

CASE REPORT

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Primary yolk sac tumor of the endometrium combined with situs inversus totalis: a case report and literature review

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Abstract

Background Yolk sac tumor (YST) is a highly malignant germ cell tumor, a majority of which originate from the gonads and are extremely rare from endometrium.

Case presentation Here we present a case of a 42-year-old woman suffered from primary pure yolk sac tumor of the endometrium complicated with situs inversus totalis. The patient presented at our hospital with irregular vaginal bleeding. Imageological examination showed a space-occupying lesion in the cervix and the serum Alpha-fetoprotein (AFP) level was significantly high (more than 1210ng/ml). Then she underwent total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection. The subsequent postoperative pathological diagnosis was yolk sac tumor arising from the endometrium. Next, the patient was treated with 6 cycles of chemotherapy with Pingyangmycin, etoposide and cisplatin regimen and was alive without evidence of recurrence or distant metastases for 13 months.

Conclusions This rare disease needs to be differentiated from endometrial epithelial neoplasia and the significant increase in AFP is helpful for diagnosis. Combined with previous literature reports, comprehensive staging laparotomy or maximum cytoreductive surgery complemented by standard chemotherapy can usually achieve a good efficacy.

Keywords Yolk sac tumor, Endometrium, Situs inversus totalis, Germ cell tumors

Background

Yolk sac tumour is a primitive germ cell tumour displaying multiple patterns reflecting endodermal extraembryonal differentiation (secondary yolk sac and allantois) or, less commonly, endodermal somatic tissues (intestine, liver, and mesenchyme). (WHO classification, 2020). It is the second most common malignant germ cell tumor

of the ovary after dysgerminoma, and it tends to occur in children, adolescents and young adults (median age, 19 years) [1]. It is generally believed to arise from undifferentiated or pluripotent embryonic carcinomas with selective differentiation into yolk sacs or yolk like structures [2]. YST is often combined with other type of germ cell tumors such as embryonal carcinoma or dysgerminoma, the cases with ovarian surface epithelial tumors have been seen in elderly patients [3, 4]. Approximately 20% of these tumors are located outside the gonads at midline sites such as the female genital tract, sacrococcygeal, retroperitoneal, mediastinal, head and neck as well as central nervous system [5]. The majority of genital

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tract YSTs are found in the vagina or cervix, and the primary occurrence in the endometrium is infrequent.

Situs inversus totalis (SIT) is a rare phenomenon in clinical practice, with an incidence rate ranging from 1:20000 to 1:5000 [6]. The organ function of the patients suffered is normal. It is generally believed that there is no exact correlation between it and tumor. A few reports have shown that SIT can coexist with tumors of lung, stomach, colon, bile duct and other organs, but not with germ cell tumors. We provide a case of pure yolk sac tumor originating from the endometrium with SIT. Meanwhile, we reviewed the available literature to enhance the understanding of this disease. We present the following article in accordance with the CARE reporting checklist.

Case presentation

A 42-year-old woman was admitted to the Department of Gynecology of our hospital due to irregular vaginal bleeding for 20 days in August 2021. The patient had regular menstruation, 3–4 days /30 days. She gave birth to a baby by cesarean section in 2015 and was diagnosed with hepatitis B in the same year, but the treatment history was

unknown. The patient denied the history of other types of hepatitis, tuberculosis, hypertension, coronary heart disease and diabetes. She had no family history of genetic disease and tumor. Ultrasound examination of the pelvis indicated the presence of a mass in the intrauterine space with a size of 5.9cm x 5.5cm x 4.6cm, irregular shape and poorly defined boundary. MRI showed a space-occupying uterine lesion involving the muscularis and the left pelvic wall (Fig. 1). She had a gynecological examination and was detected a mass protruded from the cervix with brittle texture and bleeding. No obvious abnormalities were observed in the bilateral ovaries and fallopian tubes. Tumor markers were tested and the serum AFP level elevated significantly to more than 1210 ng/ml while the serum CA125, CA199, CEA, SCC, HCG and HE4 levels were normal. Chest X-ray showed dextrocardia and CT of the pelvis and abdominal cavity confirmed situs inversus of the liver, bile, stomach and spleen, with no abnormalities in size and morphology. The patient underwent biopsy of the mass and the pathological findings indicated a yolk sac tumor. Subsequently, a surgery of total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection was performed.

The uterine body was normal in size. Gross examination revealed an irregular nodular mass arising from the lower uterine segment, measuring 4.5 cm x4.3 cm x4.1 cm and protruding into the cervical canal. The tumor was grayish-yellow in color and brittle in texture, with hemorrhage and necrosis in some areas (Fig. 2). Bilateral ovaries and fallopian tubes were not involved.

Microscopically, the tumor showed a reticular pattern coexisting with microcysts, labyrinth composed of interconnecting crevices and ducts, multivesicular structures and solid areas, surrounded by loose myxoid stroma. Typical endodermal sinus structures (Schiller–Duval bodies) were easily visible. The reticulum and microcysts were lined by flat atypical epithelial cells with vacuolated nuclei and clear cytoplasm, which appeared an active mitotic figures. Eosinophilic globules were also observed in the cells and microcysts (Fig. 3A–E). The tumor infiltrated the full thickness of the myometrium and focally involved the serosal membrane. No endometrial somatic carcinoma or other types of germ cell tumor components were observed. The cervical canal was invaded, while no tumor was found in the bilateral ovaries and fallopian tubes, and none of the pelvic lymph nodes showed metastasis (0/12). The immunohistochemical staining indicated that the tumor cells were diffusely positive for AFP and SALL-4 (Fig. 3F), and focally positive for P16 and EMA, the positive rate of P53 was 20% and the Ki-67 index was approximate to 60%, while they were negative for CK7, ER, PR, NapsinA, CA125, PAX-8, WT-1 and HCG. The eosinophilic globules were positive for PAS staining.



Fig. 1 Pelvic MRI showed a lesion (red arrow) occupying the lower uterine segment and cervix, the lesion seemingly invaded the deep muscularis. (sagittal plane, T2W1)

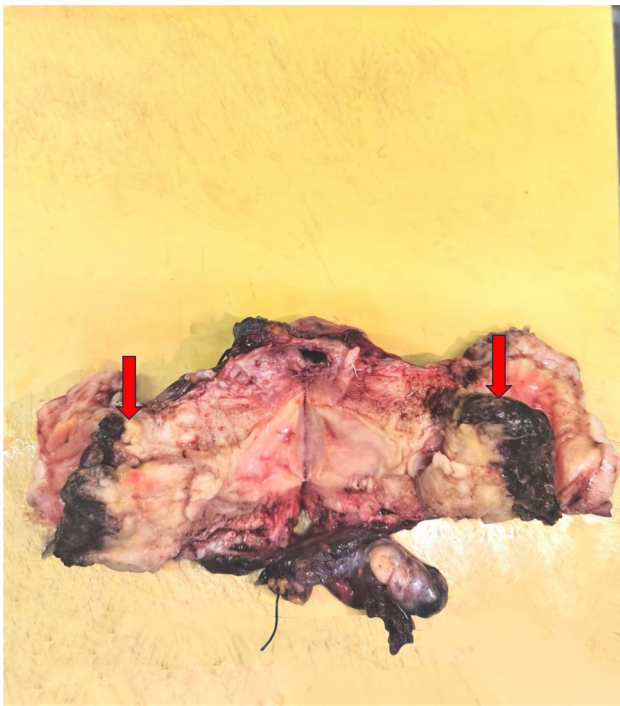


Fig. 2 Gross appearance: a grayish-yellow mass with hemorrhage (red arrow) arising from the lower uterine segment and protruding into the cervical canal

Postoperative pathologic report confirmed the diagnosis of primary endometrial YST with FIGO stage IIIA. Intravenous chemotherapy (Pingyangmycin 8 mg, etoposide 100 mg, cisplatin 20 mg) was initiated with a frequency of once every 21 days for 6 cycles. The serum AFP level decreased to 380.5ng/ml on the 20th day after operation and fluctuated from 12.28ng/ml to 26.64ng/ml during chemotherapy, which was slightly higher than normal. Then the figure had dropped to 8.84ng/ml by September 2022 continually (Fig. 4). She was remained disease free for 13 months after surgery without recurrence or metastasis.

Discussion

We conducted a systematic literature search in October 2022 of PubMed, only 34 cases (23 publications) of primary endometrial YST were included after excluding irrelevant articles (Table 1) [7–29]. The earliest report was published in 1980. Patients' age ranged from 24 to 87 years. There were 21 cases with pure YST and the median age of them was 43 years. Most of them were premenopausal (13/21) and 8 were postmenopausal. In addition, there were 13 patients with concomitant somatic neoplasms such as endometrial epithelial carcinoma, carcinosarcoma, malignant mesodermal mixed tumor and other germ cell tumors. Their median age was 64 years and the majority of them were postmenopausal

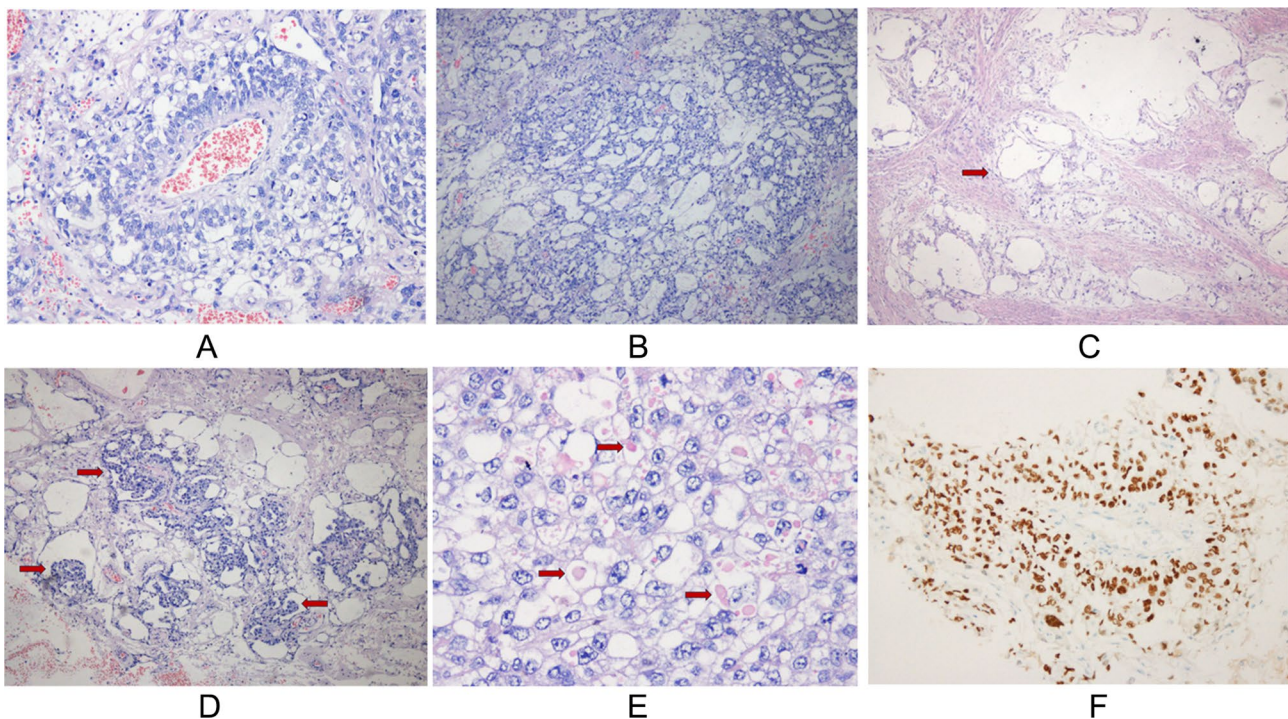


Fig. 3 Light microscopic appearance of YST. **A** Schiller–Duval bodies (H&E, X100). **B** Reticulum and microcysts surrounded by loose myxoid stroma (H&E, X40). **C** Multivesicular structures (red arrow) (H&E, X40). **D** Small papillae composed of epithelioid cells (red arrow) lining in the wall of cysts (H&E, X40). **E** Eosinophilic globules (red arrow) in the tumor cells and microcysts (H&E, X200). **F** Immunohistochemical staining showed diffuse positive for SALL-4 (X100)

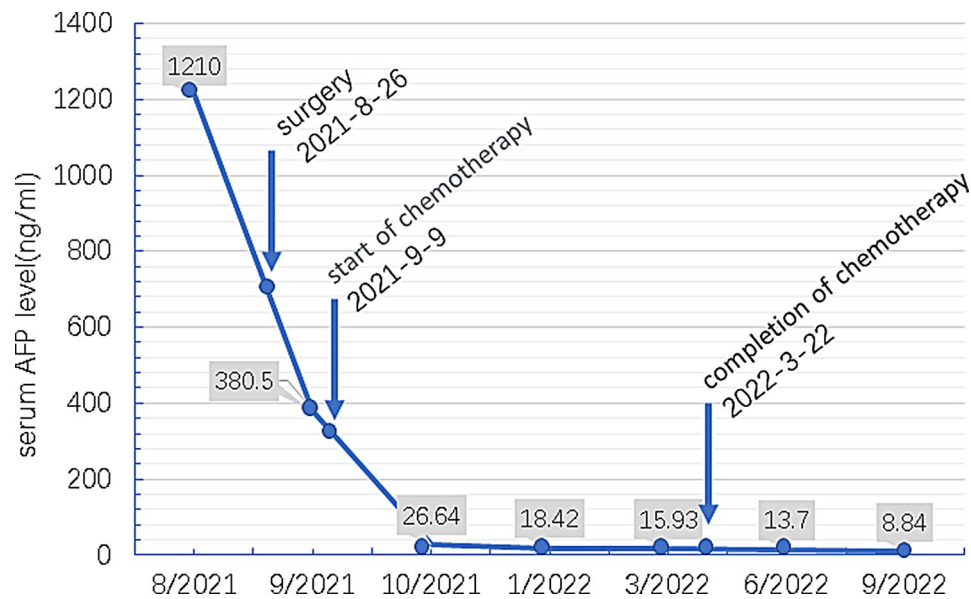


Fig. 4 The serum AFP level showed an obvious decreasing trend after surgery and chemotherapy

women (11/13), except for 2 young patients. Compared with those who had coexisting somatic tumors, simple endometrial YST patients were younger. This age difference likely stems from the respective mechanisms of tumorigenesis.

There are four theoretical hypotheses have been suggested to explain the pathogenesis of primary endometrial YST: an occult metastasis of ovarian YST; the abnormal migration of primitive germ cells and multipotential stem cells during early embryonic development, which stagnate in extra-gonadal sites during migration to the germinal crest and further differentiate into YST; the abnormal differentiation of somatic cells; embryonic tissue remaining in the uterus after an incomplete abortion [14]. Pure endometrial YST tends to be derived from the mislocation of primary germ cells and pluripotent stem cells, while YST 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 form [25].

In our case, the patient had been confirmed to have no YST in the bilateral ovaries and without a history of incomplete abortion or other uterine neoplasms but SIT. SIT is a very rare congenital malformation, caused by the dysfunction of visceral rotation during embryonic development, or by the abnormality of chromosomes and genes carried by parents, and it can be combined with organ malformations [30]. It is generally believed that SIT is not related to the pathogenesis of cancer, controversially, some studies have shown that SIT may be related to the occurrence of cancer due to congenital lack of the normal function of KIF3 complex [31]. Coexistence of YST and SIT was observed in our case, but we

found no similar cases by searching literature. Although SIT is occasionally accompanied by neoplasia, this rare association is unclear etiologically.

In the literature, the most frequent initial symptoms were abnormal vaginal bleeding and prolonged menstruation. A bulky mass can be detected by gynecological examination. In addition to 2 normal cases, 20 patients had a largely elevated preoperative or immediate postoperative serum AFP level, 12 had missing relevant details. The patient we shared was 42 years old and showed irregular vaginal bleeding with a rise in serum AFP level, which was similar to literatures reported.

The preoperative imaging examination has certain diagnostic value, but lacks specificity. On ultrasound, ovarian YSTs are mostly unilateral, large and multilocular-solid or solid, with fine-textured slightly hyperechoic solid tissue and rich vascularization [32]. Bright spots can be found on enhanced CT and MRI images, reflecting enhanced lesions in the solid component, due to the high abundance of dilated blood vessels in the tumors. The bleeding area showed high signal intensity on T1-weighted MR Images. Another imaging feature is the tearing of the envelope, which is associated with the rapid growth of the tumor leading to its rupture [33].

Reviewing the literature, we found that a subset of cases could be correctly diagnosed preoperatively by diagnostic curettage or hysteroscopic biopsies, depending on the typical histopathological morphology of the biopsy tissue, such as the S-D bodies. That’s what happened in our case. Some cases may be diagnosed as endometrial adenocarcinoma, especially as clear cell carcinoma, due to lack of typical morphology or concomitant with other

Table 1 Summary of clinicopathologic features of primary endometrial YSTs ref; references; AVB, abnormal vaginal bleeding; Abd, abdominal; PO, postoperatively; EC, endometrioid adenocarcinoma; SC, serous carcinoma; UDC, undifferentiated carcinoma; AC, adenocarcinoma; MMMT, malignant mixed müllerian tumor; CCC, clear cell carcinoma; CISH, classical intrafascial supracervical hysterectomy; BSO, bilateral salpingo-oophorectomy; TAH, total abdominal hysterectomy; OMT, omentectomy; PLND, pelvic lymph node dissection; PALND, para-aortic lymph node dissection; MRH, modified radical hysterectomy; REC, recurrence; AWD, alive with disease; DOD, died of disease; LTF, lost to follow-up; NED, no evidence of disease; NA, not available

Case(Ref)	Year of publication	Age(years)	Symptoms	AFP(ng/ml)	Associated component	FIGO stage	Metastasis site	Surgery	Chemotherapy	Radiotherapy	Follow up(months)
1[7]	1980	28	AVB, Abd pain	380	none	IB	none	TAH+BSO	VAC	No	REC,2 ; DOD,8
2[8]	1988	24	Abd pain	3600	none	IVA	ovary	CISH+BSO	VAC	YES	DOD,24
3[9]	1988	27	AVB	1580	none	IA	none	TAH+BSO+OMT	VAC	No	NED>14
4[10]	1990	42	AVB	18,530	none	IA	none	TAH+BSO	PVB	No	NED>24
5[11]	1996	64	Abd distension	15,918	none	IVB	NA	NA	NA	NO	DOD,2.5
6[12]	1998	49	AVB	Normal	none	IB	none	TAH+BSO+PLND	NO	YES	NED>28
7[13]	2001	59	postmenopausal bleeding	27,670	EC	NA	liver	TAH+BSO+OMT+PLND	BEP EP	NO	REC,16 ; AWD>16
8[14]	2006	65	Watery discharge	2306	carcinosarcoma	IIIC	LN	MRH+BSO+PLND	TP	NO	NA
9[15]	2011	29	AVB	3593.4	none	II	none	modified hysterectomy+LSO+PLND+PALND	BEP	NO	NED>39
10[16]	2011	30	AVB	1762	none	II	none	TAH	BEP	NO	NED>72
11[17]	2013	28	AVB	1522	EC	IVB	peritoneum; omentum	TAH+BSO+OMT+PLND+appendectomy+partial resection of the sigmoid colon with anastomosis	PTX ADM DDP CBDCA MTX Act-D VP16 BLM pingyangmi- ycin YCR FUDR oxaliplatin CPA	NO	REC,2 ; AWD,10
12[18]	2014	31	AVB	242.3 IU/ml	none	IA	none	TAH+BSO+OMT+PLND+PALND	BEP	NO	NED>24
13[19]	2015	44	AVB	27,522	none	IB	none	TAH+BSO+OMT+PLND+PALND	BEP	NO	NED>6
14[19]	2015	57	Abd pain	29,214	none	IVB	liver ovary lung	TAH+BSO+OMT+PLND+PALND	BEP	NO	DOD<2
15[20]	2016	63	postmenopausal bleeding	NA	none	IVB	omentum	TAH+LSO+OMT+appendectomy	BEP	NO	NED,6
16[21]	2017	71	AVB	NA	EC SC	IIIA	ovary	Yes	NA	NA	DOD,19
17[21]	2017	55	AVB	NA	complex hyperplasia	II	NA	Yes	Yes	Yes	DOD,16
18[21]	2017	59	AVB	NA	EC	IB	NA	NA	Yes	NO	LTF
19[21]	2017	68	AVB	NA	none	IV	NA	Yes	Yes	NO	DOD,14
20[21]	2017	77	AVB	NA	EC UDC	IIIC	NA	NA	NA	NA	LTF
21[21]	2017	64	AVB	NA	AC	IIIA	NA	Yes	Yes	Yes	DOD,23
22[21]	2017	87	AVB	NA	AC	II	NA	Yes	Yes	NO	AWD,7
23[21]	2017	61	AVB	NA	none	IA	NA	Yes	Yes	NO	AWD,8
24[21]	2017	63	AVB	NA	MMMT	IIIC	NA	Yes	Yes	Yes	NED,5

Table 1 (continued)

Case(Ref)	Year of publication	Age(years)	Symptoms	AFP(ng/ml)	Associated component	FIGO stage	Metastasis site	Surgery	Chemotherapy	Radiotherapy	Follow up(months)
25[21]	2017	62	AVB	NA	SC	IB	NA	Yes	Yes	NO	AWD,30
26[21]	2017	77	AVB	NA	SC, CCC, UDC	IIIC	NA	Yes	Yes	NO	AWD,17
27[22]	2019	27	AVB	800	none	IA	none	TAH+OMT+PLND+PALND	TC	NO	NED> 14
28[23]	2019	38	AVB, prolonged menstruation	Normal	CCC	IVB	none	TAH+BSO+OMT+PLND+PALND+appendectomy	BEP	NO	NED>24
29[24]	2019	68	AVB	133.4	none	II	none	TAH+BSO+OMT+PLND+PALND	BEP	NO	NED>6
30[25]	2021	43	AVB, epigastric pain	1465	none	IA	none	TAH+BSO+PLND	BEP	NO	NED, 15
31[26]	2021	73	Abd distension	10.5(PO)	none	IIIA	ovary	TAH+BSO+PALND+ partial OMT	EP	NO	NED> 14
32[27]	2021	35	AVB, prolonged menstruation	9152	none	IA	none	TAH+BSO+OMT+PLND+PALND	BEP	NO	NED, 21
33[28]	2017	38	hypermenorrhea	37.4(PO)	none	NA	omentum	TAH+BSO+OMT+PLND+PALND	BEP	NO	NA
34[29]	2020	65	AVB	359	Embryonal carcinoma; Immature teratoma	IA	none	TAH+BSO	BEP	NO	NED, 15

uterine tumors, they require definitive postoperative pathological diagnosis.

In view of the rarity and diverse histological morphology of primary endometrial YST, pathologists should be careful to differentiate it from other morphologically similar tumors such as Endometrial clear cell carcinoma (CCC) and endometrioid adenocarcinoma (EC), especially in curettage and biopsy specimens. CCC may contain edematous stroma, which is similar to the myxomatous-like background of YST, while the papillae are covered with clear cells and boot-like cells. When CCC is composed entirely of tubules and cavities, it is easily confused with multivesicular YST. However, the former lacks typical endodermal sinus or reticulum formed by microcysts and the glandular morphology is more regular. Endometrioid YST usually consist of solitary glandular duct components similar to EC with a secretory response. However, the adenocarcinomas mentioned above are generally found in elderly people and are not associated with high levels of serum AFP. In addition to morphologic differences, immunohistochemical staining is helpful in the diagnosis of YST. CK7 and EMA are diffusely expressed in CCC, HNF1β and NapsinA are also positively expressed. EC is positive for ER, PR and Vimentin, while AFP, SALL-4 and Glypican-3 are specific and sensitive in the diagnosis of YST.

As to the YST that lack a typical endodermal sinus, the increase in serum AFP and positive AFP immunohistochemical staining are helpful to identify the differentiation of the yolk sac. Furthermore, serum AFP determinations are important to evaluate efficacy, monitor recurrence and metastasis after therapy.

At present, there is no unified guideline for the treatment of YST arising from endometrium. Patients can be benefit from the treatment protocols including comprehensive staging laparotomy, tumor cytoreductive surgery and standard chemotherapy after operation. The surgical procedures include total hysterectomy and bilateral salpingo-oophorectomy, omentectomy, pelvic lymph node and paraaortic lymph node dissection. Pure YST patients seem to have a better prognosis than whom coexisted by uterine tumors. There is controversy about whether surgery can preserve the tumor-free ovaries to maintain endocrine function of young women and whether the omentum should be removed. Among the 34 cases, one retained bilateral ovaries (27 years old, staging IA) and another retained the right one (29 years old, staging II). After supplementation with platinum-based chemotherapy, their disease-free survival reached 14 and 39 months respectively [15, 22]. Simpson et al. [34] showed that comprehensive staging and cytoreductive surgery were of decisive significance for the survival and prognosis of patients. It may be safe to carry out a comprehensive staging laparotomy that preserves endocrine function for

pure YST patients under 40 with staging I and II. However, there was a report of an 18-year-old patient who retained both ovaries during surgery and was found to have recurrent tumor in the vaginal stump at 3 months after the chemotherapy, and died of extensive metastasis at 36 months after surgery [35]. A positive staining of AFP was detected in the inferior uterine margin of this patient, which may have been the main reason for the recurrence of vaginal stump, in which case a postoperative adjuvant vaginal brachytherapy should be recommended. Therefore, the preservation of normal ovaries may increase the risk of recurrence and distant metastasis, and the safety of surgery with ovarian preservation needs to be further verified.

Similar to ovarian YST, the BEP (cisplatin+etoposide+bleomycin) regimen is recommended for primary endometrial YST as the standard regimen. Chemotherapy should be timely, adequate and standardized, and insufficient chemotherapy can easily lead to tumor recurrence. Compared to the VAC (vincristine+actinomycin+cyclophosphamide) regimen used earlier, platinum-based chemotherapy regimen can achieve remission in patients with advanced tumors and other patients who have failed multidrug combination chemotherapy. In our case, because bleomycin was not available during that time, gynecologists used pingyangmycin instead of bleomycin in the chemotherapy and achieved a good results without adverse reactions. The study of Wang X et al. [35] revealed that BEP chemotherapy combined with targeted antiangiogenic drugs (bevacizumab) and immune therapy (tislelizumab) achieved a good efficacy in the treatment of postoperative multiple pelvic and lymph node metastases of tumors, may be optimal to increase the survival of patients with advanced recurrent non-endometrial YST.

Conclusions

YST originating from the endometrium is very rare, the cases accompanied by SIT were barely reported. The microscopic morphology of this disease is diverse, hence it is necessary to differentiate it from semblable tumors. AFP is an important and sensitive tumor marker for the diagnosis of YST. The appropriate treatment and prognosis need to be summarized by data from more cases and long term follow-up.

Abbreviations

CEA	Carcinoma Embryonic Antigen
SCC	Squamous Cell Carcinoma Antigen
HCG	Human Chorionic Gonadotropin
HE4	Human epididymis protein 4
ER	Estrogen Receptor
PR	Progesterone receptor
SALL-4	Spalt like transcription factor 4
BEP	bleomycin etoposide and cisplatin

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Author contributions

LR wrote the manuscript text and performed the literature review. WYR obtained histopathological images. WXF performed immunohistochemical tests. CXJ collected the data of the case. HJG supervised the writing and revised the manuscript. All authors reviewed the manuscript.

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Data availability

All data generated or used during the study are available from the corresponding author by request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare no competing interests.

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