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Alpha-Fetoprotein Producing Renal Cell Carcinoma
: A Case Report

We report a case of alpha-fetoprotein (AFP) producing renal cell carcinoma. A 53-year-old man with fever was found to have a left renal mass on computed tomography. No mass was detected in the liver. Serum AFP was 1,460 ng/ml. Radical nephrectomy showed a 10 cm mass in the upper half. A half of the tumor was whitish yellow and firm whereas another half was soft and bright yellow with hemorrhagic and necrotic areas. Histologically, the two areas were different. The lower part consisted of the clear cell renal cell carcinoma and the upper part consisted of granular cells. On immunohistochemistry, the granular tumor cells only were positive for AFP. Serum AFP level dropped abruptly to 383 ng/ml on the 6th postoperative day and gradually returned to normal during the 6 months. Multiple metastatic nodules were found in the lungs, liver and bone in 9th postoperative month and the AFP was less than 1 ng/ml. This suggest metastatic lesions are non-AFP producing clear cell type. It can be concluded that serum AFP elevation was due to synthesis by the renal cell carcinoma in the absence of liver neoplasm. Although AFP producing renal cell carcinoma is a rare entity, serum AFP can be a useful marker for the detection of the tumor.

Key Words : *Alpha-Fetoproteins; Carcinoma, renal cell*

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INTRODUCTION

This report describes a case of a renal cell carcinoma with elevated serum alpha-fetoprotein (AFP) and an area of unusual gross and histologic appearance that showed immunohistochemical localization of AFP producing lesion within otherwise usual grade 2 renal cell carcinoma. Increased plasma AFP level associated with malignant neoplasm has been well recognized in cases of hepatocellular carcinomas, yolk sac tumors and other malignancies (1) including carcinomas of the stomach (2), gallbladder, lung, endometrium, ovary and pancreas. Renal cell carcinoma with high serum AFP level is rare and only 8 cases have been reported in Japan (3, 4, 5). After surgery, the AFP level dropped abruptly from 1,460 ng/ml to 383 ng/ml on the 6th post-operative day and gradually returned to normal during the 6th post-operative month. During the followup study, multiple metastatic nodules were found in the lungs, liver, and bone after the 9th post-operative month.

CASE REPORT

A 53-year-old man who suffered from night sweat and fever for 5 weeks was found to have a left renal mass on ultrasonogram. His past medical history was unremarkable. No family history was contributory to the present illness. The left renal tumor had heterogeneous and lobulated contour on ultrasonography. On computed tomography an exophytic portion of the tumor mass in the upper pole was heterogeneously attenuated. Paraaortic lymph nodes were enlarged. No space-occupying lesion was detected in the liver and other organs were normal. A bone scan revealed no metastatic lesion. Relevant laboratory data were as follows; hematocrit 10.3 g/dL, serum AFP 1,460 ng/ml, alkaline phosphatase 379 IU/L. Urinalysis was normal except for 2-3 red blood cells. Left radical nephrectomy was performed for renal cell carcinoma.

The left radical nephrectomy specimen with adherent perinephric fat tissue measured 19×10×9 cm and

weighed 880 g. A 10 cm well circumscribed tumor mass was located in the upper half of the kidney penetrating the renal capsule and compressing overlying adrenal gland with tight fibrous adhesion. The lower half of the mass was soft and friable, showing hemorrhagic and necrotic foci alternating with bright yellow tumor tissues. The upper half of the mass was yellowish white, homogeneous and firm, clearly distinguished from the soft hemorrhagic lower half of the tumor; neither hemorrhage nor necrosis was noted (Fig. 1A). The rest of the renal parenchyma was unremarkable.

Histologically the two areas were different in tumor cell type, structural arrangement and stromal reaction. The lower part of the tumor was composed of the usual renal cell carcinoma with clear cells and grade 2 nuclear atypism. Tumor cells were arranged in sheets, alveoli and papillary configurations with a single layer of cuboidal clear tumor cells covering fibrovascular stalk, and were associated with hemorrhage and necrosis (Fig. 1B). The upper part was composed of large granular cells with grade 4 nuclear atypism (Fig. 2A). The nuclei were irregular and large with wrinkled membranes and coarsely granular chromatin. They were arranged in solid sheets, syncytium and showed areas resembling endodermal sinus tumor separated by desmoplastic stroma with heavy lympho-plasma cell infiltration. Necrosis was absent. On immunohistochemical staining, granular tumor cells of the upper part were strongly positive for AFP (Fig. 2B). Tumor cells were negative for carcinoembryonic antigen (CEA) and human chorionic gonadotropin (HCG). They were also negative on Hale's colloidal iron. Moreover, they were strongly positive for cytokeratin but negative for vimentin. Clear cells in the lower half of the tumor were weakly positive for cytokeratin, but moderately positive for vimentin. Ultrastructurally tumor cells in the lower half revealed microvilli-like cytoplasmic processes and desmosome-like junctions. Some tumor cells showed a moderate amount of glycogen particles, well developed mitochondria, and rough endoplasmic reticulum.

The serum AFP level abruptly decreased after nephrectomy. The sequential serum AFP levels were as follows: 383 ng/ml on the 6th postoperative day, 43 ng/ml in the 3rd postoperative week, and 1.1 ng/ml (reference range; less than 10 ng/ml) in the 6th post-operative month. Nine months after operation, multiple bilateral pulmonary nodules, multiple hepatic nodules, and metastatic bone lesions were detected. Serum AFP level on the 9th, 13th and 15th post-opeative month were less than 1 ng/ml.

DISCUSSION

AFP is the major fetal globulin which is synthesized

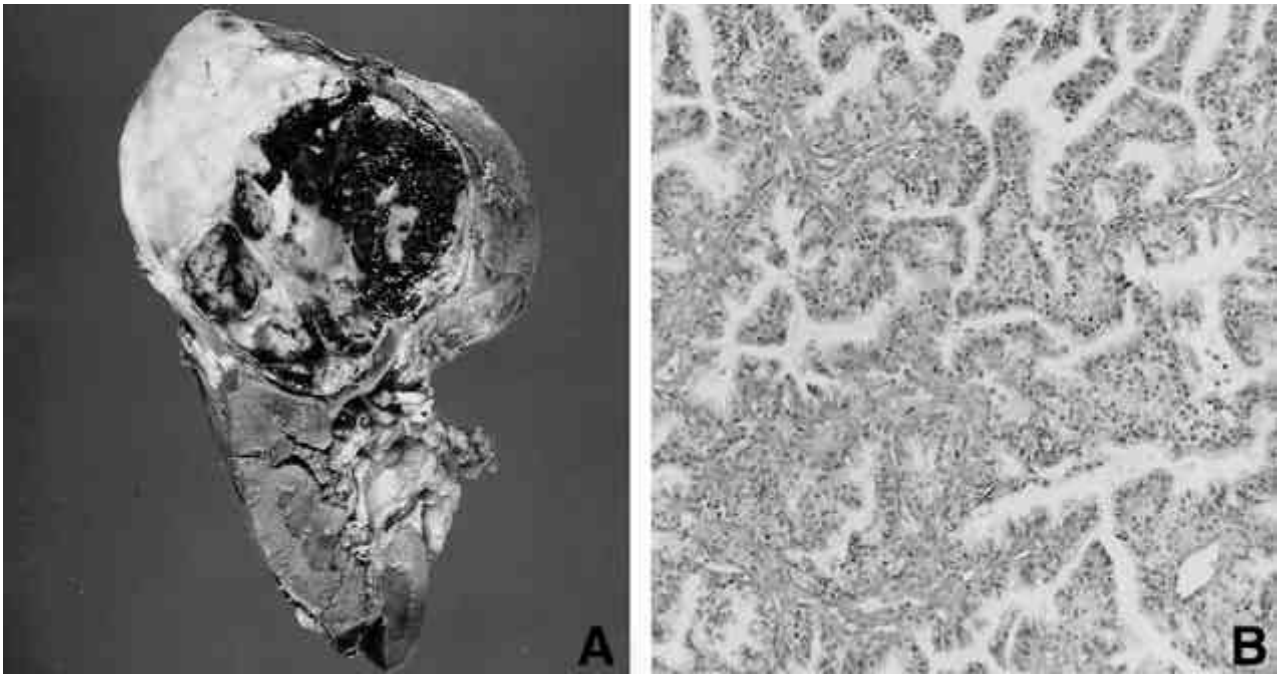

Fig. 1. A: Gross photograph of the kidney, showing a circumscribed mass located in the upper area of the kidney, penetrating the renal capsule. Upper half of the tumor was yellowish white, homogeneous and firm with no hemorrhage or necrosis. Lower half was soft, friable and bright yellow with areas of hemorrhage and necrosis. B: Tumor cells were arranged in papillary configurations with a single layer of cuboidal tumor cells covering fibrovascular stalks.

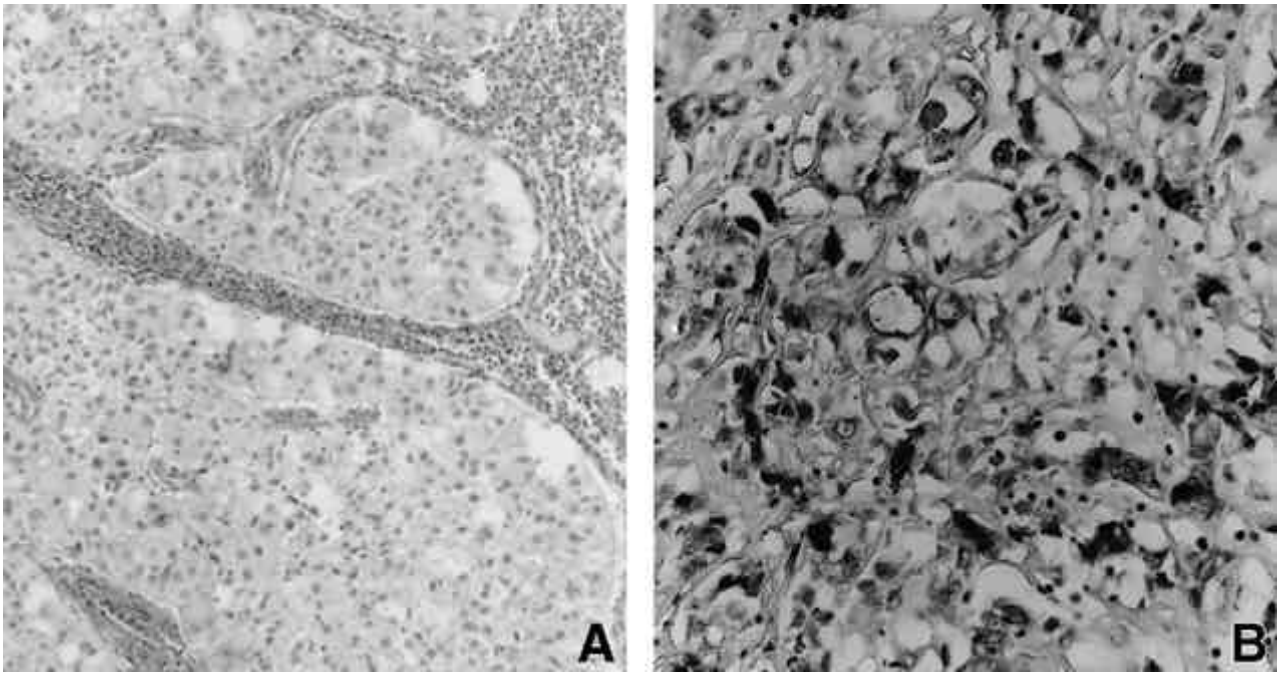

Fig. 2. A: Tumor cells were arranged in sheets and consisted of large granular cells. B: Immunohistochemical staining for AFP in the renal cell carcinoma. Many of the large granular cells were strongly immunoreactive.

by fetal liver and yolk sac from the 6th week of gestation. A trace amount of AFP is also produced in the fetal gastrointestinal tract, kidney and placenta. Its peak blood level is reached at around 12-14 weeks of gestation and thereafter falls off rapidly. After birth, the level of AFP gradually decreases to the normal adult range of 10-20 ng/ml within a few weeks or months. During the normal fetal development, AFP production is gradually switched to that of albumin. Prolonged elevations are seen in neonatal hepatitis, tyrosinemia, and ataxia telangiectasia. The serum AFP level is increased in pregnant women during the second trimester and is much higher in those carrying an abnormal fetus with anencephaly, rachischisis and spina bifida. AFP has a molecular weight of 70,000 daltons, consists of a single peptide chain and contains about 4% carbohydrate. The physiologic function of AFP has not been elucidated yet. But estrogen binding ability, copper binding ability and suppression of immune response have been proposed.

AFP is a useful tumor marker especially for hepatocellular carcinomas and yolk sac tumors. Recently, elevation of serum AFP was reported in patients with other malignancies including stomach, gallbladder, lung, endometrium, ovary, pancreas and kidney (1-5). Some of these carcinomas with high levels of serum AFP often contained cells strongly resembling hepatic cells. Ishikura et al. proposed that such carcinomas be collectively called hepatoid adenocarcinomas (6). In comparison with hepatoid adenocarcinomas, AFP producing carcinomas with no histologic characteristics of hepatocellular carcinomas are called AFP producing adenocarcinomas. Renal cell carcinoma with elevated AFP is rare and only 8 cases have been reported (Table 1). Serum level of AFP varied ranging from 153 to 234,700 ng/ml. Immunohistochemical study for AFP was done in 6 cases, and showed that clear cells were immunoreactive for AFP. In one case, poorly differentiated cells were positive for AFP. In our case, AFP was strongly positive in large poorly differentiated granular cells in the upper half of the tumor but negative in clear cells in the lower half of the tumor. A majority of reported cases revealed multiple distant metastases. Renal cell carcinomas associated with elevated AFP occurred 3 times in women and 6 in men including our case. These carcinomas were predominantly in the right kidney. Interestingly, all reported renal cell carcinomas with high levels of AFP occurred in Japan only, suggesting the effects of racial or environmental factors. AFP production is generally considered to be a result of retrodifferentiation of tumor cells into fetal cells capable of producing AFP. Peng et al. demonstrated that hypomethylation at the 5'region of the gene was associated with AFP gene expression in hepatocellular carcinoma (7). Lecitin-binding properties of patient's serum AFP are helpful in differentiating hepatocellular carcinoma from germ cell origin. Concanavalin A (Con A) can bind with AFP derived from neoplastic germ cells in only 50% to 70% of the total serum amounts. In contrast, Con A can bind with AFP derived from neoplastic liver cells in

Table 1. Cases of alpha-fetoprotein (AFP) producing renal cell carcinoma

Case no.	Reported by	Reported Year	Sex	Age (yr)	AFP (ng/ml)	Histologic type	Positive in AFP	Site
1	Ishida	1983	Male	50	699	Clear cell	Not examined	Right
2	Nishimura	1984	Male	54	600	Clear cell	Not examined	Right
3	Okada	1984	Male	58	16000	Mixed	Clear cells	Right
4	Takakura	1987	Female	51	234700	Mixed	Clear cells	Left
5	Morimoto	1988	Female	64	24240	Clear cell	Clear cells	Right
6	Takai	1989	Male	63	153	Mixed	Poorly differentiated carcinoma cells	Right
7	Saito	1989	Male	58	418	Clear cell	Clear cells	Right
8	Minamoto	1994	Female	71	204	Sarcomatoid with clear cell	Clear cells	Right
9	Present case	1998	Male	53	1460	Mixed	Granular cells	Left

about 90% of the total serum amounts.

In this case, a follow-up study during the first 6 months after surgery showed that the level of AFP tapered down to 1.1 ng/ml. The evidence of recurrence or metastasis was observed, after the 9th post-operative month in the lung, liver, and bone. In our case, followup studies after clinical evidence of metastasis showed no increase in serum AFP in 3 occasions. This may suggest metastatic lesions are clear cell type rather than large granular cell type. AFP producing renal cell carcinomas usually showed worse prognosis than conventional renal cell carcinomas. Although AFP producing renal cell carcinomas are rare, the level of serum AFP before surgery may be a useful marker for the detection of tumor and its recurrence.

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