

Case Report

Ovarian endometrioid adenocarcinoma with yolk sac tumor in a 41-year-old woman: a case report

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Abstract: Background: Yolk sac tumors (YSTs) are the second most common germ cell malignancy of the ovaries generally present in children and young women. YSTs arising in combination with epithelial ovarian carcinoma (EOC) in older women are rarely reported. The YST components in such cases often show a marked morphological and immunophenotypic overlap with epithelial neoplasms, making diagnosis difficult. Case report: A 41-year-old woman presented with irregular vaginal bleeding and a bilateral adnexal mass. The postoperative pathology confirmed a poorly differentiated adenocarcinoma and YST of the left ovary. The short tandem repeat (STR) analysis further indicated that the YST component was probably derived from an epithelial precursor neoplasm. Conclusion: This case improves our ability to detect and diagnose YST coexisting with epithelial tumors in older patients by summarizing its histopathologic characteristics and immunohistochemical stains. Molecular analysis should be used to further identify such mixed neoplasms.

Keywords: Ovarian germ cell, epithelial ovarian carcinoma, yolk sac tumor, short tandem repeat, perimenopausal, pathology

Introduction

Yolk sac tumors (YSTs) are the second most common germ cell malignancy of the ovaries generally present in children and young women. While epithelial ovarian carcinoma (EOC) is predominantly a disease of older, postmenopausal women compared with other types of ovarian cancer [1], a few studies have found that YSTs can arise in combination with EOC and result in an elevated serum AFP in older women [2].

Here, we describe an unusual ovarian neoplasm with components of poorly differentiated adenocarcinoma and YST in a 41-year-old perimenopausal woman. In addition to highlighting the microscopic features and immunohistochemical patterns of this highly unique tumor, we will briefly discuss the molecular characteristics of the two components in this case, as well as the differential diagnosis.

Case presentation

A 41-year-old woman with a history of irregular vaginal bleeding was admitted to our hospital. An ultrasound scan demonstrated a complex left adnexal mass with cystic and solid components (6.8 × 5.1 × 6.2 cm) and a cystic mass (4.6 × 4.2 × 4.5 cm) in the right appendage. The preoperative CA125 level was elevated (85.4 U/ml; normal range: 0-34 U/ml), and the serum α -Fetoprotein (AFP) level was up to 5202.5 ng/ml. The patient subsequently underwent an exploratory laparotomy. At the time of surgery, a huge bosselated mass with a partial cystic structure was noted in the left ovary, and the right adnexal had a dense adhesion with the rectum and posterior wall of the uterus. A frozen section of the left appendage suggested a poorly differentiated adenocarcinoma of the ovary. Then a radical hysterectomy, a bilateral salpingo-oophorectomy, and an omentectomy were performed.

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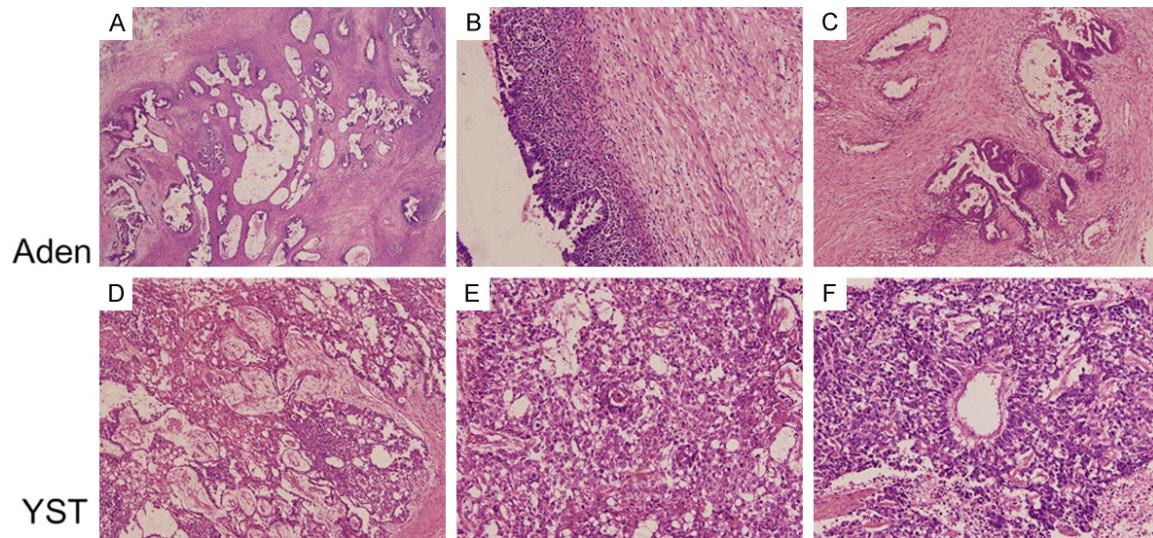


Figure 1. Microphotograph presenting H & E stained specimens of ovarian endometrioid adenocarcinoma with a component of YST. A. Irregular adenoid architectures of varying size displayed in the epithelial component. B. Adenoepithelial cells resembling an endometriosis cyst, and these cells show atypical hyperplasia. C. Crowded, hyperchromatic cells with an infiltrative growth pattern in the glandular wall. D. The YST component was characterized by primitive tumor cells with microcystic and reticular patterns surrounded by a loose and myxoid background. E. YST component showing primitive nuclei, cytoplasmic vacuolation and typical Schiller-Duval bodies. F. Pleomorphic tumor cells with hyperchromatic nuclei, little cytoplasm, and conspicuous mitotic activity were also observed.

On gross inspection, the left oophorectomy specimen consisted of a 7 cm predominantly solid mass with an irregular-surface associated with the residual left ovary and fallopian tube. The cut surface appeared to be two different structures with solid and cystic areas, while the solid part showed an extensive rotten fish-like texture with necrosis and hemorrhage, and the cystic part was multilocular, and many papilla could be seen in the inner wall. The right adnexal cystic mass contained chocolate-like, clear inflammatory liquids, but no papillary protrusions were detected in the inner lining. The uterine and endocervical cavities appeared grossly unremarkable.

Microscopically, the neoplastic areas of the left ovary exhibited two different patterns. Pattern A showed epithelioid differentiation and displayed visibly irregular adenoid structures of varying size, with dirty necrosis in the glandular cavity (**Figure 1A**). Some of the glandular epitheliums resembled an endometriosis cyst, with the cells showing atypical hyperplasia (**Figure 1B**). The glandular lining was composed of crowded, markedly atypical cells with frequent mitosis, and an infiltrative growth pattern was noted in the stroma, suggestive of poorly differentiated adenocarcinoma (**Figure 1C**). Pat-

tern B predominantly showed microcystic and reticular structures made up of primitive cells surrounded by a loose and myxoid background (**Figure 1D**). A high-power view of this pattern showed primitive nuclei, cytoplasmic vacuolation, and a structure similar to Schiller-Duval bodies (**Figure 1E**). In some areas, pleomorphic tumor cells with hyperchromatic nuclei, little cytoplasm, and conspicuous mitotic activity were also observed (**Figure 1F**).

Further immunohistochemical (IHC) stains were performed, including EMA, CK7, CA125, PAX8, Sall-4, AFP, Gly-3, ER, PR, Napsin-A, WT-1, CD30, P53, Ki67, and vimentin. The neoplastic components of the left ovary showed a distinct dividing line of the biphasic tumor markers. Epithelial tumor markers like EMA, CK7, CA125 and PAX8 were strongly positive in pattern A but completely negative for the pattern B (**Figure 2**). In contrast, a diffuse positivity of Sall4, AFP and Gly-3 presented in pattern B, but pattern A of the tumor tended to have opposite patterns of immunoreactivity (**Figure 3**). The IHC stains markedly differed between the two patterns, suggesting that this tumor was an endometrioid adenocarcinoma (pattern A) with a YST component (pattern B), instead of an endometrioid variant of YST. Additionally, the

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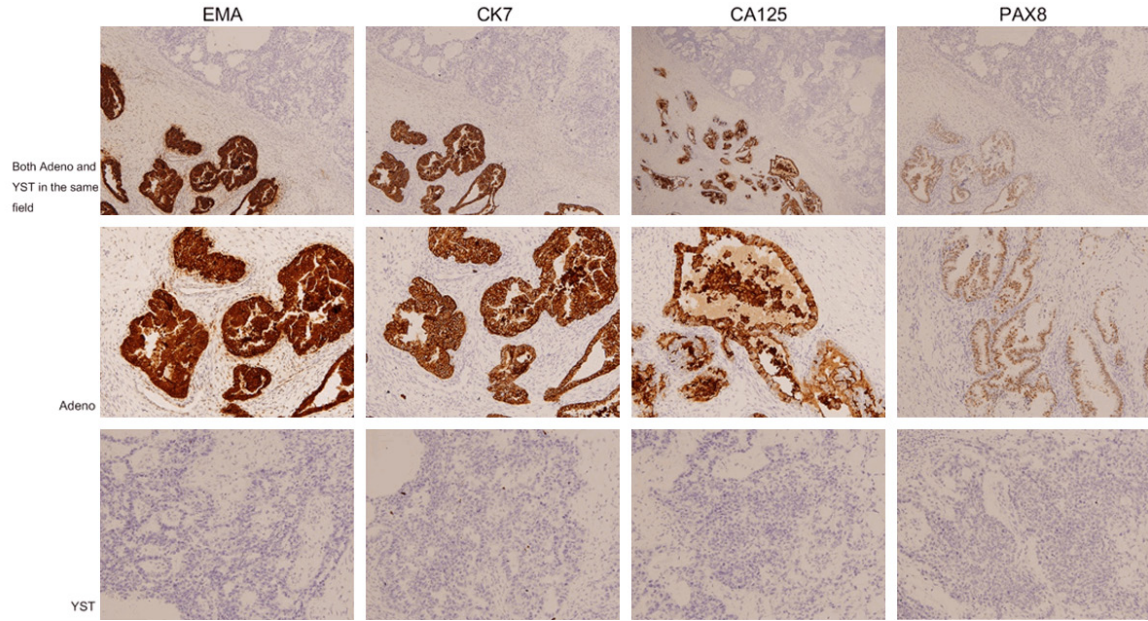


Figure 2. The epithelial tumor markers EMA, CK7, CA125, and PAX8 were positive in the adenocarcinoma components but completely negative in YST.

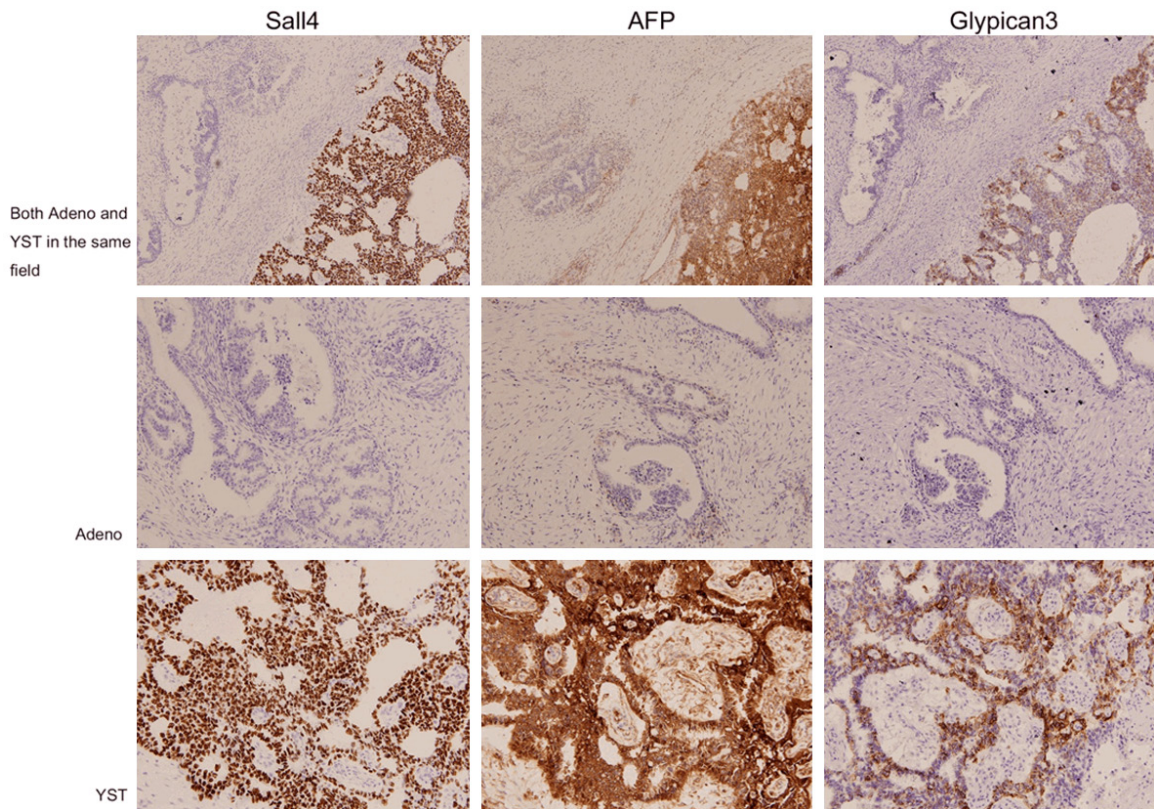


Figure 3. Immunohistochemically strong nuclear reactivity for SALL4, AFP and cytoplasmic reactivity for Glypican-3 in the YST components but negative in adenocarcinoma.

positive rate of Ki67 staining was about 80% in both patterns, but the remainder of the immu-

nohistochemical stains listed above were negative in both tumor components.

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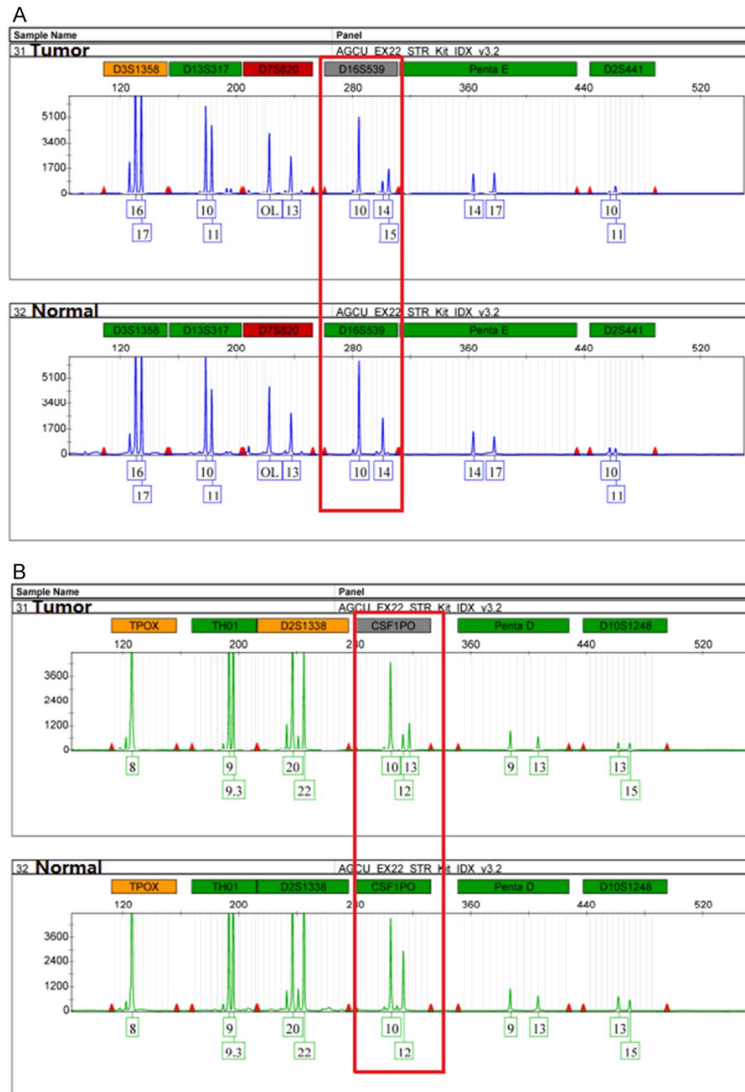


Figure 4. Short tandem repeat (STR)-based concordance study of the 22 microsatellite markers tested, two different alleles (A, D16S539 and B, CSF1PO) were found between the tumor and the patient's normal ovarian tissue.

Since there are few reports about YST in elderly patients, we wanted to carry out some further molecular investigation to confirm our suspicion. The preserved tumor specimen and a normal tissue underwent a genetic comparison to determine the tumor's origin. DNA was extracted from the tumor specimen and some normal tissue using an AllPrep® DNA/RNA kit (Qiagen, Valencia, CA, USA) following the manufacturer's instructions. An AGCU EX22 PCR amplification system (AGCU ScienTech Inc., Wuxi City, China) comprising 21 autosomal STRs and one gender determination gene of the two samples was used in this study. Electrophoresis

was performed using an ABI 3130XL Genetic Analyzer (Applied Biosystems). The fragment sizes were automatically determined using Genemapper ID software (Version 3.2.1; Applied Biosystems). The STR results showed that, of the 22 microsatellite markers tested, differences were found between the tumor cells and the patient's normal tissue (**Figure 4A** and **4B**). We presumed that the mixed-type tumor was a microsatellite instability and the YST component was probably derived from the epithelial precursor neoplasm.

Based on the morphologic, IHC features and STR results, an extremely unusual combination of poorly differentiated adenocarcinoma with malignant YST arising in the left ovary was diagnosed.

The patient recently finished 6 cycles of intraperitoneal BEP (bleomycin + etoposide + cisplatin) chemotherapy and developed neutropenia and other tolerable side effects. Her serum AFP level is normal, and she is currently alive with no evidence of disease.

Discussion

YSTs, also known as endodermal sinus tumors, are the second most prevalent malignant ovarian germ cell tumor (MOGCTs) histologic subtype after dysgerminoma. They occur most commonly before age 30 and usually in pure form, sometimes in association with other types of germ cell neoplasms like teratoma, choriocarcinoma, embryonal carcinoma, or polyembryoma [3]. YSTs coexisting with a variety of histologic patterns have been described, but those with an epithelial malignant component are extremely rare, especially in older women. Among all the ovarian epithelial neoplasms associated with YST, it seems that endometrioid carcinoma is the most common epithelial component, occurring

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in 12 cases (67%), and 6 of these were associated with an endometriotic cyst reported in a previous case report [4]. Here, we describe a rare case of ovarian endometrioid adenocarcinoma with a YST component occurring in a 41-year-old woman. Most of the cases of this type have occurred in postmenopausal or perimenopausal women, but the age distribution contrasts with the much younger age of patients with typical YST [5]. The bimodal age distribution of patients with ovarian YST suggests differing histogenetic mechanisms of tumorigenesis in the 2 age groups. As germ cells are not identified histologically in the ovaries of postmenopausal women, a direct origin of malignant neoplasms from germ cells is highly unlikely at that age. We highly suspected that this rare mixed tumor represents an adenocarcinoma with aberrant differentiation because it occurs in the same age range as EOC and shows an aggressive behavior, but the molecular events involved in this transformation have not yet been elucidated.

It is likely that the YST component can show transitional forms and a wide variety of patterns that frequently occur in combination. Some of these patterns are rare and can be confused with other types of tumors. Pathologically, the endometrioid-like variant of YST simulated primary endometrioid adenocarcinoma sometimes makes diagnosis difficult. The endometrioid-like pattern reflects an unusual form of endodermal differentiation within yolk sac tumors that should be distinguished from endometrioid carcinoma, the recognition of which should be facilitated by a panel of immunohistochemical stains that are often expressed differentially in these two neoplasms—endometrioid-like yolk sac tumors are frequently reactive for AFP, SALL4, and Gly-3, but CK7 and EMA are usually negative. Endometrioid adenocarcinomas of the ovaries tend to have opposite patterns of immunoreactivity [6, 7].

The identification of the specific morphologic features of mixed ovarian tumors is vitally important since it is very easy for the pathologist to misdiagnose these groups of tumors as having two different origins [8]. In recent years, STR (also called microsatellite) analysis has been used extensively as a diagnostic tool to compare specific loci on DNA from two or more samples for the detection and classification of

tumors [9]. Loci that show alterations in fragment length between normal and tumor tissue are considered to be unstable, but loci that exhibit no length variations between normal and tumor tissue are considered stable. Microsatellite instability in tumor DNA is defined as the presence of alternate sized repetitive DNA sequences that are not present in the corresponding germline DNA [10]. Therefore, STR analysis was used to determine the tumor origin in this case. The results showed that, compared with the normal tissue, there were mutations of 2 alleles in the mixed tumor genotypes, which means the tumor existed with unstable microsatellites. In other reported studies of endometrioid adenocarcinoma with a component of ovarian YST, the authors thought that somatic carcinomas have the ability to acquire a germ cell differentiation, and the germ cell component is thought to derive from somatic mesodermal cells and not from germ cells [11-13]. Although the exact explanation for this biologic behavior is not known, our case along with other reported reports have raised the possibility that the YST does not always have a germ cell origin and can be derived from epithelial tumors, perhaps through one of the four theories including the teratoma theory, retrodifferentiation, collision theory, and neometaplasia [14]. Additionally, the term “somatically derived YSTs” should be used to categorize these neoplasms. Further molecular analysis may also provide information about better therapeutic approaches for the treatment of these types of rare tumors in the future.

With a combined epithelial malignancy and YST, there is a dilemma for the oncologist as to which chemotherapeutic regimen to administer. Ovarian YSTs in postmenopausal women are aggressive and may have a worse prognosis compared with those in young patients. It was previously postulated that such a combination may be less sensitive to chemotherapy than that used for ovarian germ cell tumors, and adjuvant therapy should include aggressive platinum-based chemotherapy designed to treat both epithelial ovarian cancer and germ cell tumors [15]. Currently, the most evidence on the management and outcomes of ovarian YST in older women derives from single case or case series with limited statistical power. After collegial discussion, considering the predominance of the YST component, we decided on

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postoperative treatment consisting of 6 courses of the BEP regimen, and the patient is currently alive with no evidence of disease for 8 months. We hope that other authors describe their experiences to define the most appropriate approach to this rare tumor.

Disclosure of conflict of interest

None.

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