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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

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Introduction

Yolk sac tumor (YST), also known as an endodermal sinus tumor, is the third most common form of malignant ovarian germ cell neoplasms, followed by dysgerminoma and immature teratomas.[1] It is one of the most common malignant ovarian neoplasms of childhood, adolescence, and early adulthood. Although YST usually originates from the gonads (ovary and testis), it occasionally arises from midline extragonadal regions, such as the sacrococcygeal region, mediastinum, and retroperitoneum. Approximately 20% of female patients experience extragonadal YST (EGYST),[2] and the vagina is the most common site of YST growth in infants and young children.[3] Primary YST of the endometrium is very rare.[4] The first case of primary YST of the endometrium was reported in 1980.[3] To the best of our knowledge, only 29 cases have been reported in the literature to date. We report a new case of primary endometrial YST and have a systematic review of the literature.

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

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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 × 9.5 × 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.[5]

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

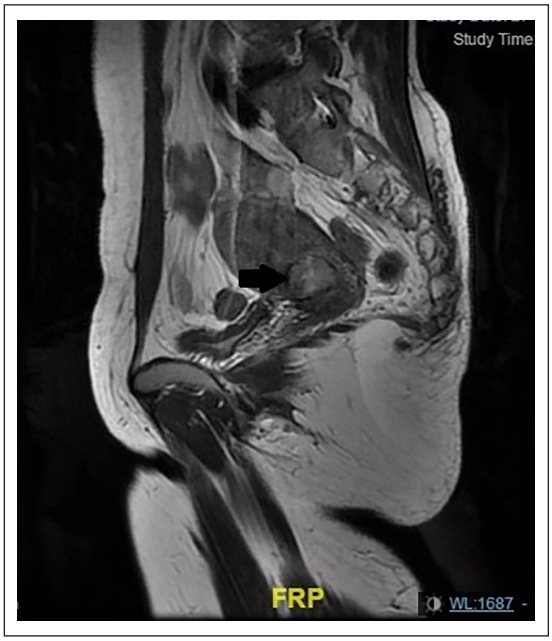

Figure 1. Pelvic-enhanced MRI showed mild enhancement of the lesion, and the lesion seemingly not invaded muscular layer.

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).

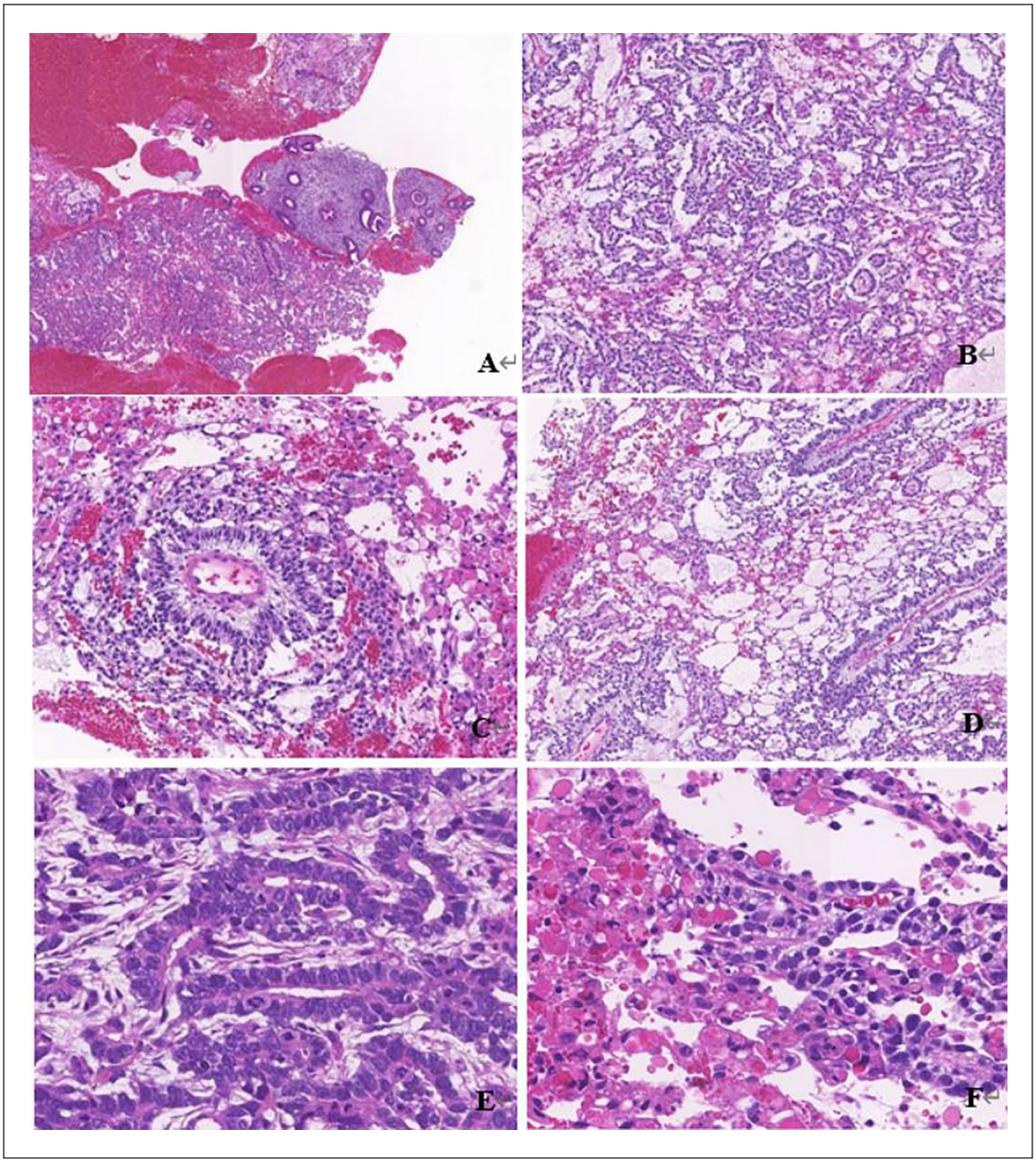

Figure 2. Histological features of endometrial YST. Multiple separated tumor tissue with a small piece of normal endometrium (A ×20), most area showing a tubulopapillary pattern (B ×40) with classical Schiller–Duval bodies (C ×100), a microcystic or reticular pattern (D ×100), and focal glandular pattern (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

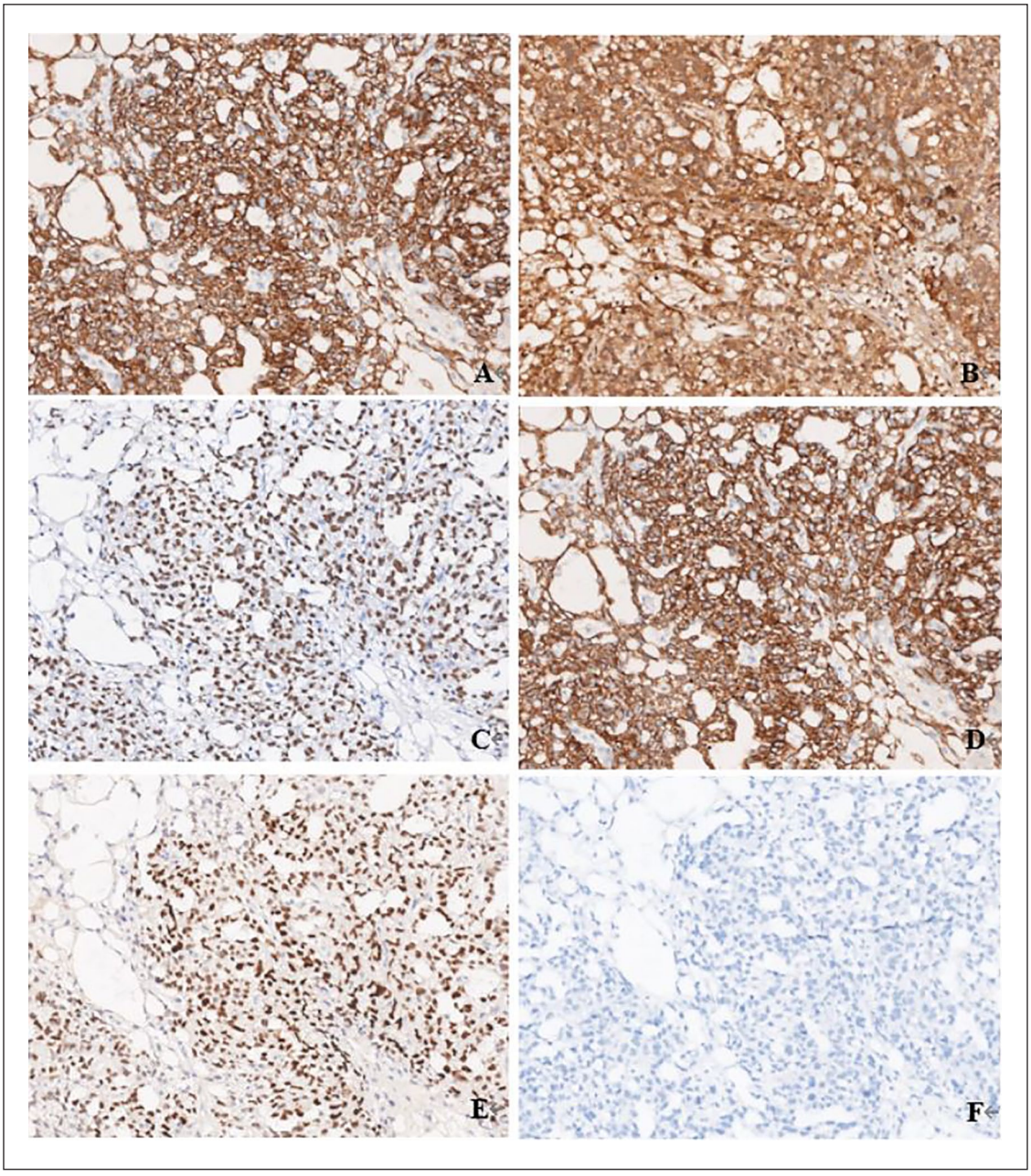

Figure 3. Immunohistochemical profile of endometrial YST. Diffuse positive for AFP (A ×100), GPC-3 (B ×100), SALL-4 (C ×100), and AE1/AE3 (D ×100). Focal positive for PAX8 (E ×100) and negative for EMA (F ×100).

form.[21] Reports of ovarian YST arising from an endometrioid carcinoma support this hypothesis.[9,22,23] YSTs of the female genital tract in older women are commonly derived from somatic epithelial neoplasms.[24] AFP is used as a significant follow-up indicator, but only a few patients have normal serum AFP levels.[19]

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.[25] Although HNF-1β and PAX8 can be patchy positive in YST,[26] both are rather than diffuse positive in clear cell carcinoma. SALL4 is a useful marker for diagnosis when combined with GPC-3 and AFP.[27] 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

Table 1. Summary of clinicopathologic features of primary endometrial YSTs.

Case	Age (years)	AFP level	Symptoms	Tumor size (cm)	Surgery	Associated component	Metastasis site	Chemotherapy	Radiotherapy	FIGO stage	Follow up (months)
13[3]	28	380	Metrorrhagia, pelvic pain	Unknown	TAH BSO	None	None	VAC	No	IB	REC, 2 (liver); DOD, 8
2[6]	27	1580	Metrorrhagia	2.4	TAH BSO OMT	None	None	VAC	No	IA	NED > 12
3[7]	24	3600	Abdominal pain	10	SH BSO	None	ovary	VAC	Yes	IVA	REC, (unknown); DOD, 24
4[2]	49	NA	Metrorrhagia	1.3	TAH BSO ILD	None	None	No	Yes	IB	NED > 28
5[8]	59	25,385	Postmenopausal bleeding	Unknown	TAB BSO PLD PALD	EC	Liver	BEP EP	Yes	IA	REC, 16; AWD > 16
6[9]	65	2306	Watery discharge	7	MRH BSO PLD PALD	Carcinosarcoma	LN	TP	No	IIIC2	NA
7[10]	42	18,530	AVB	6	TAH BSO	None	None	PVB	No	IA	NED > 24
8[11]	30	1762	AVB	6.5	TAH	None	None	BEP	No	II	NED > 72
9[12]	29	3593.4	AVB	6.7	MRH LSO PLD PALD	None	None	BEP	No	II	NED > 39
10[13]	28	1522	AVB	6	TAH BSO PLD OMT appendectomy, partial sigmoidectomy	EC	Peritoneum omental	PTX, ADM, DDP, CBDCA, MTX, Act-D, VP16, BLM, pingyangmycin, VCR, FUDR, oxaliplatin, CPA	No	IVB	REC, 2; AWD
11[14]	31	242.3	Menorrhagia	4	None	None	None	BEP	No	IA	NED > 24
12[15]	57	31,844	Abdominal pain, weight loss	10.5	TAH BSO OMT PLD PALD	None	Liver ovary lung vertebrae	BEP	No	IVB	DOD < 2
13[15]	44	>30,000	AVB, vaginal mass prolapsing	19	TAH BSO OMT PLD PALD	None	None	BEP	No	IB	NED > 6
14[16]	63	244.6 (6 wk PO)	Postmenopausal bleeding	12	None	None	Ovary omentum	BEP	No	IVB	NED 6
15[4]	71	NA	AVB	NA	Yes	SC EC	NA	NA	NA	IIIA	DOD, 19
16[4]	55	NA	AVB	NA	Yes	Complex hyperplasia	NA	Yes	Yes	II	DOD, 16
17[4]	59	NA	AVB, uterine mass	NA	NA	EC	NA	Yes	No	IB	LFT
18[4]	68	NA	AVB, uterine mass	NA	Yes	None	NA	Yes	No	IV	DOD, 14
19[4]	77	NA	AVB, uterine mass	NA	NA	EC UDC	NA	NA	NA	IIIC	LFT
20[4]	64	NA	AVB	NA	Yes	AC	NA	Yes	Yes	IIIA	DOD, 23
21[4]	87	NA	AVB	NA	Yes	AC	NA	Yes	No	II	AWD, 7
22[4]	61	NA	AVB	NA	Yes	None	NA	Yes	No	IA	AWD, 8
23[4]	63	NA	AVB	NA	Yes	MMMT	NA	Yes	Yes	IIIC1	NED, 5
24[4]	62	NA	AVB	NA	Yes	SC	NA	Yes	No	IB	AWD, 30
25[4]	77	NA	AVB	NA	Yes	SC, CCC, UDC	NA	Yes	No	IIIC2	AWD, 17
26[17]	64	15,918	Abdominal distension	NA	NA	None	NA	NA	NA	IVB	DOD, 2.5
27[18]	27	>800	AVB	5.4	TAH OMT PLD PALD	None	None	TC	No	IA	NED > 14
28[19]	38	Normal	AVB, prolonged menstruation	NA	TAH BSO OMT PLD PALD	CCC	None	BEP	No	IVB	NED > 24
29[20]	68	133.4 (6 days PO)	AVB	3.3	TAH BSO OMT PLD PALD	None	No	BEP	No	II	NED > 6
30 present	43	1465	AVB, epigastric pain	4	TAH BSO PLD	None	No	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; EP: 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.

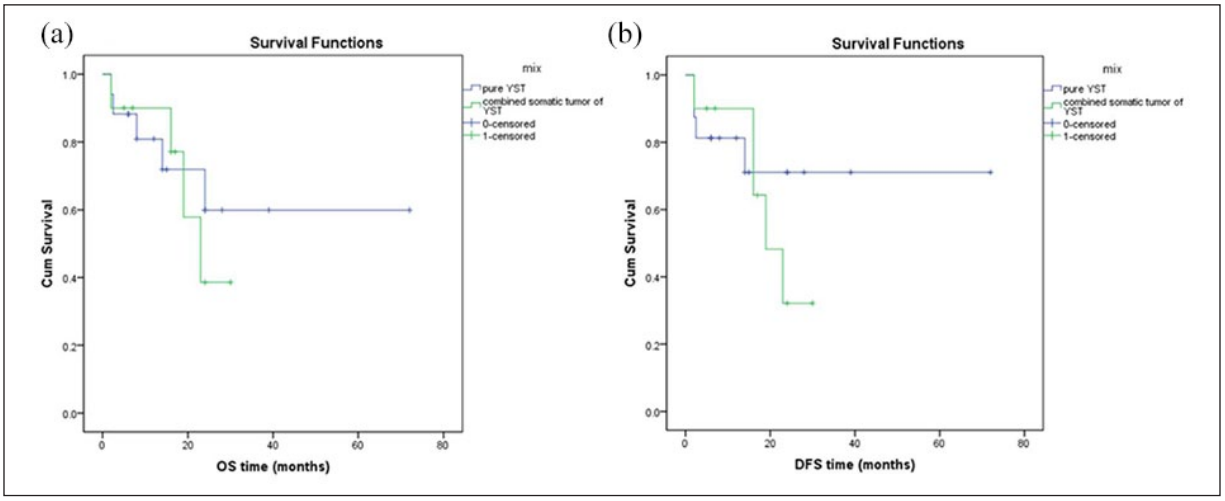

Figure 4. The OS (a) and DFS (b) of pure endometrial YST were slightly longer than those of combined somatic tumor of endometrial YSTs, though with no statistical differences (P = 0.690 and P = 0.485).

Table 2. Application of immunohistochemistry in differential diagnosis of germ cell tumors.

	AE1/AE3	HNF-1β	PAX8	SALL4	GPC-3	AFP	CD30	OCT-4	CD117
Yolk sac tumor	+	±	±	+	+	+	−	−	−
Dysgerminoma	−	−	−	+	−	−	−	+	+
Embryonal carcinoma	+	−	−	+	−	±	+	+	−

for one patient with unilateral ovary reservation and two with bilateral ovary reservation.[11,18] The patients with bilateral ovary reservation were a 30-year-old woman (stage II)[11] and a 27-year-old woman (stage IA),[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.[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.

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).

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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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