gross features
Depending on size, chromophobe renal cell tumors consist of one or more solid tumor nodules with a slightly lobulated surface. In unfixed conditions, the cut surface appears homogeneously orange and turns beige or sandy after formalin fixation. The uniform pale cut surface may be interspersed with a few hemorrhages. Lack of necrosis is a very characteristic gross feature. While most well-differentiated chromophobe carcinomas present a pale cut surface, a slight brown colored cut surface is usually associated with moderate to less differentiated chromophobe carcinoma.

Microscopic features
In general, two different cell types can be described. The basic chromophobe cell type is characterized by large polygonal cells with a transparent, slightly reticulated cytoplasm with prominent cell membranes leading to a plant cell-like appearance. The diagnostic hallmark is the lack of cytoplasmic coloring with routine dyes but a diffuse cytoplasmic staining reaction with Hale’s iron colloid stain, which is a pathognomonic feature of this special tumor type only. Electron microscopically, the cytoplasm is crowded by loose glycogen deposits and numerous, sometimes invaginated and studded vesicles, 150-300 nm in diameter, resembling those of the intercalated cells type B of the cortical collecting duct. The second cell type in chromophobe renal cell carcinoma is also characterized by an increased cytoplasmic eosinophilia or granularity, due to an augmentation of mitochondria. Both cell types can occur singly or in combination within a given tumor. A characteristic feature is the phenomenon of the lining up of huge, pale cells around blood vessels. When combined, well-differentiated tumors show condensed, shrunken and hyperchromatic nuclei, which become more atypical with increasing grade of malignancy or dedifferentiation respectively. Mitotic figures are very rare while double nuclei and multinucleated cells are very common. In general, the growth pattern is solid and compact, sometimes cribiform associated with focal scarring and sclerosing phenomena, associated with deposition of psammoma-like calcifications. Tumor infiltration by inflammatory cells is uncommon.

Immunohistochemistry
Chromophobe carcinomas do not coexpress keratins and vimentin unlike the conventional clear cell and papillary carcinoma. As there

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Figure 1. Cytogenetics of epithelial renal cell tumors.
Table 1. Differential diagnosis.

<table>
<thead>
<tr>
<th>RCA, renal cell adenoma</th>
<th>RCC, clear cell or papillary-type renal cell carcinoma</th>
<th>Epithelioid angiomyolipoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Beige-brown</td>
<td>Pink or tan-brown</td>
</tr>
<tr>
<td>Configuration</td>
<td>Circumscribed, rounded</td>
<td>Circumscribed</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Minimal to absent</td>
<td>Friable and mottled</td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Solid, cribriform</td>
<td>Not seldom</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Homogeneous and densely granular, large eosinophilic granules, no spindle cells</td>
<td>Solid sheets</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Usually round with inconspicuous nuclei, focally bizarre and hyperchromatic, many double nuclei</td>
<td>Polygonal cells, abundant eosinophilic cytoplasm</td>
</tr>
<tr>
<td>Mitosis</td>
<td>Absent/rare</td>
<td>Nuclear pleomorphism</td>
</tr>
</tbody>
</table>

RCA = renal cell adenoma. RCC = renal cell carcinoma.

is a close relationship to the collecting duct, the tumor cells express binding sites for different lectins, such as SBA, PNA and DBA, but they do not express brush border associated antigens, which can usually be found in clear cell carcinomas. They even lack expression of band 3-anion exchanger, which is a hallmark of oncocytic adenoma.

**Genetics**

Cytometry has shown that chromophobe carcinomas are hypodiploid tumors. Cytogenetic and molecular genetic analysis have proven that there is a tremendous loss of chromosomes resulting in monosomies for chromosomes 1, 2, 6, 10, 13, 17 and 21 and loss of the Y-chromosome. These results totally differ from those for conventional clear cell carcinoma, which is characterized by a mutation of the VHL-gene or a loss of a segment of chromosome 3p. A subset of oncocytic adenomas share a loss of chromosomes 1 and Y, which suggests that some oncocytic adenomas might present precursor lesions for chromophobe carcinomas (Fig. 1).

**Prognosis**

Prognosis in chromophobe carcinoma is better than in conventional clear cell and papillary carcinoma. Lymph node metastasis and infiltration of neighboring organs are rare. A sarcomatoid spindle cell phenotype (dedifferentiated chromophobe carcinoma) shows the worst prognosis (Table 1).

**References**


**Unclassified renal cell carcinomas**

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With the evolution of renal cell carcinoma classification it is accepted that some tumors have an atypical morphology and that these tumors cannot be included in any specific subtype. For this reason, the expression unclassified renal cell carcinoma is used, representing 2.4% of tumors in all series.

A renal cell carcinoma can be considered unclassifiable for different reasons: i) when there is undetermined cellular type and/or growth pattern; ii) when a cancer has a mixture of cellular types; iii) in atypical spindle cell growth tumors; and iv) in anaplastic tumors.