α-Fetoprotein–Producing Non-Germ Cell Tumors of the Urological System

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Elevated serum levels of α-fetoprotein (AFP), a fetal serum protein, occur mainly in the development of hepatocellular carcinoma (HCC) or germ cell tumors, mainly yolk sac tumor. Rarely, other tumors of the urological system produce AFP. This article reviews the AFP-producing non-germ cell tumors of the urological tract reported to date. These include different types of tumors of the adrenal glands, kidney, ureter, urinary bladder, and testis. It is important for pathologists, urologists, and oncologists to be aware of such cases as the diagnosis affects the management plan for the patient.
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Key words: α-Fetoprotein • Germ cell • Tumors • Urological system

α-Fetoprotein (AFP) is a useful diagnostic tool for hepatocellular carcinoma (HCC) and germ cell tumors.[1] Clinical and laboratory studies have confirmed the efficacy of AFP as a tumor marker in the diagnosis, staging, monitoring, and detecting recurrence of testicular cancer. Serum AFP level is elevated in 75% of yolk sac tumors, 70% of embryonal carcinomas, and 62% of teratomas.[2] However, there are non-germ cell tumors of the urological tract that have been reported to produce AFP. Because the urological system is a site of germ cell tumors, it is important to be aware of other AFP-producing tumors arising in this system, which should be considered in the differential diagnosis of tumors in a patient with elevated serum AFP. We recently reviewed AFP-producing non-germ cell tumors of the female genital tract, which shares embryological origin and some tumor entities with the urological system.[3] This article reviews AFP-producing non-germ cell tumors reported in different parts of the urological system.

AFP-Producing Non-Germ Cell Tumors of the Urological System

Adrenal Gland

Two cases of adrenal gland carcinomas associated with elevated serum AFP have been reported. One case was an adrenal tumor in a 40-year-old woman. Blood and pathologic studies revealed that the tumor was an AFP-producing adrenocortical carcinoma.[4]

Yoshioka and colleagues reported on a case of a 57-year-old man who presented with a left adrenal mass and markedly increased levels of AFP (30,500 ng/mL). Histologic examination showed that the tumor was a hepatoid carcinoma (HC), and AFP was positive in the tumor cells.[5] HC is a tumor that develops outside the liver but shows features similar to those of HCC.[6] The minimum criteria for classifying a tumor as HC include evidence of AFP production and abundant eosinophilic cytoplasm.[7]

Kidney

Different types of renal neoplasms in different age groups have presented associated with raised serum AFP, including:

Wilms tumor. AFP is a common tumor marker in pediatric neoplasms; increased serum levels are usually encountered in tumors arising from tissues producing AFP during fetal life. However, elevation of such protein is rarely found in patients with Wilms tumor (WT). Very few cases of WT associated with elevated serum AFP have been reported.

A teratoid WT with elevated serum AFP level was reported in a 12-month-old boy presenting with a lumbar mass.[8] Another case of cystic partially differentiated nephroblastoma with immunohistochemical (IHC) and serological demonstration of AFP production was reported. Serum AFP levels decreased after preoperative chemotherapy and returned to normal after nephrectomy.[9]

A series of three other patients was also reported. One patient had left renal WT with invasion of aorto-caval lymph nodes and lung metastases. The second patient had bilateral WT with subsequent abdominal recurrence. The third patient showed right renal WT with inferior vena cava thrombosis. AFP levels were increased with higher levels in metastatic disease.[10]

Renal cell carcinoma. Renal cell carcinoma (RCC)–producing AFP is a rare condition with only a few cases reported.[11,12] A 69-year-old man presented with RCC in the right kidney. Serum level of AFP was elevated and normalized 7 weeks after nephrectomy. IHC proved the expression of AFP in the tumor cells.[13]

A 71-year-old woman had a high serum AFP level of 204 ng/mL and a renal RCC. The RCC consisted mainly of spindle-shaped or bizarre sarcomatous tumor cells alongside a clear cell component. AFP was immunolocalized only in the concomitant clear cell component.[14]

A 58-year-old man was found to have a renal neoplasm and a preoperative serum AFP level of 418 ng/mL normalized 3 weeks after surgery. The tumor was clear cell RCC and AFP was detected in tumor cells by IHC.[15] It has been demonstrated that several messenger RNA (mRNA) isoforms are transcribed from the AFP gene through alternative splicing.[16] Using a sensitive technique for lectin-affinity immunoelectrophoresis using concanavalin A (Con A) and lentil agglutinin (LCH)–binding tests, AFPs can be classified into three subtypes: benign hepatic condition type, hepatocellular carcinoma type, and yolk sac (fetal) type.[17] A Con A Sepharose affinity chromatogram was performed to detect the component of AFP in this case. The Con A nonreactive fraction rate was as high as 47%, which indicated that the AFP of this RCC was of the fetal type.[15]

A 51-year-old woman presented with an abdominal mass and a raised serum AFP level (234,700 ng/mL). The enlargement of the left kidney and the adrenal gland was noted by computed tomography (CT) scan. The patient underwent a left nephrectomy. The patient's AFP level gradually decreased after surgery. The tumor was diagnosed as RCC and the presence of AFP was demonstrated in the tumor cells by IHC.[18]

A 53-year-old man with fever was found to have a left renal mass and a serum AFP level of 1460 ng/mL. Radical nephrectomy showed a 10-cm mass in the upper half. On macroscopic examination, half the tumor was whitish yellow and firm, whereas the other half was soft and bright yellow with hemorrhagic and necrotic areas. Histologically, the two areas were different. The lower part consisted of clear cell RCC and the upper part consisted of granular cells. On IHC, the granular tumor cells only were positive for AFP. Serum AFP level dropped abruptly to 383 ng/mL on the sixth postoperative day and gradually returned to normal after 6 months. Multiple metastatic nodules were found in the lungs, liver, and bone 9 months postoperatively, yet AFP was less than 1 ng/mL, suggesting the metastatic lesions were of the non-AFP–producing clear cell component.[19]

Hepatoid carcinoma. A right renal pelvic mass in a 72-year-old man was resected and proved on histologic examination to be an HC. The intraoperative level of serum AFP was 2246 ng/mL, and the postoperative level ranged from 183.6 to 285.6 ng/mL. Lectin-binding assays showed that

the serum AFP was of the HC type. AFP was IHC evident in the neoplastic cells. In addition to the hepatic differentiation, the tumor had differentiated into intestinal absorptive or pancreatobiliary tract cells, as deduced from the frequent presence of spicular bodies, a unique light microscopic feature equivalent to microvilli with an actin core.[20]

Collecting duct carcinoma. A 62-year-old man presented with a mediastinal mass, supraclavicular lymph node enlargement, and elevated serum AFP level. Histologic examination and IHC of a renal mass confirmed this was an AFP-producing collecting duct carcinoma.[21]

Ureter

A single case of a patient who presented with a ureteric tumor associated with raised serum AFP level was reported. Total nephroureterectomy was performed and histopathological examination revealed adenocarcinoma of the ureter with a component of transitional cell carcinoma (TCC). The tumor cells were proved to express AFP using IHC, and the serum AFP level normalized after tumor resection.[22]

Urinary Bladder and Urachus

Elevated serum AFP is very uncommon in bladder cancer with few reported cases of different types of carcinoma and sarcoma reported.

TCC

A 76-year-old man presented with a bladder tumor and raised serum AFP (1428 ng/mL) level. Transurethral resection of bladder tumors (TURBT) and subsequent pathologic examination revealed a grade III TCC. The tumor partially responded to concomitant chemoradiotherapy, but eventually progressed with multiple lung metastases, and serum AFP levels increased to 3906 ng/mL.[23] Another case of a 74-year-old man, diagnosed with TCC of the bladder, showed an increased level (410 ng/mL) of serum AFP, which dropped to normal after partial cystectomy.[24] In both cases, tumor cells showed AFP expression by IHC.

Mixed Tumors

A case of bladder adenocarcinoma was diagnosed in a 71-year-old man who had presented with hematuria. The tumor was composed of areas showing features of HC, together with areas of typical adenocarcinoma. IHC showed cytoplasmic reactivity to AFP, α-1-antitrypsin (A1AT), albumin, and keratin (CAM 5.2). Membrane reactivity was seen for epithelial membrane antigen (EMA), and there was also positivity to carcinoembryonic antigen (CEA) showing a canalicular pattern. The cells also expressed hepatocyte growth factor and its receptor, c-met.[25]

A tumor mass resected from the anterior bladder wall of a 68-year-old woman displayed sheets of hepatoid cells merging focally with a component of adenocarcinoma. Intracytoplasmic hyaline globules and bile production as well as immunoreactivity for AFP and A1AT and a striking canalicular immunostaining pattern for CEA and EMA all indicated hepatocellular differentiation within this bladder tumor.[26]

Kawamura and colleagues reported on a case of a 79-year-old man who presented with bladder tumors. TURBT was performed and histology revealed non–muscle-invasive HC that produced AFP and TCC. There were numerous subsequent tumor recurrences as different types of non–muscle-invasive carcinoma, which were removed by TURBT. The tumor recurred after 5 months as AFP-producing nonhepatoid adenocarcinoma, then recurred again after 8 months as TCC. However, the serum AFP level remained above 35 ng/mL, and only normalized after intravesical instillations.[27]

A 45-year-old man presented with hematuria and multiple metastatic lesions in the lungs. Cystoscopic examination demonstrated a large tumor mass protruding from the dome of the urinary bladder. Ultrasonography and CT highlighted a solid and cystic urachal tumor continuous from the vesical dome to the navel. Serum level of AFP was elevated to 17,100 ng/mL. The patient underwent palliative curettage of the vesical dome tumor twice, followed by chemotherapy, but died of progressive metastases to the lungs, left pleura, liver, and brain. The tumor histologically showed hepatoid and adenocarcinoma components. The cancer cells were rich in glycogen and were immunoreactive diffusely for AFP. This is the only reported case of AFP-producing carcinoma of urachal origin.[28]

Bladder Sarcoma

A single case of bladder sarcoma associated with elevated serum AFP has been reported. This was a case of rhabdomyosarcoma in which IHC showed the tumor cells expressed AFP.[29]

Some cases of bladder tumors may be associated with raised serum AFP that is not necessarily produced by tumor cells but elevated due to associated lesions. Urinary bilharziasis is associated with elevated levels of AFP even without liver pathology that would explain this elevation.

Some cases of bladder tumors may be associated with raised serum AFP that is not necessarily produced by tumor cells but is elevated due to associated lesions. Urinary bilharziasis

is associated with elevated levels of AFP even without liver pathology that would explain this elevation. Hence, bladder tumors in patients with bilharziasis may be associated with elevated levels of serum AFP more frequently than cases in nonbilharzial patients. A total of 112 cases, which included patients of varying ages, were diagnosed as having carcinoma of the bladder by cystoscopy and biopsy and were investigated for the presence of raised serum AFP. A total of 59 cases (52.6%) showed raised serum AFP. All cases were proved by liver scan and laparotomy to be free of metastasis and there was no liver pathology that was responsible for the elevated serum AFP, but all patients had bilharziasis since childhood.[30]

Pregnancy also seems to influence the level of serum AFP and, hence, tumors associated with elevated serum AFP in pregnant women, particularly those with history of bilharziasis, should be interpreted with caution. Ahmed and Bahgat conducted a trial to demonstrate the changes that took place in AFP levels as a tumor marker among pregnant Egyptian women suffering from bilharzial infestation. They found an extremely significant increase in AFP levels among pregnant patients with urinary and intestinal schistosomal infection compared with healthy pregnant women. This was higher in intestinal infection and more pronounced in early pregnancy than late. Malignancy in combination with pregnancy caused a statistically significant increase compared with nonpregnant patients, and the increases were slightly higher in bladder than colonic cancer cases. AFP levels gradually increased with progression of both pregnancy and malignancy.[31]

Urethra

A rare case of adenocarcinoma of the female urethra with raised serum AFP was reported in a 52-year-old woman. The tumor was polypoid, localized in the posterior wall of the midurethra, and microscopically showed three cell types. The cell types included intestinal-type cells positive for EMA and CEA, EMA-negative and AFP-positive columnar vacuolated cells, and mainly EMA-positive clear cells.[32]

Prostate

No AFP-producing prostate tumors have been reported.

Epididymis and Vas

No AFP-producing tumors of the epididymis or vas have been reported.

Testis

AFP and β-human chorionic gonadotropin (β-hCG) are well established serum markers for germ cell tumors of the testis, useful for diagnosis and monitoring response to therapy and tumor recurrence.[33]

Studies reported that there is a close relationship between HCC and testicular tumors. Both tumors can present as synchronous tumors, as testicular metastases of HCC, or as hepatic metastases of testicular tumor. Like HCC, germ cell tumors of the testis also release AFP, but it is shown that some Sertoli cell tumors of the testis can also release AFP. Ersoy reported the first case of HCC in the literature that presented concomitantly with Sertoli-Leydig tumor (SLCT) of testis, leading to an extremely high level of AFP in a 21-year-old man.[34]

Testicular SLCTs are exceptionally rare,[35] so it is not surprising that, unlike the ovary, fewer cases with raised serum AFP level have been reported. Approximately 25 cases of ovarian SLCT-expressing AFP have been reported.[17,36-42] Most were of the retiform or poorly differentiated type. In these cases, AFP was IHC detected in Sertoli cells,[17] in Leydig cells,[43] or hepatocytic cells,[44] and heterologous gastrointestinal epithelium.[42]

We recently reported the first case of ovarian juvenile granulosa cell tumor associated with elevated serum AFP in a 17-year-old girl.[45] Testicular juvenile granulosa cell tumor is the most common neoplasm of the testis during the first 6 months of life.[35] However, it should be noted that, in very young infants, there is normally a physiologically high serum AFP level, so serum determinations of that marker are not helpful in this age group.[35]

Unlike other parts of the urological tract, unless histologic examination shows a different diagnosis, a testicular neoplasm associated with raised serum AFP levels should be managed as a germ cell tumor on presentation because other testicular tumors are generally rare, and, in particular, ones associated with raised AFP.

In conclusion, the objective of this review was to discuss the AFP-producing non-germ cell tumors that may develop in the urological system. It is very important for pathologists, urologists, and oncologists to be aware of these tumors, which would have a different chemotherapeutic regimen and different prognosis from germ cell tumors. The review demonstrates that raised serum AFP is not pathognomonic of a germ cell tumor and does not warrant giving the

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patient a treatment regimen for germ cell tumor if such a component is not identified by histology. Serological results need to be interpreted in the context of the patient's age, clinical presentation, and histologic features of the lesion. ■

References

1. Marshal WJ, Bangert SK, eds. *Clinical Biochemistry*. Philadelphia: Churchill Livingstone. Elsevier; 2008.
2. Akaza H, Kameyama S, Aso Y. Significance of tumor markers in the treatment of urological malignancies. [Article in Japanese] *Gan To Kagaku Ryoho*. 1987;14:3034-3040.
3. El-Bahrawy M. Alpha-fetoprotein-producing non-germ cell tumours of the female genital tract. *Eur J Cancer*. 2010;46:1317-1322.
4. Hamanaka W, Yoneda S, Shirakusa T, et al. Alpha-fetoprotein (AFP)-producing adrenocortical carcinoma–long survival with various therapeutic strategies including a lung resection: report of a case. *Surg Today*. 2008;38:275-278.
5. Yoshioka M, Ihara H, Shima H, et al. Adrenal hepatoid carcinoma producing alpha-fetoprotein: a case report. [Article in Japanese] *Hinyokika Kiyo*. 1994;40:411-414.
6. Kato K, Suzuka K, Osaki T, et al. Primary hepatoid adenocarcinoma of the uterine cervix. *Int J Gynecol Cancer*. 2007;17:1150-1154.
7. Lazaro J, Rubio D, Repolles M, Capote L. Hepatoid carcinoma of the ovary and management. *Acta Obstet Gynecol Scand*. 2007;86:498-499.
8. Parikh B, Trivedi P, Shukla K. A unilateral teratoid Wilms' tumor with raised serum alpha-fetoprotein level. *Indian J Pathol Microbiol*. 2007;50:317-319.
9. Patriarca C, Orazi A, Massimino M, Luksch R. A cystic partially differentiated nephroblastoma producing alpha-fetoprotein. *Am J Pediatr Hematol Oncol*. 1992;14:352-355.
10. Crocoli A, Madafferi S, Jenkner A, et al. Elevated serum alpha-fetoprotein in Wilms tumor may follow the same pattern of other fetal neoplasms after treatment: evidence from three cases. *Pediatr Surg Int*. 2008;24:499-502.
11. Aoyagi Y, Mori S, Naitoh A, et al. Alpha-fetoprotein-producing renal cell carcinoma with increased activity of N-acetylglucosaminyl-transferase III. *Nephron*. 1996;74:409-414.
12. Poulakis V, Witzsch U, de Vries R, et al. Alpha-fetoprotein-producing renal cell carcinoma. *Urol Int*. 2001;67:181-183.
13. Aoki K, Nakanou I, Takashima K, et al. A case of renal cell carcinoma producing alpha-fetoprotein. [Article in Japanese] *Hinyokika Kiyo*. 2001;47:477-480.
14. Minamoto T, Kitagawa M, Amano N, et al. Renal cell carcinoma producing alpha-fetoprotein (AFP) with a unique lectins-affinity profile. *J Surg Oncol*. 1994;55:215-221.
15. Saito S, Hatano T, Hayakawa M, et al. Studies on alpha-fetoprotein produced by renal cell carcinoma. *Cancer*. 1989;63:544-549.
16. Tagaya H, Fukasawa H, Shoda T, et al. Novel alpha-fetoprotein-V messenger RNA isoforms in humans. *Reprod Sci*. 2009;16:794-801.
17. Motoyama I, Watanabe H, Gotoh A, et al. Ovarian Sertoli-Leydig cell tumor with elevated serum alpha-fetoprotein. *Cancer*. 1989;63:2047-2053.
18. Takakura N, Mimura H, Hamazaki K, et al. A case of alpha-fetoprotein, carcinoembryonic antigen and human chorionic gonadotropin producing renal cell carcinoma. [Article in Japanese]. *Gan No Rinsho*. 1987;33:1385-1390.
19. Hong SM, Yu E, Ahn H, Kim OJ. Alpha-fetoprotein producing renal cell carcinoma: a case report. *J Korean Med Sci*. 1998;13:321-324.
20. Ishikura H, Ishiguro T, Enatsu C, et al. Hepatoid adenocarcinoma of the renal pelvis producing alpha-fetoprotein of hepatic type and bile pigment. *Cancer*. 1991;67:3051-3056.
21. Blandamura S, Vendraminelli R, Aversa S, Fedrigo M. Collecting duct carcinoma of kidney producing alpha-fetoprotein. *Eur J Surg Oncol*. 2005;31:1039-1041.
22. Hosomi M, Sagawa S, Kotou Y. Alpha-fetoprotein-producing adenocarcinoma of the ureter. *Urol Int*. 1992;48:226-227.
23. Lu CH, Chou WC, Hung YS, et al. Alpha-fetoprotein-producing transitional cell carcinoma of the urinary bladder: a case report. *Int Urol Nephrol*. 2009;41:567-570.
24. Takayama H. A case of bladder cancer producing alpha-fetoprotein (AFP). [Article in Japanese]. *Hinyokika Kiyo*. 1995;41:387-389.
25. Burgués O, Ferrer J, Navarro S, et al. Hepatoid adenocarcinoma of the urinary bladder. An unusual neoplasm. *Virchows Arch*. 1999;435:71-75.
26. Sinard J, Macleay L Jr, Melamed J. Hepatoid adenocarcinoma in the urinary bladder. Unusual localization of a newly recognized tumor type. *Cancer*. 1994;73:1919-1925.
27. Kawamura N, Hatano K, Kakuta Y, et al. A case of hepatoid adenocarcinoma of the urinary bladder. [Article in Japanese] *Hinyokika Kiyo*. 2009;55:619-622.
28. Lertprasertsuke N, Tsutsumi Y. Alpha-fetoprotein-producing urachal adenocarcinoma. *Acta Pathol Jpn*. 1991;41:318-326.
29. Badve SS, Saxena R, Soman CS, et al. Alpha-fetoprotein production by rhabdomyosarcoma of the urinary bladder. *Indian J Cancer*. 1992;29:177-180.
30. Alsabti EA. Serum alphafetoprotein in bladder carcinoma. *Oncology*. 1977;34:78-79.
31. Ahmed SA, Bahgat MM. Comparative study on the levels of alpha-fetoprotein (AFP) in different pathological cases. *J Egypt Soc Parasitol*. 1995;25:81-92.
32. Hanai J, Lin M. Primary adenocarcinoma of the female urethra with three histologic patterns and partial AFP positivity. *Acta Pathol Jpn*. 1990;40:838-844.
33. Favilla V, Cimino S, Madonia M, Morgia G. New advances in clinical biomarkers in testis cancer. *Front Biosci (Elite Ed)*. 2010;2:456-477.
34. Ersoy O. Very high alpha-fetoprotein in a young man due to concomitant presentation of hepatocellular carcinoma and Sertoli cell testis tumor. *World J Gastroenterol*. 2005;11:7051-7053.
35. Young RH. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. *Mod Pathol*. 2005;18(suppl 2):S81-S98.
36. Larsen WG, Felmar EA, Wallace ME, Frieder R. Sertoli-Leydig cell tumor of the ovary: a rare cause of amenorrhea. *Obstet Gynecol*. 1992;79 (Pt 2):831-833.
37. Mann WJ, Chumas J, Rosenwaks Z, et al. Elevated serum alpha-fetoprotein associated with Sertoli-Leydig cell tumors of the ovary. *Obstet Gynecol*. 1986;67:141-144.

Main Points

- α-Fetoprotein (AFP)-producing non-germ cell tumors may develop in the urological system. Pathologists, urologists, and oncologists need to be aware that these tumors have a different chemotherapeutic regimen and different prognosis from germ cell tumors.
- Different types of renal neoplasms in different age groups have presented associated with raised serum AFP. These include Wilms tumor, renal cell carcinoma, hepatoid carcinoma, and collecting duct carcinoma.
- Elevated serum AFP is very uncommon in bladder cancer with few reported cases of different types of carcinoma and sarcoma. These include transitional cell carcinoma, mixed tumors, bladder sarcoma, and adenocarcinoma.

38. Poli UR, Swarnalata G, Maturi R, Rao ST. Recurrent alpha-fetoprotein secreting Sertoli-Leydig cell tumor of ovary with an unusual presentation. *Indian J Cancer*. 2009;46:64-66.
39. Sekiya S, Inaba N, Iwasawa H, et al. AFP-producing Sertoli-Leydig cell tumor of the ovary. *Arch Gynecol*. 1985;236:187-196.
40. Sun X, Hawkins H, Castro CY, Eltorky MA. Immunohistochemical and ultrastructural analysis of a poorly differentiated pediatric age Sertoli-Leydig cell tumor. *Exp Mol Pathol*. 2007;82:63-67.
41. Tetu B, Ordóñez NG, Silva EG. Sertoli-Leydig cell tumor of the ovary with alpha-fetoprotein production. *Arch Pathol Lab Med*. 1986;110:65-68.
42. Watanabe T, Yamada H, Morimura Y, et al. Ovarian Sertoli-Leydig cell tumor with heterologous gastrointestinal epithelium as a source of alpha-fetoprotein: a case report. *J Obstet Gynaecol Res*. 2008;34:418-421.
43. Gagnon S, Têtu B, Silva EG, McCaughey WT. Frequency of alpha-fetoprotein production by Sertoli-Leydig cell tumors of the ovary: an immunohistochemical study of eight cases. *Mod Pathol*. 1989;2:63-67.
44. Mooney EE, Nogales FF, Tavassoli FA. Hepatocytic differentiation in retiform Sertoli-Leydig cell tumors: distinguishing a heterologous element from Leydig cells. *Hum Pathol*. 1999;30:611-617.
45. Smith R, Moss J, Shore I, El-Bahrawy M. Juvenile granulosa cell tumour with hepatocyte-like cells and raised serum alpha-foetoprotein. *Histopathology*. 2010;57;637-641.