Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/poamed

Case report

Renal cell carcinoma with alpha-fetoprotein secretion and tissue expression – A case report

Dawid Sigorski [a,*], *Rafał Pęksa* [b], *Wojciech Rogowski* [c,d], *Tomasz Milewski* [e], *Ewa Iżycka-Świeszewska* [f]

[a] *Clinical Department of Oncology and Immunooncology, Ministry of Internal Affairs Hospital with Warmia and Mazury Oncology Centre in Olsztyn, Poland*
[b] *Chair and Department of Pathomorphology, Faculty of Medicine, Medical University of Gdańsk, Poland*
[c] *Department of Oncology, NZOZ Magodent, Warsaw, Poland*
[d] *Department of Oncology, Faculty of Medical Sciences, University of Warmia and Mazury in Olsztyn, Poland*
[e] *Department of Diagnostic Imaging, Ministry of Internal Affairs Hospital with Warmia and Mazury Oncology Centre in Olsztyn, Poland*
[f] *Department of Pathology and Neuropathology, Medical University of Gdańsk, Department of Pathomorphology, Copernicus PL Hospitals, Poland*

ARTICLE INFO

Article history:
Received 25 January 2016
Received in revised form
31 July 2016
Accepted 24 November 2016
Available online 14 December 2016

Keywords:
Renal cell carcinoma
Alpha-fetoprotein
Biomarker

ABSTRACT

Introduction: Alpha-fetoprotein (AFP) is a glycoprotein which can be elevated in some non-oncological conditions, and in few types of cancers being a diagnostic and monitoring biomarker. Kidney cancer can produce several substances, which have biological activity and even cause paraneoplastic syndromes. AFP elevation in course of renal cancer is extremely rarely encountered.
Aim: To present diagnostic difficulties in a case of a 43-year-old man with a kidney tumor.
Case study: Clinical and pathological case description.
Results and discussion: The patient initially presented with features of urogenital infection and lumbar pain. Performed diagnostics revealed at first epididymitis, then serum elevation of AFP, and finally renal tumor. Based on wide immunophenotyping, the tumor was histopathologically recognized as high grade clear cell renal cell carcinoma with AFP expression. Clinically the patient presented unexpected rapid cancer progression with parallel increase of above biomarker level, causing repeated exclusion assessment of germ cell tumor.
Conclusions: The diagnostics of kidney mass in our patient was interfered and complicated by concomitant genital infection and AFP serum elevation. Clinically found increased level of AFP requires extensive evaluation, including diagnostics of different tumors.

* *Correspondence to*: Clinical Department of Oncology and Immunooncology, Ministry of Internal Affairs Hospital with Warmia and Mazury Oncology Centre in Olsztyn, Wojska Polskiego 37, 10-228 Olsztyn, Poland. Tel.: +48 89 539 8515; fax: +48 89 539 8303.
E-mail address: dawidsigorski@wp.pl (D. Sigorski).

http://dx.doi.org/10.1016/j.poamed.2016.11.021

1. Introduction

1.1. *Symptoms of kidney cancer*

Kidney cancer accounts about 3% of all adult type cancers in Europe. Typical symptoms of advanced renal cell carcinoma are: flank mass, pain and hematuria. However, nowadays renal tumors are often diagnosed incidentally at the ultrasonographic screening. Kidney cancer may produce several factors that may have systemic effects.[1] It is the most frequent genitourinary neoplasm that causes paraneoplastic syndromes (PNS), although PNS in course of genitourinary neoplasia occur rarely. Kidney cancer may produce substances with a potential of biological activity such as adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH; Cushing syndrome), parathyroid hormone-related protein (PTHrP; hyperkalcemia), renin and erythropoietin (hypertension), insulin, glucagon (hypoglycemia, hyperglycemia), human chorionic gonadotropin (HCG), prolactin, and antidiuretic hormone (ADH).[2] It may also secrete factors that cause pyrexia, cachexia, neuromyopathy, amyloidosis and abnormal liver dysfunction.[1,3] Moreover, very rarely kidney cancer can produce alpha-fetoprotein (AFP).

1.2. *Characteristics of AFP*

AFP is a glycoprotein of 70 kD consisting of 591 amino acids with sequence similar to albumin, vitamin D and alpha albumin.[4] The exact physiological role of AFP has not been determined, but probably it is involved in the transport of hormones, bilirubin, fatty acids, retinoids, and heavy metals.[4] AFP is the main protein in fetal plasma being produced by cells of yolk sac, and later by the cells of liver, kidneys and the gastrointestinal tract, reaching up to 500 μm/L in the third trimester.[5,6] Its level is used as a 'triple test' in the prenatal diagnostics of some genetic disorders and neural tube defects.[7] After birth, AFP plasma level decreases rapidly to the end of the first year of life and it achieves a normal low level up to 15 μm/L.[8] AFP is one of the established tumor markers which is used to diagnose and monitor treatment of malignant germ cell tumors, as well as hepatic malignancy.[9]

2. Aim

The aim of this paper was to report a rare case of AFP producing renal cell carcinoma.

3. Case study

A 43-year-old man visited his general practitioner in December 2012 because of a left-sided lumbar colic pain. In January 2013 he reported pain in the region of his left testis, accompanied by fever and dysuria. Diagnostic imaging and laboratory tests were performed. Abdominal ultrasonography revealed slight enlargement in the lower pole of the left kidney and significant thickening of the left epididymis. Both testicles were without abnormalities. Laboratory tests showed leukocyturia and elevated CRP level. Due to genitourinary tract infection with high fever, antibiotic treatment with ciprofloxacin was prescribed, with a good therapeutic effect in 2 weeks. In the end of February 2013 the patient was hospitalized due to hematuria with blood clots and urinary retention. At that time laboratory tests revealed slight anemia and elevated levels of AFP (more than 1 318 IU/mL), with normal B-HCG level. Suggestion of germ cell tumor was considered.

Extended diagnostic imaging with CT and MRI showed tumor of the left kidney especially in the inferior pole with thrombus filling left renal vein. Liver was without abnormalities, and chest X-ray was normal. In March 2013 patient underwent uncomplicated left-side nephrectomy with adrenalectomy. Pathological gross examination disclosed a tumor of kidney measuring 10.0 × 7.5 cm with fibrous capsule, perineural, fat and renal vein invasion. Microscopic examination showed malignant epithelioid predominantly clear cell tumor with focal papillary pattern, dense vasculature and focal perivascular arrangements. Differential diagnosis included various types of neoplasm, but mainly renal cell carcinoma and germ cell tumors (yolk sac tumor). On immunohistochemical staining tumor cells were CD10 (+), Vimentin (+), Cytokeratin CAM5.2 (+), racemase (AMACR) (+), placental alkaline phosphatase (PLAP) (−), EMA focally present, PAX_8 (+) and negative for cytokeratin 7, cytokeratin 19, Glypican 3, HMB45.[10] Moreover, AFP expression was found in neoplastic cells (Figs. 1–4). High grade renal clear cell carcinoma, G3 according to Fuhrman, in stage pT2b was recognized. All resection margins were free from the cancer. In the end of April 2013 a control thoracic CT scan detected a conglomerate of metastatic lesion measuring 20 × 17 mm in the right lung and right pulmonary hilar lymph nodes enlargement. Moreover, it showed numerous hypodense metastatic foci in liver and a mass 50 × 38 mm within the space of removed kidney (Fig. 5). Blood tests showed slight anemia and significantly increased level of AFP (more than 10 000 IU). The patient was admitted to chemotherapy department with treatment intention. Due to an unusual dynamic clinical course and increasing AFP level, ultrasound and MRI of testes and core

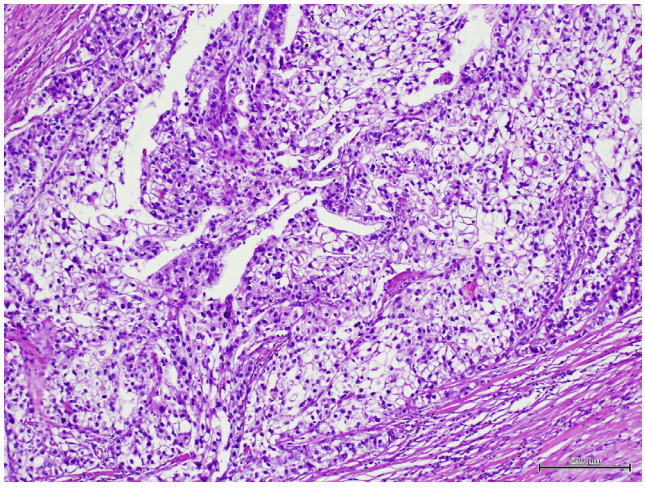

Fig. 1 – Renal cell carcinoma with papillary features (HE, magnification 100×).

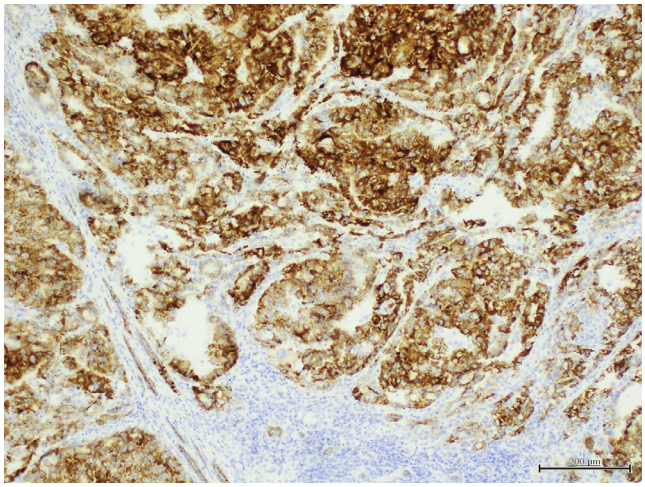

Fig. 2 – Racemase expression in tumor cells (racemase, magnification 100×).

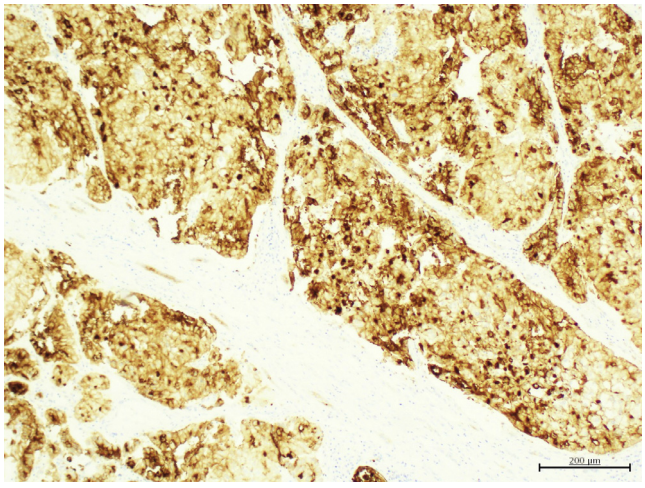

Fig. 3 – Positive CD10 expression in tumor cells (CD10, magnification 100×).

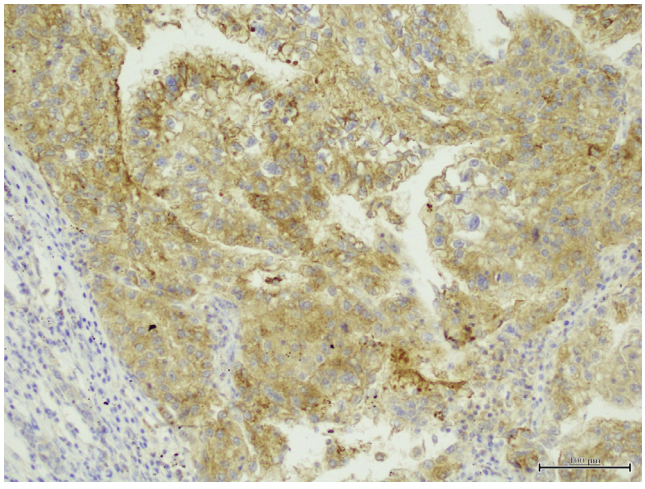

Fig. 4 – Cytoplasmic AFP expression in tumor cells (AFP, magnification 100×).

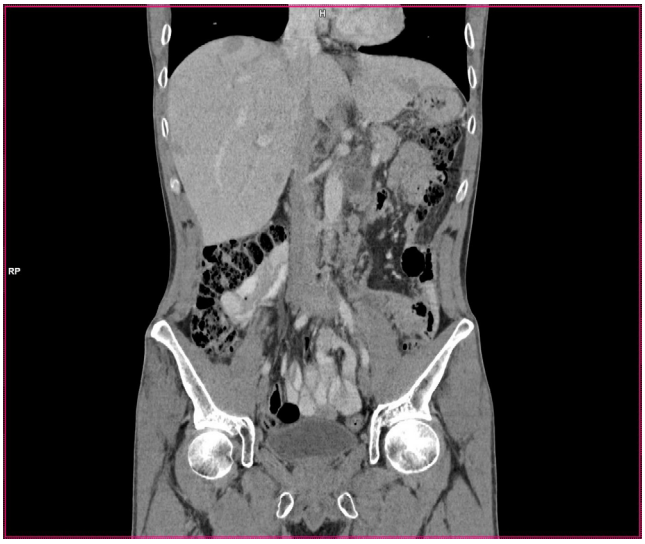

Fig. 5 – Metastatic foci in liver and within the space of removed kidney.

needle biopsy of liver metastases were performed to exclude coexistence of germ cell tumor. Testicles did not disclose any focal lesions. The liver tumor biopsy showed morphology and immunophenotype identical to the primary renal tumor, corresponding with clear cell nephrogenic carcinoma. The unusual progressive outcome of the patient's disease caused difficulties also in therapeutic decision. The patient had five unfavorable renal cancer prognostic factors according to the Motzer scale: performance status WHO2, corrected calcium level 10.06 mg/dL, LDH 2.156 U/L, Hgb 10.4 g/dL, and time from nephrectomy to metastatic disease circa 1 month. In addition, number of platelets and neutrophils was elevated. Considering the aggressive course of the disease and patient's young age, it was decided to qualify him to palliative care. Treatment with Sunitinib was introduced in July 2013. The level of AFP in serum was still increasing. The patient received two cycles of treatment but control CT revealed a massive progression of metastatic lesions and local relapse. Due to osteolytic lesion within Th12, the palliative radiotherapy was performed. In the following weeks, the clinical and imaging progression accelerated, causing patient's disqualification from further treatment. He was referred to a palliative care unit where he died in December 2013 – one year after the initial symptoms of the disease.

4. Results and discussion

4.1. *Conditions with elevated levels of AFP and clinical importance*

AFP can be elevated in both oncological and non-oncological conditions. Increased AFP levels in the children may be indicative of tyrosinemia, cardiac defects, hepatitis or ataxia telangiectasia syndrome.[5] AFP elevation is also observed in cancers, mainly in non-seminomatous germ cell tumors such as yolk sac and mixed germ cell tumors, as well as in liver

malignancy, including hepatocellular carcinoma (HCC), hepatoblastoma and some types of hepatic metastases.[11] Serum AFP level happens to be elevated in adult patients with gastrointestinal, biliary, pancreatic, lung, and rarely gynecologic cancer.[5,6] In differential diagnosis β-hCG and PLAP are additional germ cell tumors markers. In children when the level of AFP is high, together with high risk tumor in typical location, it is possible to start an oncological treatment as for germ cell tumors without histopathological examination. This procedure is however subject to the rare risk of error. Literature describes several cases of children treated with chemotherapy according to the international guidelines, which after histopathological examination were identified as cholangiocarcinoma and pancreatoblastoma.[12] Interestingly, increased levels of AFP in serum do not correlate with immunohistochemically proved expression of this protein in tumor tissue. Tissue cellular expression of AFP is observed in liver cancer, germ cell tumors, craniopharyngioma, Wilms tumor, and in some gliomas.[13] In some tumors, this reactivity can be extracellular. Clinical and tissue expression of AFP in kidney cancer is rare and so far only few similar cases have been described.

4.2. *Biological implication of AFP in cancer progression*

AFP secretion by non-typical tumors is recognized as a result of the neoplastic cells dedifferentiation. Hypomethylation within 5′ region of AFP gene is associated with the expression of AFP gene within HCC. This phenomenon is also found in renal cell cancer as a result of genetic instability of tumor cells during progression.[6] It is postulated that AFP is involved in the mechanisms of tumors progression. AFP due to connection with PTEN causes a lack of inhibition of signaling pathway PI3 K/AKT/mTOR.[14] It has also been proved that the AFP level is related to telomerase activity which enables cancer cells to be immortal.[7] One function of mTOR complex is to control the transcription of HIF-1alpha and HIF-2alpha, which being a transcription factors, activate genes that activate neoangiogenesis. The increased activity of mTOR and mutation of VHL gene is the cause of increased angiogenesis and disease progression in RCC.[15]

4.3. *Review of literature with a correlation to described case*

So far only few similar cases of kidney cancer with elevated serum AFP level have been described. Histologically the most common type was clear cell carcinoma and granular cell carcinoma. These cases occurred mostly in Asians with mean age of 50 years. In these cases AFP levels ranged from 36.3 IU/mL to 534.07 IU/mL and depended on the stage of the disease. Distant metastases occurred in bones, lung, lymph nodes, but in the majority of patients there were no metastases within the liver. The differential diagnosis included primary tumors of the kidney as well as gonadal and extragonadal germ cell tumors with kidney involvement. On immunohistochemistry, clear cell type cancer showed the highest expression of AFP. These tumors had generally poor prognosis with dissemintaion.[5,6,9] Our patient initially was in advanced stage of disease. His diagnosis was delayed due to the acute genital tract infection at the clinical presentation.

Table 1 – Changes in AFP level in time.

Date	AFP (IU/mL)
February 12, 2013	>1 318
June 11, 2013	23 967
June 19, 2013	34 555
July 1, 2013	41 704
October 1, 2013	70 868

The main tumor which was histologically ruled out during diagnostics was yolk sac tumor. Its exclusion was based on the profound morphological analysis and immunoprofile revealing CD10, racemase, and PAX8 positivity, together with glypican 3 and PLAP negativity. Histology together with immunophenotype of the tumor confirmed clear cell renal carcinoma. The patient belonged to the unfavorable group in Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scale, which indicates the way of the treatment. The MSKCC/Motzer Score for Metastatic Renal Cell Carcinoma is the most widely used prognostic scale for metastatic kidney cancer. After introduction of targeted therapies MSKCC score was validated to Heng criteria which additionally include levels of platelets and neutrophils. Number of platelets and neutrophils greater than upper limit of normal are considered negative prognostic factors. The median of overall survival for patients with favorable risk group is 43 months, intermediate 27 and poor 8.8 months. The risk score is under research and is expected to be validated.[1] In unfavorable MSKCC patients, temsirolimus is recommended. Because temsirolimus was not available at that time in our region, we administrated sunitinib without therapeutic effect. The dynamics of the disease was unusually high, with very fast metastatic dissemination and local postoperative relapse which is not typical for renal cell carcinoma, so germ cell tumor was suspected. Interestingly, since the diagnosis was made, the permanent progression of AFP level was observed, reaching 70 868 IU/mL (Table 1). Our case presented very high concentration of AFP in serum together with its expression within the neoplastic tissue.

5. Conclusions

The diagnostics of kidney tumor in our patient was interfered and complicated by concomitant genital infection and atypical AFP serum elevation. Elevated AFP in patient's serum requires extensive evaluation including different tumors, with possibility of disease monitoring.

Conflict of interest

None declared.

REFERENCES

1. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2014;25(suppl 3):iii49–iii56. http://dx.doi.org/10.1093/annonc/mdu259.

2. Özlük Y, Kılıçaslan I. Syndromes that link the endocrine system and genitourinary tract. *Türk Patoloji Derg*. 2015;31 (suppl 1):155–171. http://dx.doi.org/10.5146/tjpath.2015.01322.
3. Marston L, Rini B, Yang J. Cancer of the kidney. In: De Vita VT, Lawrence TS, Rosenberg SA, eds. *Cancer Principles and Practice of Oncology*. Philadelphia: Wolters Kluwer Health; 2011:1166.
4. Mizejewski GJ. Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants. *Exp Biol Med (Maywood)*. 2001;226(5):377–408.
5. Hong SM, Yu E, Ahn H, Kim OJ. Alpha-fetoprotein producing renal cell carcinoma: a case report. *J Korean Med Sci*. 1998;13 (3):321–324. http://dx.doi.org/10.3346/jkms.1998.13.3.321.
6. Lin CM, Meng E, Lee SS, et al. Alpha-fetoprotein-producing renal cell carcinoma. *J Med Sci*. 2004;24(3):141–144.
7. Tahtouh R, Azzi A-S, Alaaeddine N, et al. Telomerase inhibition decreases alpha-fetoprotein expression and secretion by hepatocellular carcinoma cell lines: in vitro and in vivo study. *PLOS ONE*. 2015;10(3):e0119512. http://dx.doi.org/10.1371/journal.pone.0119512.
8. Samaratunga H, Samaratunga D, Dunglison N, Perry-Keene J, Nicklin J, Delahunt B. Alpha-fetoprotein-producing carcinoma of the renal pelvis exhibiting hepatoid and urothelial differentiation. *Anticancer Res*. 2012;32(11): 4987–4992.
9. Morimoto H, Tanigawa N, Inoue H, Muraoka R, Hosokawa Y, Hattori T. Alpha-fetoprotein-producing renal cell carcinoma. *Cancer*. 1988;61(1):84–88.
10. Delahunt B, Srigley JR. The evolving classification of renal cell neoplasia. *Semin Diagn Pathol*. 2015;32(2):90–102. http://dx.doi.org/10.1053/j.semdp.2015.02.002.
11. Ip S, Schaeffer DF, Yoshida EM, Kwan WP. Alpha fetoprotein-secreting gastric cancer in the setting of chronic hepatitis B: the role of endoscopy. *ACG Case Rep J*. 2015;2(3):152–154. http://dx.doi.org/10.14309/crj.2015.38.
12. Drozynska E, Bien E, Polczynska K, et al. A need for cautious interpretation of elevated serum germ cell tumor markers in children. Review and own experiences. *Biomark Med*. 2015;9 (9):923–932. http://dx.doi.org/10.2217/bmm.15.42.
13. The Human Protein Atlas. http://www.proteinatlas.org/ Accessed 19.10.16.
14. Zhu M, Lin B, Zhou P, Li M. Molecular analysis of AFP and HSA interactions with PTEN protein. *Biomed Res Int*. 2015;2015:256916. http://dx.doi.org/10.1155/2015/256916.
15. Żołnierek J, Wysocki P, Nurzański P. Everolimus – oral mTOR inhibitor used in treatment of tyrosine kinase inhibitors-resistant advanced kidney cancer. In: Szczylik C, Wcisło G, eds. *Kidney cancer. Current treatment and diagnostics*. Poznań: Termedia; 2010:226 [in Polish].