Ovarian clear cell adenocarcinoma producing alpha-fetoprotein: case report

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Summary

Background: Alpha-fetoprotein (AFP) is a useful tumor marker for germ cell tumors of the ovary and is valuable for both diagnosis and follow-up. However, it is very rare for an epithelial ovarian carcinoma to secrete AFP.

Case: We report a case of a 63-year-old woman with a ovarian clear cell carcinoma with serous component of less than 10%. Both histological components were producing AFP as demonstrated by immunohistochemistry. After surgery and chemotherapy, AFP decreased to normal range. The patient also had elevated CA-125 levels but the tumor was negative for CA-125 which suggested the increased CA-125 might have been due to the associated ascites.

Conclusion: Ovarian clear cell type carcinomas rarely secrete only AFP and it might be the single marker that could be used in follow-up.

Key words: Clear cell carcinoma; Serous adenocarcinoma; Epithelial ovarian carcinoma; Tumor marker; AFP; CA-125.

Introduction

α-Fetoprotein (AFP) is an oncofetal antigen that is synthesized by the liver and yolk sac in the developing embryo [1]. However, during adult life, it can also be produced by hepatocellular, testicular and ovarian germ cell cancer [2, 3]. Even though AFP production is one of the characteristics of endodermal sinus tumors (EST) also known as yolk sac tumors (YST) of the ovary, rarely can Sertoli-Leydig cell tumors, dysgerminomas and epithelial ovarian carcinomas (EOC) produce AFP [2-4]. AFP production of some of the EOC can be attributed to the foci of yolk sac tumors [5]. Clear cell type of EOC is rare and it has been seldomly reported to produce alpha-fetoprotein [6, 7]. Herein, we present a case of clear cell carcinoma of the ovary that was producing AFP with no yolk sac component.

Case Report

A 63-year-old woman (G6, P4) was admitted to the hospital with postmenopausal vaginal hemorrhage. Gynecologic ultrasound showed a mass in the right ovarian area which was 20 x 13 cm in diameter with cystic and solid components, and also ascites. There was no distal metastasis in detailed imagining examinations. CA-125 and AFP were significantly elevated up to 627 U/ml (N: 0-35 U/ml) and 1210 IU/ml (N: 0-5.5 IU/ml), respectively, while CA 19-9, beta-HCG, carcinoembryonic antigen (CEA) and CA 15-3 were within normal range. There was no abnormality in the liver or renal function tests. For tumor debulking; bilateral salpingo-oophorectomy, total abdominal hysterectomy, partial omentectomy, and pelvic lymphadenectomy were performed with resection of intestinal fragments having macroscopically tumoral invasion. The surgery was optimal for debulking.

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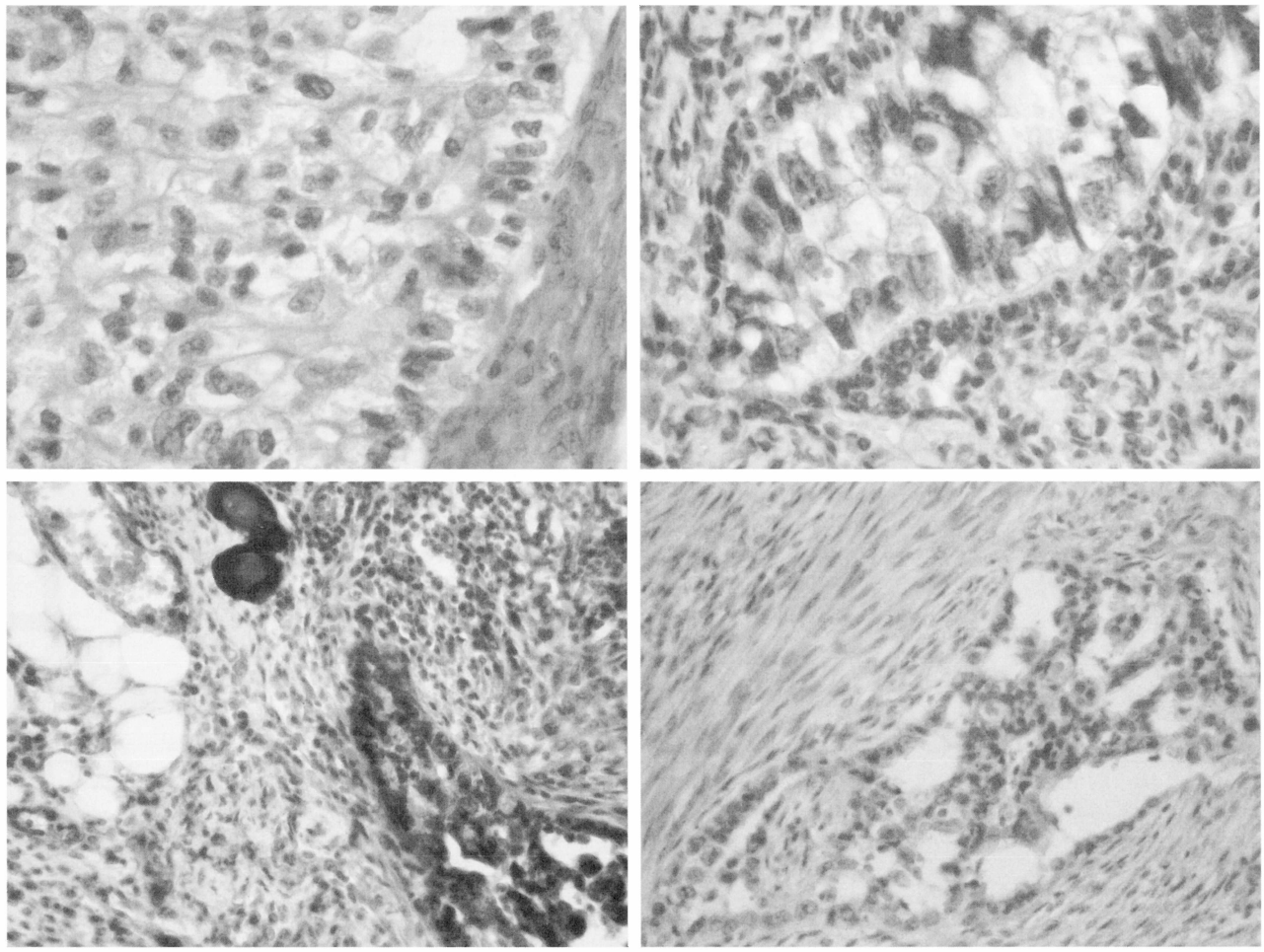
At pathological examination macroscopically, the right ovarian tumor was in 22 x 14 x 4 cm in diameter with multiple yellow serous fluid cysts (the biggest being almost 3.5 cm) and yellow solid nodules (the biggest being almost 4.0 cm). At microscopic examination of the right ovary specimen, the tumor was clear cell carcinoma (CCC) consisting of solid, tubulopapillary and tubulocystic patterns. There were polyhedral cells with clear cytoplasm and a pleomorphic nucleus. Some of the cells lining the glands were columnar with a hobnail appearance. Some of the cells lining the cysts were flattened. Immunohistochemically, the tumor cells were diffusely stained positive with pancytokeratin; focally positive with EMA and with AFP. RCC, PLAP, vimentin, calretinin, cytokeratin 20, inhibin, CD 15, and CA-125 were negative (Figure 1). There was no tumoral finding in the left ovary, the right and left tuba, uterus and cervix. While there were seven metastatic lymph nodes (LN) and one reactive LN in the right pelvic LN area, there was no tumoral infiltration in the left pelvic LN area. The sections of the invasive peritoneal implants revealed a haphazard infiltrative pattern of glandular structures and psammoma bodies. The existence of psammoma bodies revealed a serous component. However, the serous component was less than 10% of the tumor. Therefore, it was reported as "clear cell carcinoma of the ovary". Immunohistochemically, metastatic peritoneal implants were also stained positive with AFP, while negative for CA-125 (Figure 2).

After the surgery, AFP and CA-125 levels decreased to 65 IU/ml and 53 U/ml, respectively, but they were still above the normal ranges. Routine adjuvant chemotherapy consisting of paclitaxel (175 mg/m^2) and carboplatin (6 AUC) was administered four weeks after the surgery. In the third cycle of the adjuvant chemotherapy, AFP and CA-125 decreased to normal ranges (1.84 IU/ml and 6.26 U/ml, respectively). Adjuvant chemotherapy was completed to six cycles.

After completion of the chemotherapy at her 9-month control, the AFP level was found to have increased to 87 IU/ml, while CA-125 was in normal range (8 U/ml). Although in the abdominopelvic ultrasound (US) and computed tomography (CT) there was no lesion indicating recurrence, AFP levels



(1A) (1B)

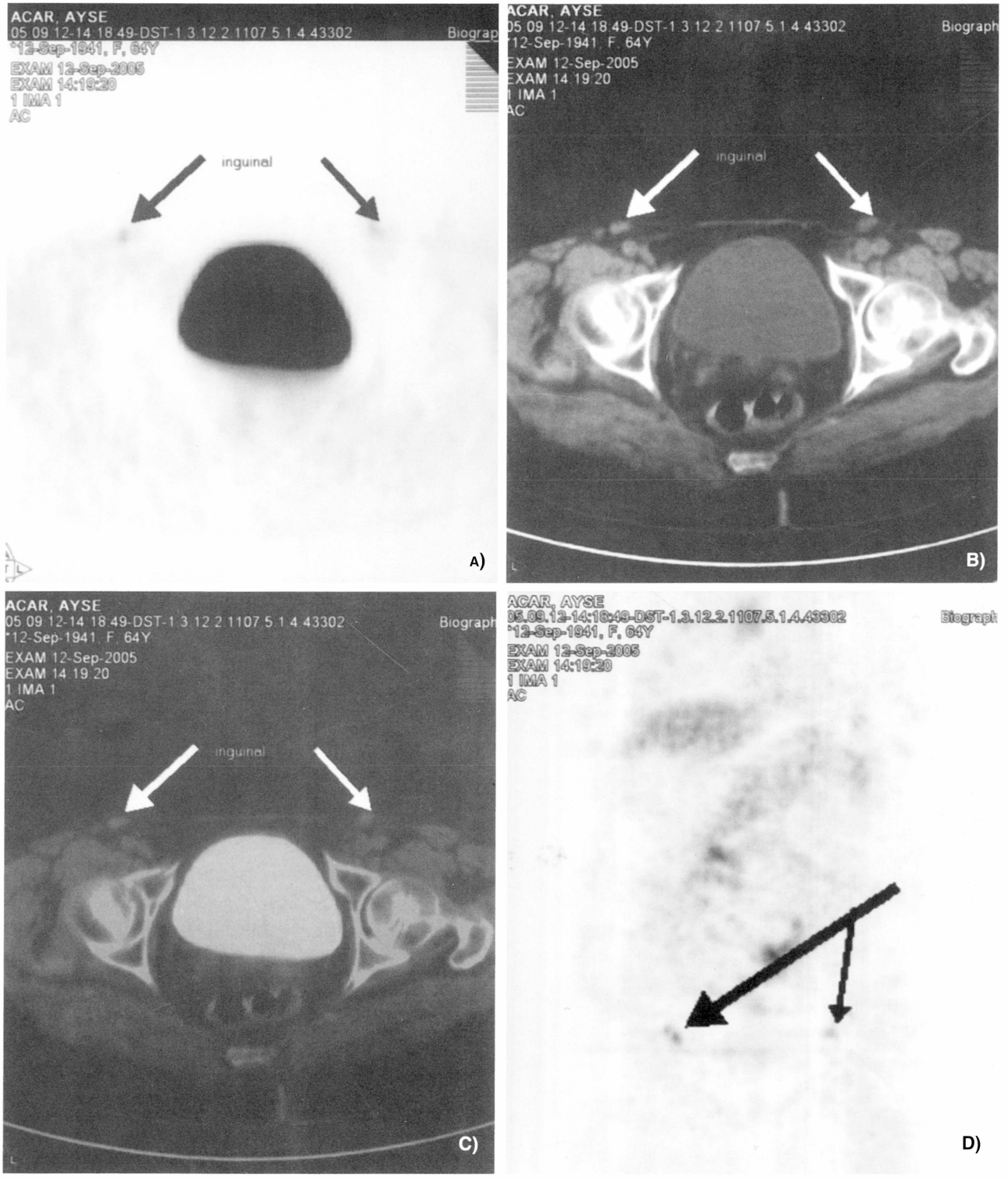
(2A) (2B)

Figure 1. — (A) Solid sheet formed by neoplastic cells with enlarged hyperchromatic nuclei and clear moderately abundant cytoplasm (hematoxylin and eosin x 400 original magnification) (B) Positive cytoplasmic immunostaining for AFP on neoplastic cells (Anti AFP-AEC-Mayer's hematoxylin x 400 original magnification).
Figure 2. — (A) Positive immunostaining for alpha fetoprotein on neoplastic cells of the glandular structure, displaying findings of omentum metastasis from the ovarian carcinoma. Note nonimmunstaining of a psammoma body (anti AFP-AEC-Mayer's hematoxylin x 200 original magnification). (B) No immunostaining for CA-12.5 on the metastatic carcinomatous glandular structure in the omentum. (Anti CA-12.5-AEC-Mayer's hematoxylin x 200 original magnification).

increased gradually up to 290 IU/ml in a month. F-18 flourodeoxyglucose (FDG) positron emulsion tomography (PET/CT) was planned to detect any recurrence but due to insurance problems of the patient, it could not be performed. Therefore, although there was no imaging evidence, the consistent and progressive increase in AFP led us to the presumptive diagnosis of recurrence of the tumor. Since the time to recurrence was more than six months, this case was accepted as sensitive to platin. Thus, paclitaxel and carboplatin were again introduced but this time as second-line chemotherapy for six cycles upon which AFP levels decreased. Three months after completion of the second-line chemotherapy, AFP levels increased to 300 IU/ml. Again, abdominopelvic CT was performed and found negative for recurrence. This time, PET/CT could be performed and yielded slightly increased FDA uptake in the mediastinal and inguinal areas which were suspicious for malignancy, and a slightly increased FDA uptake was noted in the anterior wall of the abdomen which could be interpreted as a postoperative inflammatory change (Figure 3). There was a nodule at the right posterobasal segment of the inferior lobe of the right lung showing normal FDG uptake. Due to suspicious malignant involvement in PET/CT, thorax CT and abdominopelvic MR were performed. Thorax CT was normal but at the pelvic MR, pathological enlargement of the inguinal lymph nodes was detected. In the period of imaging, AFP elevated to 1879 IU/ml. It was accepted as a second relapse. Etoposide and cisplatin chemotherapy was given as the third-line chemotherapy. After four cycles of chemotherapy, AFP gradually decreased to 432 IU/ml. However, the patient died due to sepsis and multiorgan failure which had begun ten days after the last cycle of the chemotherapy in the neutropenic period.

Discussion

Alpha-fetoprotein (AFP) is an oncofetal antigen that is synthesized by the liver and yolk sac in the developing embryo [1]. Although it is a useful tumor marker in the diagnosis and follow-up of EST, it is well known to be secreted also in some other tumors; like hepatocellular



(3A) (3B) (3C) (3D)

Figure 3. — Inguinal lymph node lesions in the patient, (A) axial PET scan (B) axial CT scan (C) axial fused PET-CT scan (D) coronal PET scan showing slightly increased FDG uptake.

carcinoma and testicular carcinoma. Rarely have Sertoli-Leydig cell tumors, dysgerminomas and epithelial ovarian tumors been reported to produce AFP [2-4]. Considering clear cell carcinoma specifically, in their report Ramalingham *et al.* reported that of eight clear cell carcinoma patients none was found to secrete AFP [6]. AFP production of some epithelial ovarian tumors is attributed to the foci of yolk sac tumors [5].

Maida *et al.* [4] reported a case of endometrioid ovarian carcinoma with small foci of the clear cell com-

ponent which was secreting AFP and CA-125 significantly, and CEA slightly. After the surgery and second course of chemotherapy, all these markers decreased to normal range. However, in this report, immunohistochemically AFP expression was observed in the endometrioid tumor components but not in the clear cell components. Our case was a mixed clear cell and serous papillary carcinoma of the ovary where AFP expression was also shown in the clear cell component in addition to the serous part.

Konishi *et al.* [3] published a case of ovarian mucinous cystadenocarcinoma, composed of both intestinal type and endocervical type cells, and secreting CEA and AFP together. Preoperative serum CEA and AFP levels were reported to be elevated to 660 and 1120 ng/ml, respectively. After surgery, both decreased to their normal ranges. Immunohistochemically, AFP positive cells were usually negative for CEA and vice versa. There were few cells which were positive for both CEA and AFP at the same time. However, in our case, all of the tumoral cells were positive for AFP simultaneously but not for CA-125.

Some mixed ovarian tumors may produce AFP in all the histological components as in our case. Matsuta *et al.* [2] reported a case of mixed hepatoid carcinoma of the ovary in which most of the tumor consisted of undifferentiated carcinoma cells resembling hepatocellular carcinoma. The remainder of the tumor was a tubular adenocarcinoma with transition between the two patterns. In their case, AFP was detected in both the tubular adenocarcinoma and hepatoid regions.

Our patient also had CA-125 elevation approximately 17-fold at presentation which was less pronounced than AFP elevation (approximately 220-fold). However, the tumor was found negative for CA-125 by immunohistochemistry. This was surprising because CA-125 is known to be the most commonly associated tumor marker for serous and clear cell carcinoma. It is well known that diseases with serous tissue invasion can cause elevation of CA-125 due to mesenchymal cell response [8]. Thus we determined that the origin of CA-125 in our patient was not the tumor itself but the associated ascites. Actually, when the degree of increase in AFP and CA-125 was compared, the significantly higher proportion of increase in AFP also indicated this conclusion.

Conclusion

Ovarian clear cell type cancer rarely may secrete only AFP as a tumor marker and therefore AFP may be the single tumor marker that can be used in the follow-up of those cases. Also, in clear cell type ovarian cancer, increase in CA-125 might not be due to the disease itself but to some serous involvement which may or may not be associated with tumoral involvement.

References

[1] Tsukamoto N., Imachi M., Uchino H., Ono M., Kamura T., Saito T., Matsukuma K.: "Modified VAB-3 combination chemoterapy of advanced and recurrent endodermal sinus tumors of ovary". *Gynecol. Oncol.*, 1985, *20,* 336.

[2] Matsuta M., Ishikura H., Murakami K., Kagabu T., Nishiya I.: "Hepatoid cancer of the ovary: a case report". *Int. J. Gynecol. Pathol.*, 1991, *10,* 302.

[3] Konishi I., Fujii S., Kataoka N., Noda Y., Okamura H., Yamabe H., *et al.*: "Ovarian mucinous cystadenocarcinoma producing alpha-fetoprotein". *Int. J. Gynecol. Pathol.*, 1988, *7,* 182.

[4] Maida Y., Kyo S., Takakura M., Kanaya T., Inoue M.: "Ovarian endometrioid adenocarcinoma with ectopic production of alpha-fetoprotein". *Gynecol. Oncol.*, 1998, *71,* 133.

[5] Nogales F.F., Bergeron C., Carvia R.E., Alvaro T., Fulwood H.R.: "Ovarian endometrioid tumors with yolk sac tumor component, an unusual form of ovarian neoplasm: Analysis of six cases". *Am J. Surg. Pathol.*, 1996, *20,* 1056.

[6] Ramalingam P., Malpica A., Silva E.G., Gershenson D.M., Liu J.L., Deavers M.T.: "The use of cytokeratin 7 and EMA in differentiating ovarian yolk sac tumors from endometrioid and clear cell carcinomas". *Am. J. Surg. Pathol.*, 2004, *28,* 1499.

[7] Clear Cell Adenocarcinoma World Health Organization Classification of Tumours Pathology and Genetics/Tumours of Breast and Female Genital Organs. In: H.A. Tavassol and P. Device (eds.). International Agency for Research on Cancer (IARC) Lyon, France, 2003, 137.

[8] Topalak O., Saygili U., Soyturk M., Karaca N., Batur Y., Uslu T. *et al.*: "Serum, pleural effusion, and ascites CA-125 levels in ovarian cancer and nonovarian benign and malignant diseases: a comparative study". *Gynecol. Oncol.*, 2002, *85,* 108.

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