Abstract. Neoplasms commonly associated with alpha-fetoprotein (AFP) production are hepatocellular carcinomas and some germ cell tumors, typically yolk sac tumor. Rare tumors of visceral origin may also be associated with AFP production and those exhibiting a distinctive morphology are now known as hepatoid adenocarcinomas. To date, eight such tumors have been reported from the bladder and a further four from the renal pelvis. We report a unique case of a mixed hepatoid adenocarcinoma and urothelial carcinoma of the renal pelvis and ureter, in which both components were found to express AFP.

An 84-year-old woman with a serum AFP level of 701 ng/ml was found to have advanced high-grade renal pelvi-calyceal and ureteral urothelial carcinoma exhibiting focal hepatoid adenocarcinoma differentiation. Both components displayed strong immunostaining for AFP. The patient was treated by radical nephro-uretectomy and postoperatively the serum AFP level declined to normal at a rate commensurate with its biological half-life. The presence of AFP expression in both the urothelial and hepatoid components of the tumor suggest that the molecular pathway changes associated with AFP production precede the hepatoid differentiation of tumor cells.

Alpha-fetoprotein (AFP) is produced by the yolk sac and liver during fetal development, with serum levels being high at birth (1, 2), but decreasing to normal adult levels after about one year (3, 4). Serum AFP elevation may be seen in association with pregnancy (5) and a variety of hepatic diseases such as hepatitis (6), steatosis (7), cirrhosis and hepatocellular carcinoma (8). AFP production with associated elevation of serum AFP has been also noted in extrahepatic tumors, and these include germ cell tumors, most typically exhibiting yolk sac differentiation, and adenocarcinomas of the endometrium, stomach, lung, pancreas and of the adrenal gland (9-15). These extrahepatic adenocarcinomas typically display a hepatocellular morphology and in some areas may also show features of clear cell adenocarcinoma. In view of this characteristic morphology and associated elevated AFP, these tumors are now known as hepatoid adenocarcinomas. Metastatic renal cell carcinoma which did not necessarily involve infiltration of the liver has also been reported to be associated with elevated serum AFP (16).

To date only four AFP-positive carcinomas of the renal pelvis have been documented to our knowledge, with two exhibiting hepatoid morphology and the third being a urothelial carcinoma. We report a unique case of AFP-producing renal pelvic and ureteric carcinoma displaying both urothelial and glandular differentiation, with each component exhibiting AFP expression.

Case Report

An 84-year-old Caucasian female was found by her general practitioner to have iron deficiency anemia. An ultrasound examination revealed a pelvic tumor which was suspected to be of ovarian origin. As part of her clinical workup, serum AFP was found to be 701 ng/ml (normal <12 ng/ml), serum carcinoembryonic antigen (CEA) was 4.2 ng/ml (normal range <5.0 ng/ml) and cancer antigen 125 (CA-125) was 36.5 U/ml (normal range <35 U/ml). Radiological examination revealed the presence of a large right renal pelvi-calyceal and ureteric tumor (Figure 1), while a left ovarian tumor was also seen. No other primary or metastatic tumors were identified.
A radical nephro-ureterectomy was performed and the left ovarian tumor was also removed surgically during the same procedure.

Upon examination, the kidney weighed 290 g. There was a soft creamy-white fleshy friable polypoid tumor with foci of hemorrhage, necrosis and cavitation involving the entire pelvi-calyceal system, a large part of the renal parenchyma and the proximal ureter (Figure 2). Within the kidney, there was gross infiltration of tumor into the renal sinus.

Histological examination revealed a high-grade urothelial carcinoma with extensive glandular differentiation (Figure 3). The glandular component had features of hepatoid adenocarcinoma consisting of trabeculae and sheets and cords of glandular tumor cells with focal clear cells. The carcinoma extended through the full thickness of the renal pelvic and ureteric wall to infiltrate periureteric and peripelvic tissues. The carcinoma also extensively infiltrated the renal parenchyma. There was microvascular invasion of the kidney and involvement of small blood vessels of the renal sinus, as well as the segmental branches of the renal vein, but not the main renal vein. Immunostaining (details given in Table I) revealed that the urothelial carcinoma and the foci of glandular differentiation were both strongly-positive for AFP (Figure 3). Staining for alpha-methyl acyl COA racemase was also strongly-positive in both components of the tumor. Staining for cytokeratin 7, cytokeratin 20 and 34ßE12 showed focal positivity, while that for CD30 and placental alkaline phosphatase (PLAP) was negative. The ovary contained a fibrothecoma. No primary malignancy or metastatic tumor was seen within the ovary.

One month after surgery, the patient’s serum AFP level had decreased to 34 ng/ml. In view of the biological half-life of AFP ($t_{1/2}=7.2$ days) (2), the decline in serum AFP level was considered consistent with complete tumor clearance and after a further five months, serum AFP levels were normal.

**Discussion**

Eight cases of AFP-positive adenocarcinoma of the bladder have been reported and these all exhibited features of hepatoid adenocarcinoma (Table II) (17-23). In two further cases of urothelial carcinoma without glandular differentiation from Japan and Taiwan, there was associated serum AFP elevation and the tumors exhibited positive immunoexpression of AFP (Table II) (22, 23). An additional case of bladder cancer with elevated serum AFP was included in a series that investigated the utility of serum markers for monitoring tumor progression for patients with urothelial carcinoma. The patient was noted to have metastatic disease, however, no further clinical details were reported (24).

There are four previous reports of AFP-producing carcinoma of the renal pelvis and interestingly all of these cases were from Japan (25-28). In three of the cases the tumors showed glandular differentiation with features of hepatoid adenocarcinoma, although in one case, focal keratinisation was present. In two of these patients, there was associated urothelial carcinoma, however, this component of the tumor was found to be immunonegative.
for AFP. In all of these cases, elevated serum AFP levels were detected. The reported preoperative levels in two cases were 75 and 116 ng/ml (25), and 1220 ng/ml (26), while in the third case, a preoperative level of 2246 ng/ml was estimated from serum samples taken from day 9 to day 17 postoperatively (27).

The other reported AFP-positive tumor of the renal pelvis was a grade 2 urothelial carcinoma in a 70-year-old female (28). The patient had undergone cystectomy and right lower ureterectomy for carcinoma in situ. Four years later, the patient presented with hematuria and a right renal pelvic tumor was found. The tumor was reported as invading the

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Table I. Antibodies and dilutions used for immunohistochemical staining of the tumor

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Name in full</th>
<th>Supplier</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>Alpha-fetoprotein</td>
<td>Ventan (TUSCON, AZ, USA)</td>
<td>Prediluted</td>
</tr>
<tr>
<td>AMACR</td>
<td>alpha-methyl acyl COA racemase</td>
<td>Biocare (Concord, CA, USA)</td>
<td>Prediluted</td>
</tr>
<tr>
<td>34β E12</td>
<td>34 beta E12</td>
<td>Biocare (Concord, CA, USA)</td>
<td>Prediluted</td>
</tr>
<tr>
<td>CK 7</td>
<td>Cytokeratin 7</td>
<td>Biocare (Concord, CA, USA)</td>
<td>1:200</td>
</tr>
<tr>
<td>CK 20</td>
<td>Cytokeratin 20</td>
<td>Biocare (Concord, CA, USA)</td>
<td>1:200</td>
</tr>
<tr>
<td>PLAP</td>
<td>Placental alkaline phosphatase</td>
<td>Dako (Carpinteria, CA, USA)</td>
<td>1:50</td>
</tr>
<tr>
<td>CD30</td>
<td>Cluster differentiation Antigen 30</td>
<td>Dako (Carpinteria, CA, USA)</td>
<td>1:50</td>
</tr>
</tbody>
</table>
superficial smooth muscle of the renal pelvis and was strongly immunopositive for AFP. At the time of diagnosis, the serum AFP was 24,000 ng/ml and this decreased to normal limits four months postoperatively. After a further five months, the serum AFP was again found to be elevated and computed-tomographic (CT) scan showed pelvic lymph node metastasis. Following radiotherapy, the serum AFP level returned to normal after a further seven months.

The molecular changes associated with AFP expression in tumors is poorly understood. AFP is encoded by the AFP gene located on chromosome 4q25. In gastric carcinoma, it has been suggested that AFP production is due to an absence of AT motif binding factor I, a transcription factor that binds to the AFP-regulatory element and down regulates the AFP gene (29).

In hepatoid adenocarcinomas human albumin mRNA in situ hybridization has shown cytoplasmic positivity and this has been considered to be further evidence of hepatocellular differentiation of these tumors (30). As noted, in our case, both the hepatoid and urothelial carcinoma components exhibited strong AFP expression. This suggests that the molecular pathway alterations responsible for AFP production precede the genetic changes that give rise to a hepatoid morphology. This conclusion is also supported by the observation noted earlier that in the bladder, very rare carcinomas exhibiting urothelial differentiation can express AFP and be associated with elevated serum AFP levels, in the absence of associated hepatoid adenocarcinoma.

References


Table II. Reported cases of alpha-fetoprotein (AFP)-positive bladder tumor.

<table>
<thead>
<tr>
<th>Case (Reference)</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Stage</th>
<th>Serum AFP (ng/ml)</th>
<th>AFP IH</th>
<th>Treatment</th>
<th>Post treatment AFP (ng/ml)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatoid adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (16)</td>
<td>F</td>
<td>68</td>
<td>pT3a</td>
<td>NA</td>
<td>+</td>
<td>TURB</td>
<td>NA</td>
<td>AWD 3 years</td>
</tr>
<tr>
<td>2 (17)</td>
<td>F</td>
<td>89</td>
<td>pT2b</td>
<td>12700</td>
<td>+</td>
<td>C</td>
<td>617</td>
<td>Lost</td>
</tr>
<tr>
<td>3 (18)</td>
<td>M</td>
<td>71</td>
<td>pT2N+</td>
<td>N</td>
<td>+</td>
<td>TURB,Ct</td>
<td>NA</td>
<td>AWD 4 months</td>
</tr>
<tr>
<td>4 (19)</td>
<td>M</td>
<td>66</td>
<td>pT3a</td>
<td>1065</td>
<td>+</td>
<td>C</td>
<td>NA</td>
<td>DOD 14 months</td>
</tr>
<tr>
<td>5 (19)</td>
<td>M</td>
<td>85</td>
<td>pT2</td>
<td>NA</td>
<td>+</td>
<td>TURB</td>
<td>NA</td>
<td>DOD 12 months</td>
</tr>
<tr>
<td>6 (19)</td>
<td>M</td>
<td>61</td>
<td>pT3a</td>
<td>2025</td>
<td>+</td>
<td>C</td>
<td>NA</td>
<td>DOD 19 months</td>
</tr>
<tr>
<td>7 (19)</td>
<td>M</td>
<td>68</td>
<td>pT1</td>
<td>1070</td>
<td>+</td>
<td>TURB</td>
<td>NA</td>
<td>AWD 26 months</td>
</tr>
<tr>
<td>8 (20)</td>
<td>M</td>
<td>79</td>
<td>pT1</td>
<td>39</td>
<td>+</td>
<td>TURB</td>
<td>N</td>
<td>Alive 19 months</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 (21)</td>
<td>M</td>
<td>74</td>
<td>NA</td>
<td>410</td>
<td>+</td>
<td>PC</td>
<td>N</td>
<td>Alive 4.5 years</td>
</tr>
<tr>
<td>10(22)</td>
<td>M</td>
<td>76</td>
<td>pT2a</td>
<td>1428</td>
<td>+</td>
<td>TURB,Ct,Rt</td>
<td>966</td>
<td>DOD 20+ months</td>
</tr>
</tbody>
</table>

IH, Immunohistochemistry; TURB, transurethral resection of bladder tumor; C, cystectomy; PC, partial cystectomy; Ct, chemotherapy; Rt, radiotherapy; N, normal; NA, not available; AWD, alive with disease; DOD, dead of disease.

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