Alpha Fetoprotein Secreting Mucinous Epithelial Ovarian Carcinoma in a Young Woman- a Rare Case Report and Review of Literature

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Abstract
Germ cell tumors are known to secrete alpha fetoprotein. Epithelial ovarian cancers rarely secret alpha fetoprotein and mucinous variety is rarest among them that too in young woman. In addition to the case discussion, literature on this entity has been reviewed.

A 24 years, parous woman presented with 28 weeks sized abdominopelvic mass. CECT confirmed this as right adnexal malignant mass. Tumor markers for ovarian cancer were within normal limits except alpha fetoprotein which was marginally raised (21.4ng/dl). Under the diagnosis of malignant germ cell tumor, she underwent staging laparotomy, right salpingo-oophorectomy performed. Final histology returned as stage I mucinous adenocarcinoma without any germ cell component. Cells of invasive mucinous gland expressed reactivity for AFP on immunostaining. AFP fell to normal level following surgery.

Only three case reports concerning this topic have been described in the literature till date. All were advanced stage disease in the postmenopausal women. Given the late stage diagnosis, mortality was also high. Owing to its atypical presentation, immunostaining was required for differentiating it from other AFP secreting tumors of ovary.

Keywords: Alpha fetoprotein, immunohistochemistry, mucinous adenocarcinoma

Case Report
A 24 years old woman, G1P1, presented with complaints of pain lower abdomen, abdominal distension & dyspepsia for last 2 months and menstrual irregularity for last 1 month. She had no complaints of fever or vomiting and her bowel habits were normal. She did not have any significant past medical or surgical history. On abdominal examination a 28 weeks size, smooth, cystic, non-tender, mobile lump was palpable. Pelvic examination confirmed the finding as adnexal mass. Routine investigation were within normal
limits. USG pelvis showed 17.9x12.7 cm cystic mass with internal echoes & septation (cotton ball appearance) arising from right ovary. Tumor markers CA 125, CEA, CA19-9, LDH, and HCG were within normal limits. Alpha fetoprotein was marginally raised to 21.4 ng/ml (normal range <10ng/ml). A subsequent contrast enhanced computed tomography (CECT) was performed which showed a large well defined cystic attenuating lesion measuring 21x19x20 cm arising from right adnexa with enhancement of septa on post contrast study (Fig. 1 a, b). Based on clinical and radiological findings a provisional diagnosis of malignant ovarian tumor was made and patient was planned for staging laparotomy. Significant operative findings were–minimal peritoneal fluid, 20x19 cm solid cystic mass arising from right adnexa, right fallopian tube was stretched over it, 2700 ml of serous fluid was aspirated from the mass to ease its exteriorization, uterus, left tube and ovary was normal, undersurface of liver and diaphragm were free of tumor deposits. Right salpingoophorectomy along with biopsy from left ovary and multiple peritoneal site had been performed. Pelvic lymph node dissection was omitted as CECT was not suggestive of lymph node involvement. Fertility sparing surgery had been performed as she was desirous of future reproduction. Gross specimen (Fig. 2) submitted for histopathological examination. Histology showed that tumor was mainly comprised of large columnar cells of intestinal type with apical mucin (Fig. 3 a, b). Cells were focally reactive to AFP (Fig. 3g). To further differentiate the cell type reacting to AFP, immunohistochemical staining was used. Cells were diffusely positive for CK7 (Fig. 3c), and strongly positive for CK 20 (Fig. 3d) but negative for WT1 and PLAP (Fig. 3 e, f). Final impression was invasive mucinous carcinoma grade I with FIGO stage of pT1apNx. Patient is under regular follow up and disease free 8 month post treatment.

**Discussion**

Ovarian cancer is the most common cause of death among patients with gynecological malignancy. Yearly incidence of ovarian cancer in Asia is 5 to 7 cases per 100000 women. More than 90% of ovarian cancer are histologically epithelial ovarian cancer and only 3–5% are of mucinous type. AFP is commonly secreted by germ cell tumor and useful for detection and surveillance of the disease.

**Ovarian Mass with Raised AFP-Differential Diagnoses**

The presence of unilateral mass, in a young patient with raised alpha fetoprotein led to the suspicion of yolk sac tumor primarily as it is the second most common germ cell tumor after dysgerminoma, associated with production of AFP and occurring in second decade of life. But usually they present as the large solid mass which are highly malignant and rapidly spread to distant site, which were absent in the present case making the diagnosis unlikely. Sometimes Immature teratoma can also present with raised AFP but the absence of solid component containing calcification and foci of fat on imaging making this diagnosis improbable.

![Figure 1](image1.jpg)

**Figure 1.** (a) Contrast enhanced axial CT image shows cystic component with thick enhancing septa in the abdomen. (b) Contrast enhanced coronal CT image shows a large solid cystic abdominopelvic mass.

![Figure 2](image2.jpg)

**Figure 2.** Gross pic of specimen shows right ovary, fallopian tube and solid-cystic mass.
Non germ cell tumors have also been described to secrete AFP. These include sex cord stromal cell tumor (SCST), epithelial tumor, and metastatic tumors to the ovary.

SCST is an uncommon tumor occurring in young adults presenting as large solid mass with the features of virilization and occasionally associated with elevated AFP level. Clinical and radiological picture of the present case made this diagnosis also less likely.

Clinical and radiological findings excluded the metastatic tumor to the ovary.

Few epithelial ovarian carcinoma (EOC) have been reported to secrete AFP but most of them are reported in the postmenopausal women. The histological variety include clear cell carcinoma, hepatoid carcinoma, serous carcinoma, endometrioid carcinoma, undifferentiated carcinoma, mixed Mullerian tumors and mucinous adenocarcinoma. Among these only clear cell carcinoma has been reported in under 30 years of age. Clinically it is difficult to rule out these diagnosis. Histology and immunohistochemistry is vital in differentiating these tumors.

On literature review, only three cases of mucinous epithelial ovarian carcinoma (mEOC) with elevated AFP have been reported till date. Detailed information of these cases including the present one are briefed in Table 1. All the case reports described previously are in postmenopausal women, with tumor sizes varying from 8 to 14 cm and advanced stage disease. None of them were seen in young patient. So this is the first case of early stage, huge sized mucinous adenocarcinoma occurring in young patient with elevated AFP. AFP producing epithelial tumors can be of two types-with and without the yolk sac component. AFP secretion is ascribed to the foci of yolk cell clusters in few mucinous adenocarcinoma, but present case lacked any germ cell component and source of AFP had been the cuboidal cells. Ectopic tumor marker denote dedifferentiation by indicating autonomous activation of unrelated genes for the given tumor tissue type.

### Histopathology and Immunohistochemistry

Malignant mucinous carcinoma of ovary displays characteristics gross and microscopic features. Microscopically these tumors are comprised of glands and stroma, glands are almost always intestinal type with apical mucin. Based on the presence of stromal invasion, it has been divided into two category, intraepithelial (non-invasive) carcinomas and invasive carcinoma. Intra-epithelial carcinoma exhibit marked cellular atypia in the absence of stromal invasion. Invasive carcinoma is characterized by presence of stromal invasion of >5mm. Invasive carcinoma is further subdivided into two type i) expansile (confluent) type-characterized by the presence of confluent glandular growth uninterrupted by normal ovarian parenchyma, ii) infiltrative type which is identified by the presence of small glands or individual cells in the stromal infiltration. Infiltrative carcinoma has more aggressive course compared to expansile variety.

The use of selected immunohistochemical markers in conjunction with the microscopic characteristics of individual mucinous tumors is valuable in accurately differentiating atypical mucinous tumors. In the present case, cells were focally reactive to AFP. To further differentiate the cell type reacting to AFP, immunohistochemical staining was performed. Cells were diffusely positive for CK7 and strongly positive for CK20 but were negative for WT1 and PLAP. Almost 80–100% ovarian mucinous carcinoma stains positive for CK7 whereas CK20 positivity is seen in 40–83% of mucinous adenocarcinoma of ovary. CK20 is not expressed in endometrial adenocarcinomas. WT1 is of significance in differentiating primary serous adenocarcinoma with meta-
static endometrial adenocarcinoma and also in typing primary surface epithelial tumor. WT1 is strongly positive in case of serous adenocarcinoma but negative in mucinous carcinoma and metastatic endometrial carcinomas. PLAP is highly sensitive immunohistological marker for malignant germ cell tumor thus helps in differentiating epithelial tumor from germ cell tumor. In the current case diagnosis of mucinous adenocarcinoma without germ cell component was based on these findings.

Keel et al.[13] used primary monolayer culture system of procrine granulosa cell from small ovarian follicle to illustrate the miotogenic effect of AFP. In this study they found that AFP, in dose dependent manner, act synergistically with epidermal growth factor, insulin like growth factor 1 and platelet derived growth factor to induce proliferation of granulosa cells. This study has demonstrated that AFP can function to modulate growth factor mediated cell proliferation during the development of neoplasia.

Management

Optimum debulking surgery is the mainstay of treatment for the mucinous epithelial ovarian carcinoma (mEOC). Different histotypes have different biological behavior and different pattern of sensitivity to chemotherapy. This is particularly true for mEOC. Hess et al.[14] in 2004 reported that woman with advanced stage mucinous adenocarcinoma had worse prognosis compared to other histological type and response rate to platinum based chemotherapy was 26% in stage III/IV mEOC compared to 63% in matched control non mEOC group. Though it has been recognized that platinum based chemotherapy is less efficacious in mEOC than the other EOCs, we lack the proven alternatives. As stated in American Cancer National Comprehensive Cancer Network (NCCN) guidelines 2016, and also highlighted in,[15] adjuvant therapy is not required in mEOC stage I, as survival rate is excellent, while adjuvant therapy should be given for stage III–IV (3–6 cycles of carboplatin/paclitaxel or 5-flavourouracile/ oxaliplatin or capecitabine/ oxaliplatin). Due to rarity of AFP secreting mEOC, appropriate chemotherapy regimen is not described. As the patient was young and desirous of fertility, fertility sparing surgery was performed. Tumor marker is helpful in monitoring the disease. AFP fell to normal level following surgery. As she had stage Ia disease, adjuvant chemotherapy was not required and was kept on regular follow up.

Conclusion

This case report highlights the atypical features of mucinous ovarian tumors that is young age, alpha fetoprotein secretion and without any yolk sac component on histology. As the diagnosis would affect the management, it is important for both gynecologist and pathologist to be aware of such cases and its clinicohistological distinction from germ cell tumor. Thus this study along with highlighting the atypical presentation of mucinous adenocarcinoma emphasizes the need for early diagnosis and intervention.
in young women presenting with adnexal masses with clinico-radiological suspicious of malignancy.

Disclosures
Ethics Committee Approval: No ethical approval required and the study was performed in accordance with the principles of the declaration of Helsinki.
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