Pure primary yolk sac tumor of the endometrium tends to occur at a younger age: A case report and literature analysis

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Abstract
We present a case of primary yolk sac tumor of the endometrium. This rare tumor occurred in a 43-year-old woman with a pure primary yolk sac tumor. The tumor resembled yolk sac tumor morphology of the ovary. Tumor cells expressed SALL4, AFP, GPC-3, and AE1/AE3 and were focal positive for PAX8. EMA, ER, and PR, among others, were negative. We further analyzed 29 reported cases of this rare tumor in the literature. In total, 17 of 30 patients (57%) had pure endometrial yolk sac tumor, and 13 (43%) had a concomitant somatic neoplasm (endometrial adenocarcinoma was the most common). Although the average age was 52 years (range: 24–87 years), patients with pure yolk sac tumor were younger than those with concomitant somatic tumors, with a mean age of 44.41 years (24–68 years) versus 61.92 years (28–87 years), P = 0.008. Patients with endometrial yolk sac tumor combined with somatic tumor tend to have a slightly higher stage and a poor prognosis.

Keywords
Yolk sac tumor (YST), endometrial, SALL4, differential diagnosis, prognosis

Case report
A 43-year-old woman was admitted with abnormal vaginal bleeding for 2 months and epigastric pain for 4 months. In the local hospital, she received a transvaginal ultrasound, which showed a hyperechoic endometrial mass. A 4-cm prominent mass was observed on the left side of the uterine isthmus by hysteroscopy. A pelvic computerized tomography (CT) scan revealed a uterine mass with no significantly enlarged lymph nodes. Pelvic-enhanced magnetic resonance imaging (MRI) showed a mild enhancement of the lesion, and the lesion seemingly not invaded muscular layer (Figure 1). An increasing level of alpha fetoprotein (AFP; 1465 µg/mL, reference level <20 ng/mL) was observed. The serum levels of β-HCG, CA125, CA199, and CEA were normal. The diagnostic fractional curettage specimen was diagnosed as endometrial carcinoma in a local hospital. For treatment, the dilatation and curettage specimen was subjected to a...
consultation diagnosis in our department, and the diagnosis was modified to primary YST of the endometrium.

The patient underwent total abdominal hysterectomy with bilateral salpingectomy, bilateral ovary biopsies, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, omentectomy, and appendectomy. The intraoperative exploration revealed that the uterus was enlarged equivalent to 50 gestational days. No abnormalities were observed on the surface of the uterus, bilateral ovaries, or oviducts, and no enlargement or hardening of the pelvic and abdominal para-aortic lymph nodes was observed.

Adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP) was performed for six cycles. The tumor response was monitored by serial determination of the serum level of AFP, which was decreased to normal before the first cycle of chemotherapy. The patient was alive without evidence of disease for 15 months.

The uterus measured $12.5 \times 9.5 \times 5.5$ cm$^3$. An area of hemorrhage and necrosis was observed at the lower uterine segment. The residual tumor infiltrated the superficial myometrium, less than half of the myometrium. The tumor did not involve the cervix, fallopian tubes, bilateral ovaries, or omentum. No metastatic tumor was observed in 12 pelvic lymph nodes or in 3 para-aortic lymph nodes. The case was classified as stage IA according to the FIGO (International Federation of Gynecology and Obstetrics) staging system.

Microscopically, pure endometrial YST without any other type of germ cell tumor or somatic carcinoma components was found (Figure 2). A reticular pattern coexisted with papillary growth. The reticulum comprised a labyrinth of channels lined by primitive cells expanding to form microcysts with flattened, clear atypical epithelial cells. Papillary growth showed papillary fibrovascular structures in which a central blood vessel with tumor cells projects into the surrounding space (endodermal sinuses, Schiller–Duval bodies (S-D bodies)). Hyaline globules were observed in the cells. The stroma was hypocellular and myxoid.

Immunohistochemically, the tumor cells were diffuse positive for AFP, SALL4, GPC-3, and AE1/AE3. They were focal positive for PAX8. ER, PR, CD30, OCT4, HNF-1β, Napsin A, and CD117 were all negative (Figure 3).

**Results**

We summarized the clinicopathological features, therapies, and prognosis of 30 primary endometrial YSTs (the present case and 29 cases from the literature, Table 1). The average patient age was 52 years (range: 24–87 years). The mean tumor size was 6.94 cm (range: 1.3–19.0 cm). The main clinical symptom was abnormal vaginal bleeding. Increasing serum levels of AFP were reported in 18 of 19 patients with recorded materials and in only 1 patient with a normal AFP level.

Among 16 of 25 patients with detailed surgical resection ranges, 3/16 underwent bilateral adnexal resection. The FIGO stages were as follows: I (n=11), II (n=5), III (n=6), and IV (n=7). In total, 26/30 (87%) patients underwent chemotherapy after the operation. BEP was the most common chemotherapy regimen in 11/26 patients (42%). Only 6 patients (6/30, 20%) endured radiotherapy.

Of all 30 patients, 17 (57%) had pure endometrial YST, and 13 (43%) had a concomitant somatic neoplasm representing <10% to 90% of the tumor. The somatic neoplasms followed the histological types endometrial adenocarcinoma (n=4), carcinosarcoma (n=2), clear cell carcinoma (n=1), adenocarcinoma (n=1), serous carcinoma (n=1), serous carcinoma and endometrial adenocarcinoma (n=1), serous carcinoma and clear cell carcinoma (1), and endometrial complex hyperplasia (n=1). Patients with pure YST were younger than those with a concomitant somatic tumor (range: 24–68 years (mean: 44.5 years) vs 28–87 years (mean: 61.92 years), P=0.008).

Of the 30 cases, follow-up information was obtained for 90% (27/30) of the patients. The mean follow-up time was 17.25 months (range: 2–72 months); 48.1% (13/27) of patients had no evidence of disease during the follow-up time, 8 patients (8/27, 29.6%) died of disease (range: 2.5–24 months), and 6 patients (6/27, 22.2%) were alive with disease (range: 7–30 months). The rate of early-stage pure endometrial YST was 70.6% (12/17); it was 38.5% (5/13) for those combined with somatic tumors. There was no statistical differences (P=0.082). The OS and DES for pure endometrial YSTs were slightly longer than for somatic tumor, though with no statistical differences (mean OS: 48.1 vs 21.9 months, P=0.690; mean DFS: 53.0 vs 20.7 months, P=0.485) (Figure 4).
Figure 2. Histological features of endometrial YST. Multiple separated tumor tissue with a small piece of normal endometrium (A ×20), most area showing a tubulopapillary pattern (B ×40) with classical Schiller–Duval bodies (C ×100), a microcystic or reticular pattern (D ×100), and focal glandular pattern (E ×400), hyaline globules in the cytoplasm (F ×200).

Discussion

The histogenesis of extragonadal YST remains speculative and controversial. There are four potential mechanisms by which a germ cell neoplasm can arise in the endometrium.10 The first is the aberrant migration of primordial germ cells in a lateral direction during embryogenesis, which can remain in the basal layer of the endometrium for many years. The second potential mechanism is metastasis from occult ovarian YST. Residual fetal tissues remaining in the uterus because of an incomplete abortion and somatic cells that have undergone aberrant differentiation by which YST originates in unusual sites are the other two potential mechanisms.

Patients with pure YSTs were younger than those with a concomitant somatic tumor. Therefore, pure endometrial YST and endometrial YST with somatic tumors may have had different histogeneses. Pure endometrial YSTs may originate from pluripotent germ cells, while endometrial YSTs with somatic tumors may arise from malignant pluripotent somatic stem cells or possibly via “retrodifferentiation,” by which a differentiated cell transforms into a more primitive...
Figure 3. Immunohistochemical profile of endometrial YST. Diffuse positive for AFP (A ×100), GPC-3 (B ×100), SALL-4 (C ×100), and AE1/AE3 (D ×100). Focal positive for PAX8 (E ×100) and negative for EMA (F ×100).

form. Reports of ovarian YST arising from an endometrioid carcinoma support this hypothesis. YSTs of the female genital tract in older women are commonly derived from somatic epithelial neoplasms. AFP is used as a significant follow-up indicator, but only a few patients have normal serum AFP levels.

Since primary endometrial YST is rare, inexperienced pathologists likely make an incorrect diagnosis, especially in biopsy specimens. In particular, the immunohistochemical profile overlaps with that of YST and carcinoma; for example, AE1/AE3 is positive in the current YST, which is not a good marker for differential diagnosis of carcinoma. Although HNF-1β and PAX8 can be patchy positive in YST, both are rather than diffuse positive in clear cell carcinoma. SALL4 is a useful marker for diagnosis when combined with GPC-3 and AFP. Overall, a panel of markers is necessary for the diagnosis and differential diagnosis of YST at rare sites (Table 2).

Given the rarity of primary endometrial YSTs, there is no consensus on the treatment of this extremely rare tumor. Surgery combined with adjuvant chemotherapy is the main reported treatment. Most patients undergo TAH BSO treatment, except
| Case | Age (years) | AFP level | Symptoms | Tumor size (cm) | Surgery | Associated component | Metastasis site | Chemotherapy | Radiotherapy | FIGO stage | Follow up (months) |
|------|-------------|-----------|----------|----------------|---------|----------------------|----------------|-------------|--------------|------------|------------------|
| 1    | 28          | 380       | Metrorrhagia, pelvic pain | Unknown | TAH BSO | None | None | VAC | No | IB | REC, 2 (liver); DOD, 8 |
| 2    | 27          | 180       | Metrorrhagia | 2.4 | TAH BSO OMT | None | None | VAC | No | IA | NED > 12 |
| 3    | 24          | 3600      | Abdominal pain | 10 | SH BSO | None | ovary | VAC | Yes | IVA | REC, (unknown); DOD, 24 |
| 4    | 49          | NA        | Metrorrhagia | 1.3 | TAH BSO ILD | None | None | No | Yes | IB | NED > 28 |
| 5    | 59          | 25,385    | Postmenopausal bleeding | Unknown | TAB BSO PLD PALD | EC | Liver | BEP EP | Yes | IA | REC, 16; AWD > 16 |
| 6    | 65          | 2306      | Watery discharge | 7 | MRH BSO PLD PALD | Carcinosarcoma | LN | TP | No | IIIC2 | NA |
| 7    | 42          | 18,530    | AVB | 6 | TAH BSO | None | None | PVB | No | IA | NED > 24 |
| 8    | 30          | 1762      | TAH | 6.5 | TAH BSO | None | None | BEP | No | II | NED > 72 |
| 9    | 29          | 3593.4    | AVB | 6.7 | MRH BSO PLD PALD | None | None | BEP | No | II | NED > 39 |
| 10   | 28          | 1522      | AVB | 6 | TAH BSO PLD OMT | EC | Peritoneum | omental | PVB | No | IVB | REC, 2; AWD |
| 11   | 31          | 242.3     | Menorrhagia | 4 | None | None | None | BEP | No | IA | NED > 24 |
| 12   | 57          | 31,844    | Abdominal pain, weight loss | 10.5 | TAH BSO OMT PLD PALD | None | Liver | ovary lung | BEP | No | IVB | DOD < 2 |
| 13   | 44          | >30,000   | AVB vaginal mass prolapsing | 19 | TAH BSO OMT PLD PALD | None | None | BEP | No | IB | NED > 6 |
| 14   | 63          | 244.6 (6 wk PO) | Postmenopausal bleeding | 12 | None | None | None | Ovary omentum | BEP | No | IVB | NED 6 |
| 15   | 71          | NA AVB    | NA | Yes | SC EC | NA | NA | NA | NA | IIIC1 | DOD, 19 |
| 16   | 55          | NA AVB    | NA | Yes | Complex hyperplasia | NA | Yes | Yes | No | IB | LFT |
| 17   | 59          | NA AVB uterine mass | NA | NA | EC | NA | Yes | No | No | IV | DOD, 14 |
| 18   | 68          | NA AVB uterine mass | NA | NA | None | NA | NA | Yes | No | IIIC1 | DOD, 23 |
| 19   | 77          | NA AVB uterine mass | NA | NA | EC UDC | NA | NA | NA | NA | LFT |
| 20   | 64          | NA AVB    | NA | Yes | AC | NA | Yes | Yes | No | IIIA | DOD, 7 |
| 21   | 87          | NA AVB    | NA | Yes | AC | NA | Yes | No | No | II | AWD, 17 |
| 22   | 61          | NA AVB    | NA | Yes | MMMT | NA | Yes | Yes | No | IA | AWD, 8 |
| 23   | 63          | NA AVB    | NA | Yes | MMMT | NA | Yes | Yes | No | IB | NED, 5 |
| 24   | 62          | NA AVB    | NA | Yes | SC | NA | Yes | No | No | IB | AWD, 30 |
| 25   | 77          | NA AVB    | NA | Yes | SC, CCC, UDC | NA | Yes | No | IB | AWD, 17 |
| 26   | 64          | 15,918    | Abdominal distension | NA | NA | None | NA | NA | No | IVB | DOD, 2.5 |
| 27   | 27          | >800      | AVB | 5.4 | TAH BSO OMT PLD PALD | None | None | TC | No | IA | NED > 14 |
| 28   | 38          | Normal AVB | Prolonged menstruation | NA | TAH BSO OMT PLD PALD | None | None | BEP | No | IVB | NED > 24 |
| 29   | 68          | 133.4 (6 days PO) | AVB | 3.3 | TAH BSO OMT PLD PALD | None | None | BEP | No | II | NED > 6 |
| 30   | 43          | 1465      | AVB, epigastric pain | 4 | TAH BSO PLD | None | None | BEP | No | IA | NED, 15 |

PO: postoperatively; YST: yolk sac tumor; AVB: abnormal vaginal bleeding; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; OMT: omentectomy; SH: supracervical hysterectomy; ILD: iliac lymphadenectomy; PLD: pelvic lymphadenectomy; PALD: paraaortic lymphadenectomy; MRH: modified radical hysterectomy; LSO: left salpingo-oophorectomy; EC: endometrioid adenocarcinoma; SC: serous carcinoma; UDC: undifferentiated carcinoma; AC: adenocarcinoma; MMMT: malignant mixed Mullerian tumor; CCC: clear cell carcinoma; VAC: vincristine, actinomycin D, and cyclophosphamide; BEP: bleomycin, etoposide, and cisplatin; VP: etoposide and cisplatin; TP: taxol and cisplatin; PVB: bleomycin, vincristine, and cisplatin; PTX: paclitaxel; ADM: Adriamycin; DDP: cisplatin; CBDCA: carboplatin; MTX: methotrexate; Act-D: actinomycin D; VP16: etoposide; BLM: bleomycin; VCR: vincristine; FUDR: 5-fluoro-2-deoxy-β-uridine; CPA: cyclophosphamide; REC: recurrence; DOD: dead from the disease; NED: no evidence of disease; AWD: alive with disease; LFT: lost to follow-up; NA: not available; AFP: alpha fetoprotein.
for one patient with unilateral ovary reservation and two with bilateral ovary reservation.\textsuperscript{11,18} The patients with bilateral ovary reservation were a 30-year-old woman (stage II)\textsuperscript{11} and a 27-year-old woman (stage IA),\textsuperscript{18} who survived for more than 6 years and 14 months, respectively. A 29-year-old woman in stage II in whom the right adnexa was preserved was alive without recurrence for 39 months.\textsuperscript{12} These data demonstrate the possibility of ovary reservation for young patients with early-stage primary YST of the endometrium, retaining ovarian endocrine function and improving quality of life.

Of 30 cases, compared with those combined with somatic tumor (5/13, 38.5%), pure endometrial YSTs were more likely in an early stage (12/17, 70.6%) though no statistical difference was detected ($P = 0.082$). The OS and DES were slightly longer in pure endometrial YSTs than in somatic tumor, but with no statistical differences (mean OS: 48.1 vs 21.9 months, $P = 0.690$; mean DFS: 53.0 vs 20.7 months, $P = 0.485$). These findings suggest that patients with endometrial YST combined with somatic tumor tend to be at a slightly higher stage and have a poor prognosis. However, additional cases need to be further analyzed for a better understanding of these rare tumors.

**Conclusion**

Primary YST of the endometrium, a highly malignant germ cell tumor, is extremely rare. Surgery combined with postoperative chemotherapy is considered effective for the treatment of primary endometrial YST. Ovarian conservation is optional in young patients. Patients with pure YST are younger than those with concomitant somatic tumors. Patients with endometrial YST combined with somatic tumor tend to be at a slightly higher stage and have a poor prognosis. However, additional cases need to be further analyzed for a better understanding of these rare tumors.

**Author contribution**

R.B. provided the case and critically revised the manuscript. H.G. was responsible for the acquisition and interpretation of patient data and manuscript preparation. R.B. and H.G. performed pathological examination. All authors approved the final manuscript.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**

This study was approved by the Institutional Review Board Facility Ethical Committee (Fudan University Cancer Center Ethics Committee, China; approval no. 050432-4-121B, 13 December 2012).

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was funded by the National Natural Foundation Science of China (grant no. NSFC 81802597).
Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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