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Case Report

High-grade serous carcinoma of fallopian tube with yolk sac tumor differentiation in a postmenopausal patient

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Abstract: Yolk sac tumors (YSTs) are the second most common germ cell malignancy of the ovaries, generally presenting in children and young women. However, they rarely occur in the fallopian tubes of postmenopausal patients. The current rare case is composed of yolk sac tumor differentiation within high-grade serous carcinoma (HGSC) arising in the fallopian tube of a 68-year-old woman. Serum α-fetoprotein was much higher than normal level. This case exhibited some areas of glandular architecture with positivity for SALL4, AFP, and Glypican-3 and negative staining for PAX8, supporting a germ cell tumor differentiation. By reviewing the published literature, we believe that YSTs, whether or not associated with an epithelial component detected histologically in older patients, constitute a single entity that is different from YSTs in younger patients. Above all, the pathologist must check carefully tissue stained with hematoxylin-eosin especially in postmenopausal women with ovarian, fallopian tube, or endometrial mass and an elevated serum α-fetoprotein level. Neoplasms of this type should be treated aggressively, and should respond to platinum-based chemothotherapy.

Keywords: High-grade serous carcinoma of fallopian tube, postmenopausal, yolk sac tumor, alpha-fetoprotein, SALL4, hepatoid carcinoma

Introduction

Yolk sac tumors (YSTs) are the second most common germ cell malignancy of the ovaries. They present in children and young women. Primary yolk sac tumor of the fallopian tube associated with high-grade serous carcinoma (HGSC) is extremely rare, especially in postmenopausal patients [1, 2]. As germ cells are not identified histologically in the ovaries of postmenopausal women, malignant neoplasms that originate directly from germ cells are highly unlikely to occur at that age and organ. However, in this study, we report a complex case of primary HGSC in the fallopian tube with YST differentiation, posing the conceptual problem of an unusual transition from Müllerian epithelium to germ cells.

Clinical summary

A 68-year-old postmenopausal patient, G1P1, underwent vaginal ultrasound-guided biopsy that revealed a hypoechoic solid tumor about 7.2*2.4*2.1 cm in the upper-left part of the uterus during her annual routine physical examination. MRI enhanced images of the pelvic cavity showed the left adnexal mass was obviously enhanced, sausage-shaped, and extended the same direction as the fallopian tube (**Figure 1A**). Color Doppler ultrasound showed transverse cord-shape (**Figure 1B**), and no obvious connection with uterus was observed. Bilateral ovaries were small and the uterus was unremarkable. Prior pertinent history revealed that the patient had been diagnosed by abdominal ultrasound with hepatic cyst, and there was no tumor history either benign or malignant.

Laboratory analysis revealed an α-fetoprotein (AFP) at 2493 ng/ml (normal: 0-7.02 ng/ml), CA-125 at 26.12 u/ml (normal: 0-35.0 u/ml), and HCG-beta at 3.07 mIU/ml (normal: 0.0-5.3 mIU/ml). Exploratory laparotomy, hysterectomy, and bilateral salpingooophorectomy with staging biopsies were performed. The AFP decreased from higher than 2000 ng/ml to 17.26 ng/ml two weeks after tumor debulking. App-

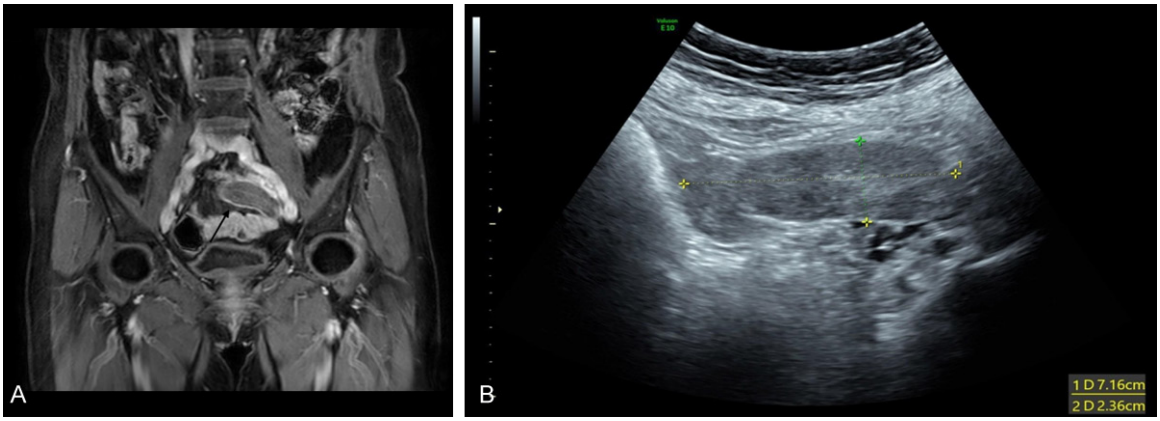

Figure 1. Medical imaging findings. A. MRI enhanced images of the pelvic cavity: the left adnexal mass was obviously enhanced, showed a sausage-shape (arrow), and had the same direction with the fallopian tube. B. Color Doppler ultrasound showed transverse cord-shaped image (star) about 7.16*2.36 cm.

roximately 1 month after the surgery, the AFP had decreased further to 3.68 ng/ml. No tumor cells were found in the abdominal cavity washing fluid. She was staged as PT1CN0M0. Chemotherapy with paclitaxel and carboplatin was used for 7 treatment courses after surgery. The patient has had no recurrence and metastasis now for about a year.

The surgical removal specimens were fixed in 10% formalin, then processed for histologic examination in the conventional methods. Sections (3-mm thick) were embedded in paraffin and stained with hematoxylin-eosin for microscopy. An immunohistochemical study was performed using formalin-fixed paraffin-embedded sections at a referring laboratory using a series of antibodies. We used the streptavidin-biotin peroxidase complex technique in immunohistochemical studies, and relevant antibodies directed against the following: cytokeratin 7 (monoclonal UMAB161 diluted), epithelial membrane antigen (EMA) (monoclonal GP1.4 diluted), α-fetoprotein (monoclonal EP209, diluted), SALL4 (monoclonal 6 E3 diluted), Glypican (monoclonal 1G12 diluted), PLAP (monoclonal EP194 diluted), OCT-4 (monoclonal NINK diluted), α-inhibin (monoclonal AMY82 diluted), WT1 (monoclonal EP122 diluted), MSH2 (monoclonal RED2 diluted), MSH6 (monoclonal EP49 diluted), MLH1 (monoclonal ES05 diluted), PMS2 (monoclonal EP51 diluted), estrogen receptor (ER) (monoclonal EP1 diluted), progesterone receptor (PR) (monoclonal EP209 diluted), HNF1β (polyclonal antibody), GATA3 (monoclonal EP368 diluted), cytokeratin 5/6 (CK5/6) (monoclonal 0T11C7 diluted), PAX-8 (monoclonal 0T16H8 diluted), P16 (monoclonal 1C1 diluted), P53 (monoclonal D0-7 diluted), Vimentin (monoclonal UMAB159 diluted), NapsinA (monoclonal IP64 diluted), and Ber-EP4 (monoclonal Ber-EP4 diluted). All antibodies were from Zhongshan Jinqiao Biotechnology Co. Ltd.

Pathology findings

Gross inspection revealed the left fallopian tube composed of friable white masses, serous surface was smooth, and malignancy involved the distal tube. Bilateral ovaries, the right fallopian tubes, uterine and endocervical cavities were unremarkable. The tumor cells were not seen under microscope in the surgical resection of peritoneum, omentum majus, appendix, bilateral pelvic lymph nodes.

Histopathologic examination revealed a transition from normal fallopian tube epithelium to high-grade serous carcinoma (**Figure 2A**), in solid, glandular, and papillary patterns. YST differentiation was observed obviously by Schill-Duval bodies in the background in a festoon pattern (**Figure 2B-E**). Glandular patters of YST differentiation are well described where there is close mimicry to a secretory endometrioid carcinoma in a form of cytologic vacuolar morphology. Under the microscope, round and tall columnar cells were arranged and these cells showed a high histologic grade, nuclear atypia, particularly high mitotic count, hyperchromatic large nuclei, and columnar cytoplasm (**Figure 2E**, **2F**). Abundant eosinophilic bodies were not seen, and hepatocyte-like fabric was not found.

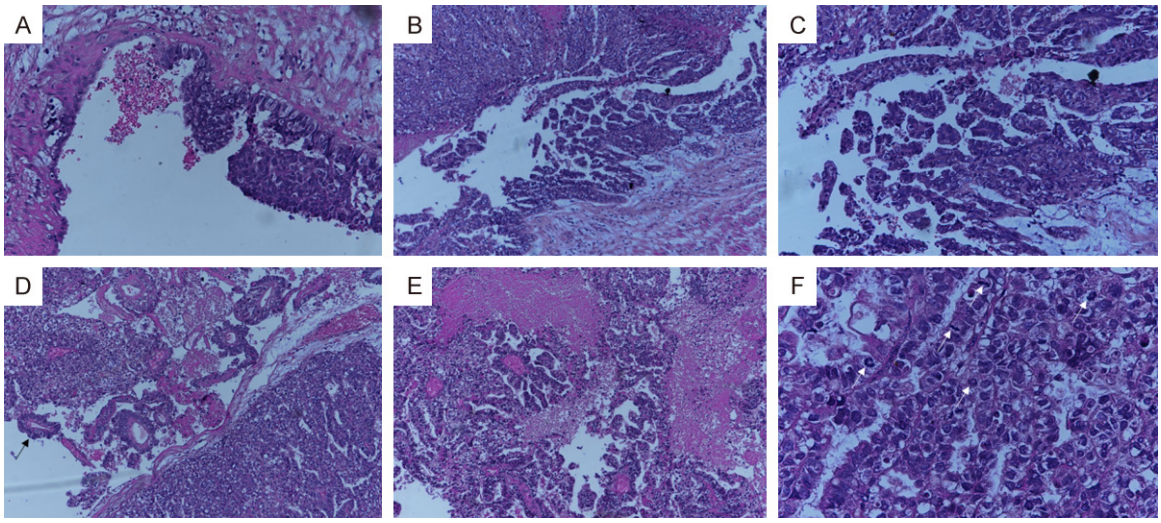

Figure 2. Histological structure and cytological features of the tumor. (A) A transition from fallopian tube epithelium (left) to high-grade serous carcinoma (right). (B) Solid and papillary growth patterns. (C) Higher magnification of (B). (D) The pathologic characteristics of YST of Schiller-Duval body was seen (arrow). (E) The area resembling clear cells and tall columnar cells with glandular arrangment. (F) High-power view of primitive nuclei, cytoplasmic vacuolation, and high mitotic count (arrow).

The entire tube wall was occupied by tumor cells, and the YST differentiation showed highly invasive.

Immunohistochemical findings

Immunohistochemistry revealed that the tumor cells were positive for CK (+), Ber-EP4 (+), CK7 (40%+), EMA (30%+), SALL4 (+), GLY-3 (50%+), AFP (30%+) P53 (80%+), P16 (focal+), HNF-1β (+), and PR (20%+). The Ki-67 antigen-labelling index was 80%. GATA3, PAX8, ER, VIM, NapsinA, PLAP, OCT4, α-inhibin and CK5/6 protein were negative. Lynch syndrome testing utilizing immunostains for mismatch repair proteins MSH6, MSH2, PMS2, MLH1 in the tumor showed normal expression.

Discussion

Yolk sac tumors arise in young premenopausal women, mainly in the ovary, and can occur in many extragonadal sites, most commonly in the sacrococcygeal region, vagina, brain, mediastinum, and retroperitoneum [3]. Our case was a postmenopausal woman with a rare a fallopian tube serous carcinoma with differentiation of yolk sac tumor. This tumor could be misdiagnosed as a pure HGSC especially when the diagnosis is based solely on morphologic assessment of a small amount of histologic sections.

In most cases, classification of tumor is based on morphology. Of note, there were some areas where the tubal epithelial cells showed a transition from normal to atypical, and other areas showing a transition between atypical and adenocarcinoma. Each carcinoma type shows a characteristic histologic structure, cytologic morphology and gene expression profile, all constituting the corresponding tumor image. For this case, serous carcinoma cells partially look like the fallopian tubal epithelial cells. In other words, the evidence for cellular differentiation warranted the validity of morphology-based tumor classification.

Sometimes, the two differentiations (serous carcinoma and yolk sac tumor) cannot be distinguished based on morphology alone. Immunohistochemistry can distinguish tumor components with similar morphology but divergent differentiation.

It is widely held that both CK and Ber-Ep4 in the distinction between YST and HGSC can be positive, and in our case, they were diffusely positive. Markers such as EMA and CK7 are useful, generally negative, or only focally positive in YST, and generally diffusely positive in HGSC. In our case, minimal cytokeratin 7 and EMA (**Figure 3B**, **3C**) expression instead of diffuse expression was a supportive factor. A diagnosis of YST differentiation was made based on the

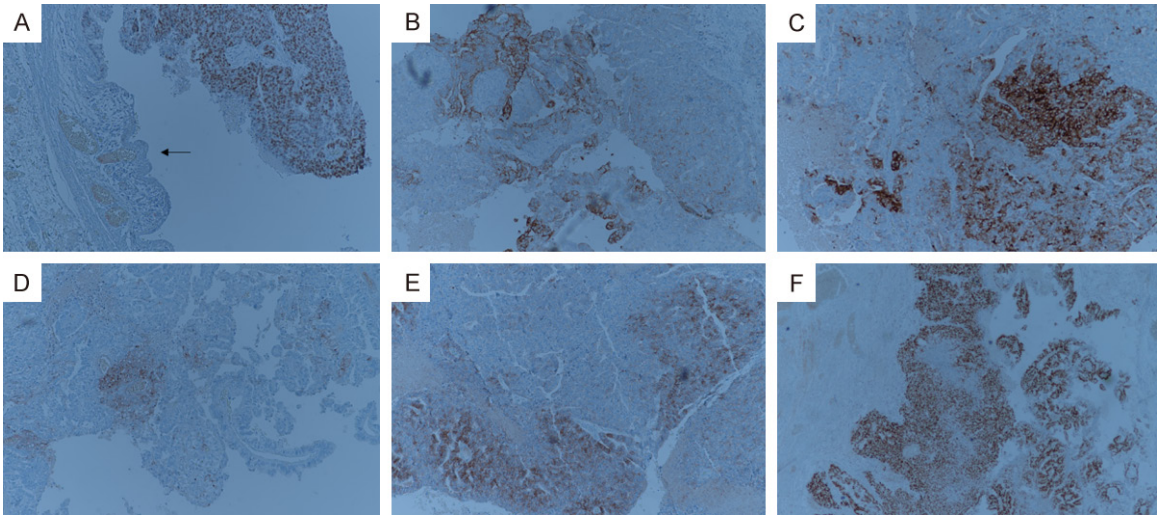

Figure 3. Immunohistochemical expression of high-grade serous carcinoma and differentiation of yolk sac tumor. Immunohistochemistry for SALL4 (A) shows diffuse positivity rate. In contrast, the fallopian tube epithelium is negative (arrow). CK7 (B) and EMA (C) is focally positive. α-fetoprotein (D) and Gly-3 (E) are also focally positive in the YST differentiation. P53 (F) is diffuse positive indicating tumor arose from high-grade serous carcinoma.

morphology together with the presence of positive staining, often diffuse and in combination, with a variety of markers such as SALL4 (**Figure 3A**). Glypican 3 (**Figure 3D**), and AFP (**Figure 3E**) are often focal positive in published cases of YSTs [5, 6].

SALL4 is positive in most malignant germ cell tumors. Sex cord stromal tumors such as granulosa cell tumor, adult or juvenile types were also included in the differential diagnosis, but EMA positivity and lack of α-inhibin expression were not supportive of these diagnoses [4]. It has also been reported positive in AFP-producing fetal-type gastric carcinoma; however, positivity is more frequent in the hepatoid pattern (strip shape) than the tubule and papillary patterns that can resemble YST. Just a few articles in English journal indicate that hepatoid carcinoma is an extremely rare variant of primary ovarian carcinoma. This has hepatoid pattern and cytologic characteristics such as: abundant eosinophilic cytoplasm, central nuclei, prominent nucleoli, and large cytoplasmic hyaline eosinophilic globules. Hepatoid carcinoma is essentially distinguished by morphology and clinical history from a primary hepatocellular carcinoma or a hepatoid variant of YST, and immunohistochemistry is of little or no value in diagnosis [7-10].

AFP and glypican 3 are more specific for YSTs. Although not diffusely positive, AFP is often only focally positive in YST while glypican 3 is usually more diffusely positive, but it is a less specific marker in fallopian tube epithelial carcinomas. In our case, positivity for SALL4, AFP, glypican-3 and negative for PAX8 established the diagnosis of YST differentiation [11]. In a recent study, GATA3 was only positive in the 'usual' type of primitive extra-embryonal YST patterns (reticular-microcystic) while glandular, hepatoid and solid areas were negative [12].

YSTs arise from germ cells and cannot occur in the fallopian tube, especially in our case, where the patient was 68-years-old at that time of diagnosis, as germ cells do not exist in the tube of postmenopausal women, and malignant neoplasms that originate directly from germ cells are highly unlikelyat that age. McNamee [13] believes that in older women the germ cell component arises through a process of transformation of the epithelial precursor neoplasm that was originally referred to as neo-metaplasia. Abe [14] proposed four theories, including the teratoma theory, retro-differentiation, collision theory, and neo-metaplasia theory. This lack of germ cells would make the possibility of a collision tumor impossible, which is in part derived from germ cells and in part from epithelium. It is reported that YSTs in older patients are often associated with endometrioid carcinoma, serous carcinoma, mucinous cystic lesions, clear cell carcinoma, and other malignant components [15]. Endometrioid carcino-

ma is the most common epithelial component [16-19]. Over 20 articles are published in international English journals about this phenomenon, and some authors indicate divergent differentiation from a Müllerian epithelial component or from a precursor endometriosis lesion. A carcinoma then develops from it with a divergent differentiation into YST [20]. It has been suggested that serous carcinoma cells 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. This phenomenon could be explained by neometaplasia (aberrant differentiation), which appears to be the most reasonable theory to explain the histogenesis of this tumor.

As both epithelial ovarian cancer and germ cell tumor components are identifiable or were postulated to be a part of the tumor at one time, the neoplasm is less responsive to the chemotherapy currently used for ovarian germ cell tumors, regardless of the clinical stage. Therefore, adjuvant therapy should include platinum-based chemotherapy designed to treat both epithelial ovarian neoplasms and germ cell tumors. It was previously postulated that, since the YST component arises by transformation of an epithelial ovarian neoplasm, it may be less sensitive to chemotherapy [21].

In summary, we report a rare case of YST differentiation within the fallopian tube high-grade serous carcinoma in a patient 68-year-old. YSTs developed from the Müllerian epithelial neoplasm, and the pathologist must distinguish the two components under a microscope. This will be difficult, and detailed work is necessary to avoid the misdiagnosis. It is important to observe that extensive histologic and various related immunohistochemical analyses should be performed when pathologists encounter high-grade carcinoma, especially in older women. Postmenopausal women with a genital system mass and an elevated serum AFP level, should be suspected to have a neoplasm of this type. In particular, if the YST component or YST differentiation is overlooked, the case will be diagnosed as a pure epithelial cancer. This will seriously affect clinical prognosis and subsequent chemotherapy regimens. Future studies should investigate the molecular events involved in the transformation from an epithelial neoplasm to YST, as these are currently unknown.

The transformation mechanism from an epithelial neoplasm to YST needs our further investigation.

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Disclosure of conflict of interest

None.

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