Alpha-fetoprotein producing endometrial serous carcinoma

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Abstract:
Elevated serum levels of alpha-fetoprotein, a fetal serum protein, occurs on development of hepatoma or germ cell tumors, mainly yolk sac tumor. Very few cases of endometrial carcinoma associated with elevated serum alpha-fetoprotein have been reported. It is important to be aware of such entities to ensure correct diagnosis and hence patient management. We report a case of a 71 years old lady presenting with postmenopausal bleeding and elevated serum alpha-fetoprotein. Investigations confirmed the patient had an alpha-fetoprotein producing endometrial serous carcinoma. This is the third case of alpha-foetoprotein producing serous carcinoma. We discuss the clinicopathological features of the case and review the literature for previously reported alpha-fetoprotein producing endometrial carcinomas. These cases show aggressive behavior and very poor prognosis.

Key words:
Alpha-fetoprotein; Endometrial carcinoma

INTRODUCTION
Elevated serum levels of alpha-fetoprotein (AFP), a fetal serum protein, occurs on development of hepatoma or germ cell tumors, mainly yolk sac tumor (YST). AFP is a useful tumor marker for germ cell tumors of the ovary and is valuable for both diagnosis and follow-up. Of the rare extra-ovarian AFP producing tumors are those arising in the uterus. AFP producing tumors of the uterus have been divided into two categories. The first category includes primary yolk sac tumors of the endometrium, which present in relatively young patients and at a low stage.¹ The second category includes high grade endometrial carcinomas, malignant mixed Mullerian tumors (MMMT),² hepatoid carcinomas³ and papillary serous carcinomas,⁴ which usually present in an older age group.

AFP producing carcinomas, particularly those of the serous type usually present in older women, at a high stage and with an overall poorer prognosis. Only two cases of AFP producing uterine serous carcinomas have been previously reported.⁴,⁵ In this report we present the third case of a primary AFP producing uterine serous carcinoma.
**CASE PRESENTATION**

A 71 years old lady presented at Hammersmith Hospital with twelve month history of post–menopausal vaginal bleeding and recent development of anorexia, abdominal pain and constipation. The patient had a past medical history of type 2 diabetes mellitus, hypertension and partial thyroidectomy for multi-nodular goitre. On examination she was thin, pale and had a distended abdomen with hard fixed masses in the right iliac fossa and lower abdomen, and right inguinal lymphadenopathy.

Chest X-ray showed apical fibrosis and lung nodules consistent with previous tuberculosis. The hematology profile and serum biochemistry were within the normal range. Her tumor markers taken at presentation revealed grossly elevated serum AFP at 94,340 (normal range 0 - 13). Other results included CA 125 165 (0 - 35), CEA 3548 (0 - 5), Ca 19-9 501 (0 - 33), LDH 371 (125 - 243) and HCG < 2 (0 - 4). The AFP had risen to 118,789 when repeated 3 weeks later.

CT scan showed an enlarged uterus measuring 9cm in length, with an enlarged left ovary (4.2 × 2.7 cm) and a complex cystic mass in the right iliac fossa measuring 7.8 × 6.0 cm. Multiple large lymph nodes were noted, with diffuse omental thickening and small volume ascites. Biopsies were subsequently taken from the endometrium and cervix. An ultrasound-guided peritoneal biopsy was performed on the omental mass.

Histological assessment of the endometrial, cervical and omental biopsies showed tumour tissue composed of cells arranged in sheets and tubulo-papillary structures (Figure 1A). The tumor cells showed large hyperchromatic nuclei with prominent nucleoli and vacuolated cytoplasm. Some cells displayed markedly enlarged, bizarre nuclei (Figure 1B). There was increased mitotic activity and extensive necrosis. No morphological features of YST or embryonal carcinoma were seen.

On immunohistochemistry, the tumour cells expressed broad range cytokeratins, cytokeratin 7 (CK7; Figure 1C), epithelial membrane antigen (EMA; Figure 1D) confirming epithelial differentiation. The cells strongly and diffusely expressed p16 (Figure 1E) and p53 (Figure 1F). The strong diffuse expression of both of these antigens in context of the morphology favoured serous differentiation. The cells showed strong expression of AFP (Figure 1G) and weak focal expression of placental alkaline phosphatase (PLAP; Figure 1H). There was strong expression of oestrogen receptors. The cells were negative for progesterone receptor (PgR), WT-1, CD15 and human chorionic gonadotrophin.

The morphology and immunoprofile we consistent with serous endometrial carcinoma.

In view of the advanced disease, the patient was offered palliative chemotherapy. She declined any systemic therapy and died within 3 months of diagnosis.

**DISCUSSION**

Non germ cell AFP producing endometrial tumours have been previously reported. To our knowledge there are only 10 reported AFP producing endometrial tumors. These are mainly pure hepatoid carcinomas, endometrioid carcinomas with hepatoid component and malignant mixed Mullerian tumor (MMMT) with hepatoid components. Hepatoid adenocarcinoma is characterized histologically by neoplastic epithelial cells that resemble hepatocellular carcinoma (HCC) where the cells have abundant eosinophilic cytoplasm and produce AFP. One endometrioid carcinoma and one MMMT did not contain hepatoid components, but showed AFP expression in the tumor cells.

Two AFP producing papillary serous carcinomas have also been reported. Similar to our case, both cases presented with postmenopausal vaginal bleeding. In our case, the high stage at presentation with peritoneal disease, is also similar to that of the two previously reported cases, in which there was tumour spread in the abdominal cavity, liver, lungs, and pelvis.

Due to the markedly elevated serum AFP, and the high grade cytomorphology, YST was theoretically considered in the differential diagnosis. However, YST is usually encountered in younger patients and the histological appearance was not typical of YST. Nevertheless, knowing that there are numerous phenotypic variants of YST with some overlap with different types of tumours, a large panel of immunohistochemistry was essential to confirm the nature of the tumor.
Figure 1 The tumor shows a solid and tubulo-papillary architecture (A; ×40). The cells have pleomorphic hyperchromatic nuclei (B; ×200). The tumor cells express CK7 (C) and EMA (D) confirming epithelial differentiation. The cells strongly express p16 (E) and p53 (F) commonly expressed in serous carcinoma. The tumor cells show strong expression of AFP (G) and focal weak expression of PLAP (H).

YSTs have a variety of morphologic patterns, some of which can resemble either endometrioid adenocarcinoma (EAC) or clear cell carcinoma (CCC). Immunohistochemical staining for AFP is usually only focal and thus is not always helpful in the diagnosis of YST and can also be expressed in some endometrial carcinomas. Moreover, pancytokeratin (CK) is expressed by all three tumors. So, a panel of immunohistochemical markers should be used in differentiating YST from EAC and CCC. CK7 is essentially not expressed in YST. Only occasional cases of YST have shown CK7 expression in 1%-2% of cells whereas carcinomas would show diffuse CK7 expression. EMA is also only expressed in epithelial tumours and not in YST. Leu-M1 (CD15) is expressed in CCC, but not in YST. WT1 may be expressed in a small percentage of uterine serous carcinomas, but is not expressed by YST. YST also stains positively for alpha-1-antitrypsin (A1AT) and PLAP.

In our case the tumor showed morphological features reminiscent of serous carcinoma of the endometrium. No germ cell, sarcomatous or hepatoid components were identified. On immunostaining the tumor cells expressed broad range cytokeratins, CK 7 and EMA confirming epithelial differentiation. The diffuse strong expression of p16 and p53
supported serous differentiation. Strong expression of ER and lack of expression of PgR is also the hormone receptor profile we usually encounter in serous carcinomas. The tumor cells expressed AFP confirming the tumor is the source of elevated serum AFP. The focal expression of PLAP seen in our tumor did not seem to be encountered in the two previously reported cases of AFP producing uterine serous papillary carcinoma, but have been previously reported in ovarian serous carcinomas.

AFP production by serous carcinoma is well recognised in primary ovarian serous carcinomas and in one case AFP production was seen to develop in a previously non-AFP secreting ovarian serous carcinoma following chemotherapy. These cases illustrate that AFP production is now an increasingly recognised feature, albeit a rare one of tumors showing serous differentiation.

In summary, we present a third case of primary AFP producing uterine serous carcinoma. We believe it is important to be aware of the presence of such entity and suggest that the possible existence of AFP-producing adenocarcinoma of the endometrium should be considered in a postmenopausal woman with gynecologically related symptoms and elevated serum AFP. Serological results should always be interpreted in context of the patient’s age, clinical presentation and tumor morphology, supported by the appropriate panel of immunostaining.

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REFERENCES