Renal Cell Carcinoma With Rhabdoid Features
An Aggressive Neoplasm With Overexpression of p53
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Rhabdoid features have been recently identified as a morphologic variant of renal cell carcinoma (RCC) associated with aggressive behavior. Rhabdoid cells are characterized by a large abundant eosinophilic cytoplasm with an irregular eccentric nucleus and a rounded eosinophilic cytoplasmic inclusion. Rhabdoid features in RCC must be differentiated from rhabdoid tumor of kidney, which is a rare pediatric neoplasm.

Only a few studies that found a poor prognosis among patients with RCC with rhabdoid features have been published. A relationship between sarcomatoid and rhabdoid transformation is not established and the molecular carcinogenetic mechanisms for these 2 phenotypes are not elucidated. The implication of p53 in kidney carcinoma progression is still debatable but several works have suggested that p53 was an independent marker of prognosis in RCC. To date p53 had not been investigated in rhabdoid carcinoma. We presented herein a consecutive series of 14 cases of rhabdoid RCC with clinicopathologic and immunohistochemical investigation.

MATERIALS AND METHODS
We reviewed, from the files of the Department of Pathology at Lille University Hospitals, France, a total of 310 cases of RCC from January 1999 to February 2005. For the selection, we used the microscopic criteria described by Gökkönen et al. Briefly, rhabdoid cells are large cells with an abundant cytoplasm and a paranuclear eosinophilic inclusion. The nuclei are large with prominent nucleoli.

We identified a consecutive series of 14 cases of RCC with a rhabdoid cell component representing 4.5% of all RCCs. For each case, the percentage of rhabdoid area was determined. Tumors were stratified by an ECOG performance status of 0 versus 1 or more. Tumor size was determined from the pathologic specimens as the greatest diameter in centimeters. The general health status was measured using the Eastern Cooperative Oncology Group (ECOG) performance status score. For statistical analysis, patients were stratified by an ECOG performance status of 0 versus 1 or more.

The following parameters were noted in each patient: age, sex, symptoms at diagnosis, ECOG performance status, tumor diameter, clinical TNM stage and grade, follow-up time, local recurrence, disease progression, and death.

At the most recent follow-up visit, the vital status was evaluated and described as alive (no evidence of disease or disease progression) or deceased (by disease, by any other cause with or without evidence of disease, and by any treatment complication). All patients underwent preoperative abdominopelvic and pulmonary computed tomography scan. Every 6 months, patients without evidence of disease, and by any treatment complication). All patients underwent preoperative abdominopelvic and pulmonary computed tomography scan. Every 6 months, patients without evidence of disease, and by any treatment complication).

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References
underwent physical examination, routine laboratory evaluation, and imaging studies, according to the local surveillance schedule. Data from patients lost to follow-up were actualized by contacting general practitioners or relatives.

Immunohistochemical stains were routinely performed on 4-μm-thick sections from the formalin-fixed embedded tissues of the 14 specimens. Two blocks were selected for each case representing rhabdoid and nonrhabdoid areas. In 1 case, a pulmonary metastasis was available. The study was conducted on an automated immunostainer Benchmark (Ventana, Strasbourg, France). Staining was performed with antibodies against cytokeratin AE1/AE3 (1:100 dilution; Dako, Trappes, France), epithelial membrane antigen (1:25 dilution; Dako), desmin (1:50; Dako), vimentin (1:100; Immunotech, Marseille, France), smooth muscle actin (1:300; BioGenex, Alphelys, Plaisir, France), CD117 (1:50 dilution; Dako), and p53 (1:100 dilution; DO-7, Dako). Endogenous peroxidase was blocked by addition of H₂O₂. Appropriate positive and negative controls were used. Immunostains were evaluated as positive or negative. For p53 evaluation, we counted at least 500 tumor cells, and a staining of more than 5% of nuclei was considered positive.

The survival rates were determined using the Kaplan-Meier method and were calculated using the date of surgery to the date of death or last follow-up. The recurrence and the survival rate were estimated using the date of surgery to the date of death or last follow-up. The significance of differences in the survival rate was determined by log-rank test. P values <.05 were considered statistically significant.

RESULTS

Clinical Features

Of the 14 patients, 8 were women and 6 were men. The mean ± SD age was 60 ± 11.2 years (range, 32–77). The tumor was located in the right kidney in 8 cases (57.1%) and in the left kidney in 6 patients (42.8%).

Of the 14 patients, 2 patients were asymptomatic at diagnosis and the tumor was discovered incidentally by abdominal ultrasonography or computed tomography. The presenting symptoms were flank discomfort (21.4%) and macroscopic hematuria (14.2%). Four patients presented with a palpable lumbar mass (28.5%). The ECOG performance status score was 0 in 9 patients (64.3%) and 1 in 5 patients (35.7%). The mean ± SD body mass index was 26.6 ± 5.5 (range, 21.7–38.6).

The ultrasonographic and tomodensitometric appearance of RCC was similar to other renal solid tumors; enhancement was observed in 94.4% of tumors, necrosis was present in 42.8% of tumors, cystic foci and calcifications were not present, and the renal vein was invaded in 2 cases.

At diagnosis, 1 tumor was stage T1a, 4 were T1b, 3 were T2, 3 were T3a, 2 were T3b, and 1 was T4. The lymph node status was N0 in 11 patients (78.5%), N1 in 2 patients (14.3%), and N2 in 1 patient (7.1%). Four patients presented with pulmonary metastases (M1, 28.5%) associated in 1 of these cases with bone metastases. Radical nephrectomy was performed in 13 patients (92.8%). In 1 case the tumor was not extirpable and large surgical biopsies were assessed. One patient received palliative radiotherapy for bone metastases and 3 patients received immunotherapy with interleukin 2 and/or interferon alfa. No adjuvant therapy was given in other cases.

The mean follow-up after surgery was 11 months (range, 2–33 months). Four patients were alive without evidence of disease (1 with pT1 tumor, 1 with pT2, and 2 with pT3). Ten patients (71.4%) experienced metastases at mean follow-up of 4.5 months (1–17 months) and 6 (42.8%) died of renal carcinoma at 11.3 months (4–24 months). The median of survival was 8 months.

Pathologic Features

All tumors were classified as RCC with areas of rhabdoid cells. Tumor size ranged from 5 to 11 cm (median, 7.5 cm). One tumor was staged pT1b, 4 were pT2, 7 were pT3a, and 2 were pT3b. By contrast with clinical stratification, 1 T1a, 2 T1b, and 1 T4 were restaged pT3b because of extrarenal extension without infiltrating the colon in the case of clinical T4. One T1b was restaged pT2 because of tumor size more than 7 cm. In 3 cases, lymph nodes metastases were individualized. Rhabdoid component represented 5% to 50% of the tumor volume. For 1 case, the percentage of rhabdoid component was evaluated only in large surgical biopsies because extirpation was not feasible. The rhabdoid component represented 50% of the tumor.

In all cases, there was a transition between rhabdoid areas and classical clear cells areas (Figure 1). In 1 case, there was a sarcomatoid area composed of highly atypical spindle cells intermingled with rhabdoid cells (Figure 2). The cells were arranged in large sheets. Rhabdoid cells were high grade round or polygonal cells with a large eosinophilic cytoplasm and a globular intracytoplasmic inclusion (Figure 3). The nuclei were large, atypical with prominent nucleoli. A lymphocytic infiltrate was focally observed in tumor stroma. Nonrhabdoid clear cell areas were nuclear grade Furhman 3 in 10 cases, Furhman 4 in 2 cases, and Furhman 2 in 2 cases. Areas of necrosis adjacent to rhabdoid component were observed in 13 of 14 cases and were extensive in 8 cases (>50%). At diagnosis, regional lymph nodes metastases were identified in 3 cases.

Immunohistochemical Findings

In all tumors, rhabdoid cells showed strong globular cytoplasmic staining for vimentin. Eleven of 14 cases were positive for epithelial membrane antigen and 9 of 14 stained for cytokeratin AE1/AE3 with a paranuclear cytoplasmic staining. No staining was obtained for desmin and smooth muscle actin. CD117 was only observed in a few tumor cells in 1 case.

A nuclear positivity for p53 was observed in 10 of 14 cases in 5% to 50% of rhabdoid cells (mean, 37%) (Figure 4). In nonrhabdoid clear cell areas, p53 was only detected in 5 of 14 cases in a smaller number of tumor cells (5%–15%) (mean, 9%) (Table). p53 was also positive in the sarcomatoid area (50% of tumor cells). In the pulmonary metastasis, p53 was strongly positive in more than 60% of tumor cells (Figure 5).

Statistical Analysis

The lymph node status was a significant prognostic factor of recurrence (P = .007) and of death from RCC (P = .002). The ECOG performance status was a significant prognostic factor of recurrence (P = .001) but not of death (P = .06). Necrosis was not a significant prognostic factor of recurrence (P = .38) and of death from RCC (P = .12). Because of the small size of the cohort, we could not evaluate if rhabdoid morphology was independent of Fuhrman grade or TNM stage.
COMMENT

Identification of rhabdoid features as a morphologic variant of RCC is a recent report in few series. Microscopically, rhabdoid cells are characteristically large round or oval tumor cells with an abundant cytoplasm containing an eosinophilic paranuclear inclusion. Nuclei are large and irregular with prominent nucleoli. Rhabdoid cells are arranged in sheets or sometimes in pseudoglandular formations. These tumor cells mimic rhabdomyoblasts of rhabdomyosarcoma or tumors cells of pediatric renal rhabdoid tumors. Rhabdoid cells must also be differentiated from eosinophilic cells frequently seen in usual RCC. Immunohistochemical and ultrastructural examinations have demonstrated that these cells have an epithelial phenotype with expression of cytokeratins and epithelial membrane antigen and intracytoplasmic accumulation of intermediate filaments arranged in whorls. No muscular differentiation is identified, so desmin, actin, and myogenin stainings are negative. In our experience, vimentin and epithelial membrane antigen were frequently coexpressed in rhabdoid cells, and cytokeratin AE1/AE3 was expressed more focally with a paranuclear cytoplasmic staining. CD117 was expressed only weakly in 1 isolated...
Summary of Immunohistochemical Results in Rhabdoid and Nonrhabdoid Areas*

<table>
<thead>
<tr>
<th></th>
<th>No. of Positive Cases in Rhabdoid Areas (%)</th>
<th>No. of Positive Cases in Nonrhabdoid Areas (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin</td>
<td>9/14 (65)</td>
<td>10/14 (71)</td>
</tr>
<tr>
<td>EMA</td>
<td>11/14 (78)</td>
<td>12/14 (85)</td>
</tr>
<tr>
<td>Vimentin</td>
<td>14/14 (100)</td>
<td>12/14 (85)</td>
</tr>
<tr>
<td>SMA</td>
<td>0/14 (0)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>Desmin</td>
<td>0/14 (0)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>CD117</td>
<td>1/14 (7)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>p53</td>
<td>10/14 (71)</td>
<td>5/14 (35)</td>
</tr>
</tbody>
</table>

* EMA indicates epithelial membrane antigen; SMA, smooth muscle actin.

In a recent series of sarcomatoid RCC,11 however, CD117 was not previously studied in rhabdoid carcinomas. Rhabdoid features were identified in 3.2% to 7.4% of renal carcinomas (4.5% in the present series). A rhabdoid component may be observed among renal clear cell carcinomas but also in papillary carcinomas, chromophobe cell carcinomas, or collecting duct carcinomas.14,12,13 Rhabdoid cells are not specific to kidney neoplasms and are also described in lung carcinoma, thyroid carcinoma, gastrointestinal adenocarcinoma, or sarcoma.4–18 In the kidney, RCCs with rhabdoid features are considered as high grade and high stage tumors with frequent extrarenal extension.2,3 In the present study, 9 of 14 tumors were staged pT3 and all rhabdoid areas were classified nuclear grade 4. Rhabdoid foci represented 5% to 50% of the tumor area. There was no direct relationship between the percentage of rhabdoid areas and the prognosis. Tumor necrosis was very common adjacent to the rhabdoid component. In the previous series, rhabdoid component represented 5% to 90% of the tumors and was admixed with usual RCC.2,3 According to the literature, we confirmed that RCC with rhabdoid features is a very aggressive neoplasm with frequent fatal outcome even when the rhabdoid component is limited. Indeed in our experience, 6 of 14 patients are dead of disease in less than 2 years; 1 of these patients had a tumor containing 5% rhabdoid cells. Four patients were alive with metastatic disease (lung and bone metastases); only 4 of 14 patients were alive without evidence of disease. Kuroiwa et al18 reported that 4 of 8 patients died of disease within 1 year of surgery, and 2 of these patients had only 10% to 15% of rhabdoid areas. The relationship between rhabdoid features and sarcomatoid transformation remains uncertain. In RCC, presence of sarcomatoid foci composed of high grade tumor spindle cells is well identified as an aggressive neoplasm encountered in all subtypes of renal carcinoma. Rhabdoid features are sometimes associated in RCC with sarcomatoid changes.2,3 Rhabdoid features may be related to sarcomatoid transformation as a final pathway of dedifferentiation with a very aggressive biologic behavior.19 Studying sarcomatoid transformation in RCCs, Oda et al20 observed that the oncoprotein p53 was overexpressed with a high mutation rate in sarcomatoid component in contrast to a low mutation rate in usual carcinomatous areas. In the present study, we investigated p53 expression in rhabdoid cells using immunohistochemistry. We observed that p53 expression was more frequent and diffuse in rhabdoid component in comparison with usual clear cells areas. The role and prognostic value of p53 in renal carcinoma is still controversial because p53 is rarely mutated in primary RCC. In several recent studies, p53 overexpression appeared to be of value to predict tumor recurrence and progression.5–10 Shvarts et al10 using a cutoff of 20% for immunostaining suggested that p53 is a strong independent predictor of tumor recurrence. Zigeuner et al8 using tissue microarray technique found an overexpression of p53 in 23% of 184 primary RCCs and in 52% of metastatic tumors. These authors observed a significant difference for the progression of the disease between p53-positive tumors and p53-negative tumors. The direct implication of the p53 pathways in RCC carcinogenesis is not clear. Gurova et al21 have found a dominant mdm2-independent mechanism of p53 repression in RCC cells lines. On the contrary, Warburton et al22 demonstrated that the p53 pathway was functional in wild-type p53 RCC lines and was regulated by mdm2. Stickle et al23 reported that p53 expression was independent of pVHL status in RCC. In the present study, an overexpression of p53 was clearly found within rhabdoid areas. We suggest that p53 may have a role in the de differentiation of RCC. A study by Nagao et al24 about dedifferentiated adenoid cystic carcinomas, showed that the dedifferentiated component was diffusely p53 positive accompanied by a p53 gene point mutation. p53 had been investigated in rhabdoid carcinoma of the lung with variable results. Miyagi et al25 found no expression of p53 in a report of 3 cases, but more recently a strong positivity of p53 in 60% of rhabdoid tumor cells was reported in a single case.26 In summary, we conclude that pathologists should carefully search for a rhabdoid component in RCC, and when present it should be reported because it is a marker of high risk for metastasis and a very poor prognosis even when the rhabdoid area is limited. Rhabdoid features may be related to sarcomatoid transformation as a pathway of tumor dedifferentiation.

References