Renal Hamartoma Associated with Renal Cell (Grawitz) Tumor: Another Indication that Grawitz Tumors Are Carcinosarcomas

J.J.L. Govaerts\textsuperscript{a}, J.C. van Gooswilligen\textsuperscript{b}, G.P. Voogs\textsuperscript{c}, F.C.S. Ramaekers\textsuperscript{d}, C.J. Herman\textsuperscript{d}, F.M.J. Debruyne\textsuperscript{a}

\textsuperscript{a}Department of Urology, Sint Radboud Hospital of the Catholic University, Nijmegen;
\textsuperscript{b}Department of Urology, Diaconessenhuis, Meppel;
\textsuperscript{c}Department of Pathology, Sint Radboud Hospital of the Catholic University, Nijmegen;
\textsuperscript{d}Department of Pathology, SSDZ, Delft, The Netherlands

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Abstract. We report a case of renal hamartoma (angiofibroma) which contained nests of renal cell (Grawitz) tumor and review the literature regarding this subject. We believe that the finding of Grawitz tumor cells within a mesodermal tumor supports our hypothesis that renal cell (Grawitz) tumors are of mixed (mesodermal and endodermal) origin, that is, they show at least one important biological characteristic of carcinosarcomas.

The hamartoma is a rare benign renal tumor. About 2% of renal parenchymatous neoplasms are hamartomas [Daponte et al., 1983]. A hamartoma is a localized overgrowth of mature elements, normally found in that organ. Most renal hamartomas are composed of three main tissue elements: blood vessels, smooth muscle and fat (angionyolipoma). Any of these tissues can predominate. Approximately 50% of renal hamartomas are associated with tuberous sclerosis [Daponte et al., 1983]. In the latter case they are often bilateral and multifocal and present at an younger age [3rd decade; Bissada et al., 1975]. Renal hamartomas that are not associated with tuberous sclerosis are usually solitary and occur predominantly in women in the 5th to 7th decade [Bissada et al., 1975]. Usually renal hamartomas are clinically silent [Price and Mostofi, 1965]. Symptoms, if present, are indistinguishable from those of other renal tumors: hematuria, lumbar pain and a palpable swelling. Preoperative diagnosis of a solitary renal hamartoma is difficult and at times impossible [van Gooswilligen et al., 1979].

The most important clinical diagnostic criterion is the demonstration of adipose tissue in the tumor, since most renal hamartomas contain it, while renal cell (Grawitz) tumors never do [Bosnick, 1981]. Before the era of the CT scan this was extremely difficult. The presence of adipose tissue within a renal mass can only be demonstrated with certainty by means of CT scan [Bosnick, 1981]. The sonographic picture of a fat-containing tumor is also fairly characteristic but sonography is clearly not as reliable as CT scan in the demonstration of fat. Arteriographically, renal hamartoma and renal cell tumor show many common features. In only 39% was the arteriographic pattern sufficiently characteristic to make a diagnosis of renal hamartoma [Viamonte et al., 1966].

Case Report

A 54-year-old woman was admitted to the hospital because of a swelling in the left hemi-abdomen. In the past she had undergone excision of several benign tumors of the breast. There were no features of tuberous sclerosis. On physical examination a hard painless mass was found occupying almost the entire left abdomen reaching the left pelvic brim. The blood pressure was 150/95 mm Hg.

Intravenous urography revealed that the mass was a tumor originating from the lower pole of the left kidney. Arteriography demonstrated a 14-cm partly hypervascular tumor with pathological blood vessels (fig. 1a, b). The arteriographic picture was considered highly suggestive of renal cell tumor. On a CT scan there was no clear distinction between the tumor and the psoas muscle, colon and abdominal wall (fig. 2). The tumor was embolized and 7 days later it was explored transperitoneally. The tumor infiltrated the mesocolon. It was mobile and free from the colon, the psoas muscle and the abdominal wall. A radical nephrectomy including a para-aortic lymphadenectomy was performed. Postoperative recovery was uneventful.

The nephrectomy specimen weighed 600 g. In the lower pole of the kidney there was an apparently encapsulated, elastic tumor of 14 × 8 × 9 cm. On cross-section the cut surface was of a uniform yellowish color. No hemorrhage or necrosis as a consequence of embolization was seen. The capsule was intact macroscopically. Microscopically, the tumor was composed of a proliferation of collagen-forming fibroblasts and numerous small blood vessels (angiofibroma). These changes had not been seen in our series of embolized renal cell tumors and could not be an effect of embolization,
Fig. 1. a, b. Arteriography shows a partly hypervascular tumor in the lower pole of the left kidney.

Fig. 2. CT scan of the abdomen shows a large solid tumor of the left kidney. There is no clear distinction between the tumor, the colon, the abdominal wall and the psoas muscle.

which was done only 7 days prior to the operation. In the middle of this angiofibroma there were multiple nests of cells with clear cytoplasmic and central, hyperchromatic, regular round nuclei, morphologically identical with renal cell tumor of the clear cell type (fig. 3a, b). Intermediate filaments, demonstrated by indirect immunofluorescence, were exclusively of the vimentin type in the fibro-angiomatous part of the tumor and of the vimentin and keratin types in the clear cells of the Grawitz tumor (fig. 4a, b). The lymph nodes only showed an inflammatory reaction.

Fig. 3. a, b. Nests of renal cell (Grawitz) tumor growing in angiofibroma. HE. a × 75. b × 200.
Fig. 4. Immunofluorographs of Grawitz tumor nests growing in angiofibroma as detected by antibodies to intermediate filament proteins. a Frozen section incubated with antibodies to vimentin, the mesodermal type of intermediate filament protein. Note positive staining in renal cell (Grawitz) tumor nests, angiofibroma and stroma. × 300. b Frozen section incubated with antibodies to keratin, the epithelial type of intermediate filament protein. Only a few cells in the renal cell tumor parts stain positive, identifying these areas as Grawitz tumor nests (arrows). The rest of this mixed tumor is negative. × 300.

Discussion

More than 300 cases of renal hamartoma have been described [Klapproth et al., 1959; Hajdu and Foote, 1969; McCullough et al., 1971; Bissada et al., 1975; Daponte et al., 1983]. Nine other cases of hamartoma and renal cell tumor in the same kidney were reported in the literature [Garini et al., 1981; Yokoyama et al., 1981] (table I). Both pathological entities were part of the same tumor in only 4 of these cases [Kaufmann et al., 1979; Lynne et al., 1979; Garini et al., 1981; Yokoyama et al., 1981]. To the best of our knowledge, an angiofibroma with only a few nests of renal cell carcinoma has never been described previously.

Most hamartomas associated with renal cell tumor were observed in patients with tuberous sclerosis [Jochimsen et al., 1969; Honey and Honey, 1977; Gutierrez et al., 1979; Kaufmann et al., 1979; Lynne et al., 1979; Garini et al., 1981]. In 3 instances, the kidney was also polycystic [Jochimsen et al., 1969; Lynne et al., 1979; Garini et al., 1981]. These 3 cases were associated with tuberous sclerosis. In 1 case, the kidney contained a transitional cell carcinoma as a separate tumor [Yokoyama et al., 1981].

The diagnosis was made pre-operatively by means of CT scan and ultrasound in only 1 case, the only case in which these investigations were performed [Tanaka et al., 1982]. The hamartomas were usually composed of the three classical elements (fat, muscle and blood vessels). There was one cystic hamartoma [Yokoyama et al., 1981].

In several reports, the description of the tissue elements in the tumor was not clear [Jochimsen et al., 1969; Kaufmann et al., 1979]. The age of the patients varied from 18 to 86. There were 7 women and 2 men. Only 1 of 6 patients in whom there was a follow-up of at least 1 year died of her tumor [Gutierrez et al., 1979].

There are several arguments that support the hypothesis that the concurrence of renal hamartoma and renal cell tumor, at least in some cases, is not merely a chance occurrence. The evolution of renal hamartoma to renal cell tumor has been described previously [Kaufmann et al., 1979].

Angiomyolipomas in patients with tuberous sclerosis often show areas where the mesothelial elements have a primitive appearance, occasionally with sufficient pleomorphism to look malignant [Honey and Honey, 1977]. Several cases of bilateral renal cell tumor in patients with tuberous sclerosis have been described [Jochimsen et al., 1969; Honey and Honey, 1977]. These tumors occurred at a much younger age than is usual for renal cell tumors. Clinically, they behave much like a benign hamartoma although microscopically they were indistinguishable from renal cell tumors. The close anatomic relationship of benign hamartomatous elements and foot of renal cell tumor within the same tumor gives a strong indication that malignant transformation of a mesenchymatous hamartoma is indeed possible. This is in contradiction to the classical concept that Grawitz tumors are adenocarcinomas originating from an epithelial component of the nephron [Bennington and Beckwith, 1975]. However, the expression of both vimentin and keratin intermediate filaments in Grawitz tumors has led to the hypothesis that this tumor may be a carcinosarcoma [Herman et al., 1983]. Intermediate filaments of the vimentin type are molecular markers of cells of mesodermal origin while intermediate filaments of the keratin type are found in cells of endo- and ectodermal origin [for detailed information on specificity of antisera reactions, see Ramaekers et al., 1983]. In the case that we describe here, the angiobromatous part of the tumor showed only vimentin filaments. The nests of Grawitz tumor were positive for both vimentin and keratin filaments. We feel that the demonstration of a renal hamartoma of mesodermal origin which contains dispersed within it nests of Grawitz tumor further supports the hypothesis that the Grawitz tumor is of mixed origin (a carcinosarcoma) and thus shows biological properties consistent with both carcinomatous and sarcomatous elements. This interpretation correlates well with some clinical features of the Grawitz tumor, especially its marked resistance to adjuvant therapy and its tendency to early blood vessel invasion and hematogenous dissemination in addition to lymph node metastasis [Herman et al., 1983].

The finding of renal cell tumor within a renal hamartoma, although very rare, raises questions about the therapy of renal hamartomas. We suggest the following therapeutic approach. In case of multiple hamartomas (this will be almost exclusively in tuberous
Table 1. Pathological and clinical features of 10 cases of renal hamartoma associated with renal cell (Grawitz) tumor

<table>
<thead>
<tr>
<th>References</th>
<th>Sex</th>
<th>Age</th>
<th>Tuberous sclerosis</th>
<th>Polycystic kidneys</th>
<th>Type of hamartoma</th>
<th>Bilateral hamartomas</th>
<th>Bilateral carcinomas</th>
<th>Hamartoma + carcinoma within same tumor</th>
<th>Symptoms + clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jochimsen et al.</td>
<td>♀</td>
<td>31</td>
<td>+</td>
<td>+</td>
<td>not specified</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>flank pain; renal failure</td>
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<td>[1969]</td>
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<td></td>
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<tr>
<td>Kavaney et al.</td>
<td>♀</td>
<td>48</td>
<td>−</td>
<td>−</td>
<td>angiofibroma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>flank pain; hematuria</td>
</tr>
<tr>
<td>[1975]</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Honey and Honey</td>
<td>♀</td>
<td>18</td>
<td>+</td>
<td>−</td>
<td>leiomyoma</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>pain iliac fossa; hematuria; palpable tumor</td>
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<tr>
<td>[1977]</td>
<td></td>
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<tr>
<td>Gutierrez et al.</td>
<td>♀</td>
<td>24</td>
<td>+</td>
<td>−</td>
<td>angiofibroma</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>hematuria; palpable tumor</td>
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<td>[1979]</td>
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<tr>
<td>Kauffmann et al.</td>
<td>♀</td>
<td>?</td>
<td>?</td>
<td>−</td>
<td>not specified</td>
<td>+</td>
<td>+</td>
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<td>[1979]</td>
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<tr>
<td>Lynne et al.</td>
<td>♀</td>
<td>27</td>
<td>+</td>
<td>+</td>
<td>angiofibroma</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>palpable kidneys; renal failure</td>
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<td>[1979]</td>
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<tr>
<td>Yokoyama et al.</td>
<td>♂</td>
<td>86</td>
<td>−</td>
<td>−</td>
<td>cystic hamartoma</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>hematuria; palpable tumor</td>
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<td>[1981]</td>
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<tr>
<td>Garini et al.</td>
<td>♀</td>
<td>22</td>
<td>+</td>
<td>+</td>
<td>angiofibroma</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>flank pain; hematuria; palpable kidneys; renal failure</td>
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<td>[1981]</td>
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<tr>
<td>Tanaka et al.</td>
<td>♂</td>
<td>42</td>
<td>−</td>
<td>−</td>
<td>angiofibroma</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>discovered by chance</td>
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<td>[1982]</td>
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<td>Present case</td>
<td>♀</td>
<td>54</td>
<td>−</td>
<td>−</td>
<td>angiofibroma</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>palpable tumor</td>
</tr>
</tbody>
</table>

Sclerosis patients): surgical intervention only in case of complication (pain, bleeding).

Follow-up is best accomplished by means of CT scan and/or ultrasonography. If one or more tumors seem to be enlarging, arteriography followed by surgical exploration should be performed. If technically feasible, we prefer a conservative approach (enucleation of the tumor – heminephrectomy). We think that this approach is justified as it is possible that the other kidney will also have to be explored and because of the relatively benign course of Grawitz tumors in patients with tuberous sclerosis. In case of a solitary tumor, the decision to perform a surgical exploration will be easier taking into account the difficulty of ruling out a renal cell tumor with certainty. When a CT scan has demonstrated unequivocally the presence of fatty tissue within the tumor, a conservative approach is justified. Regular follow-up by means of CT scan or ultrasonography, however, is indicated in order to discover eventual malignant degeneration.

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J.J.L. Govaerts, MD
Department of Urology,
Sint Radboud Hospital of the Catholic University,
NL–6500 HB Nijmegen (The Netherlands)