Yolk sac tumor of the uterus in a 2-year-old girl: a case report and literature review

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Abstract

Background: Extragonadal yolk sac tumors (YSTs) occurring in the uterus are extremely rare. To report a uterine YST case in a prepubertal girl and review literature on uterine YST to outline clinical management in diagnosis and treatment.

Case: We present a case of a 2-year-old girl who presented with vaginal bleeding and a pelvic mass. The diagnosis of YST was confirmed via biopsy. After four cycles of neoadjuvant chemotherapy combined with cisplatin, etoposide, and bleomycin (PEB), vaginoscopic examination and laparoscopy revealed a uterine YST without metastasis. The patient was treated with laparoscopic hysterectomy and two cycles of PEB postoperatively. During the 18 months of follow-up, the patient remained disease-free.

Summary and Conclusion: Primary uterine YST is extremely rare and no treatment guidelines have been established to date. Surgery combined with PEB chemotherapy is considered effective for uterine YST.

Key Words: Yolk sac tumor, Extragonadal, Uterus, Prepuberty
Introduction

Causes of vaginal bleeding that should be considered in the prepubertal age group include sexual abuse, precocious puberty, benign and malignant ovarian tumors, as well as vulvar, vaginal, and cervical lesions or tumors. A pelvic mass may be gynecologic in origin, or it may arise from the urinary tract or bowel. The gynecologic causes of a pelvic mass may be uterine, adnexal, or more specifically ovarian. Serum tumor markers are frequently abnormal and are helpful for both diagnosis and follow-up.

Malignant germ cell tumors (MGCTs) account for less than 5% of all pediatric malignant tumors. Although MGCTs typically arise in the gonads, they may also arise at extragonadal sites typically in midline structures along the presumed migration path of germ cells during embryogenesis. Yolk sac tumor (YST), also known as endodermal sinus tumor, is one of the most common histological subtypes of MGCTs. Extragonadal YST occasionally arise from the sacrococcygeal region, mediastinum, retroperitoneum, and the female reproductive tract. Primary yolk sac tumor arising from the uterus is an extremely rare condition, to our best knowledge, only 27 cases have been reported in the English literature (Table 1). Here, we present a rare case of extragonadal YST occurring in the uterus of a 2-year-old girl, with a discussion of its clinical management in diagnosis and treatment.

Case

A 2-year-old girl presented to a local hospital with a 5-month history of intermittent
vaginal bleeding and a pelvic mass. She was born at full term with a birth weight of 4000 g, with no gestational or neonatal complications. She had no family history of cancer. Magnetic resonance imaging (MRI) revealed a large mass measuring 6.3×4.7 cm behind the bladder in the pelvic cavity without obvious metastasis and nodal abnormalities in the abdominal cavity (Fig. 1). Serum alpha-fetoprotein (AFP) was 41,250 ng/mL(<20 ng/mL), while carcinoma antigen (CA) 125 was 141 U/mL(<35 U/mL). An ultrasound-guided biopsy of the pelvic mass was performed and the histopathological and immunohistochemical studies were consistent with YST. Chemotherapy combined with cisplatin, etoposide, and bleomycin (PEB) was initiated and performed every three weeks for 4 cycles. A post-chemotherapy CT showed a reduction in the size of the pelvic mass, now measured at 2.8×2.1 cm. The serum AFP decreased to 5.81 ng/mL, and CA125 was 13.6 U/mL.

For further treatment, the patient presented to our institution, a national center for rare diseases. We conducted a comprehensive evaluation including physical examination, blood tests, and imaging examination. She was 92 cm tall (90% for age) and weighed 12.5 kg (72% for age). Normal breast development at Tanner stage 1 without growth of pubic and axillary hair. On abdominal examination, there was some fullness and mild direct tenderness in the lower abdomen. The vulva was normal, no blood or discharge was noted. The rectal bimanual examination was refused. Before the operation, we discussed the advantages and risks of more radical forms of therapy versus conservative fertility-sparing surgery with her parents, and they didn’t consider
cryopreserving ovarian tissue for fertility preservation.

On Jun 15th, 37 days after the last neoadjuvant chemotherapy, we performed vaginoscopy and laparoscopy. Vaginoscopy revealed that the cervix and vaginal mucous membrane were smooth and were not occupied by any tumor. On laparoscopy, there were no ascites in the peritoneal cavity and the peritoneal washings were negative for malignant cells. A yellow tumor, approximately 2.5 cm in diameter, protruded from the left lower segment of the uterus (Fig. 2A). During surgical exploration, the bilateral ovaries are macroscopically normal. No obvious abnormalities were observed in the inspection of peritoneal surfaces, omentum, and the upper abdominal cavity. Paraortic and pelvic lymph nodes were grossly normal without enlargement during surgical exploration. Intraoperatively, we communicate with her parents about the laparoscopic exploratory results: the tumor had infiltrated the whole myometrium, there was no chance to preserve the uterus. Finally, they agreed to a laparoscopic hysterectomy. Gross examination of the specimen showed a smooth uterine cavity, and the soft yellow tumor had infiltrated the full thickness of the uterine muscle (Fig. 2B). Microscopically, the endometrium was in the stationary phase, which appeared thin and lined by one layer of cuboidal or columnar surface epithelium. A large number of foam-like cells were seen in the lower uterine segment (Fig. 3A). Immunohistochemical staining of the tumor showed patchy positive for CD68 (Fig. 3B), 30% positive rates for Ki67, and negative for AE1/AE3, AFP, CD30, EMA, OCT3/4, SALL-4 and SOX2.

According to the Children's Oncology Group (COG) germ cell tumor staging system
(Table 2), the diagnosis of stage I uterine YST was made. On the second postoperative day, PEB chemotherapy was initiated. This cycle was repeated twice every 3 weeks. After the last chemotherapy on Jul 13th, 2020, AFP was 4.9 ng/mL. Follow-up continued monitoring of AFP levels and imaging examination was carried out. The patient remained disease-free for more than 18 months after the treatment was completed.

**Summary and Conclusion**

YST is a common histological subtype of MGCTs, which are frequently located in the ovaries and testes. Primary yolk sac tumors of the uterus are extremely rare.

In March 2021, we searched the PubMed, Cochrane library and Embase databases for articles published since 1980. A combination of the following keywords was used in the search: endodermal sinus tumor, yolk sac tumor, uterine neoplasm and uterus cancer. Only articles published in English were included. In Table 1, we summarized 27 cases of uterine YSTs and therapeutic strategies described in the literature.

To the best of our knowledge, this is the first report of uterine YST in a 2-year-old child. The age distribution of uterine YSTs seemed to be bimodal. Only approximately one-third of the patients were less than 50 years of age (10/27), whereas the majority of reported cases involved postmenopausal women.
Uterine YST is a rare pediatric malignant tumor that should be considered in the differential diagnosis for a prepubertal child with vaginal bleeding and pelvic masses. Vaginal bleeding in the prepubertal child has several etiologies including structural anomalies, endocrinologic dysfunction, infection, trauma, foreign body, and hematologic disorders. While bleeding in this age group is often benign, a comprehensive evaluation to exclude serious medical conditions is important. An ovarian mass that is abdominal in location can be confused with other abdominal masses occurring in children, such as Wilms tumor or neuroblastoma. The most commonly increased serum tumor markers in germ cell tumor patients include AFP, β-human chorionic gonadotropin (HCG), and lactate dehydrogenase. Application of tumor markers such as CA19-9, CA125, and carcinoembryonic antigen (CEA) has value in various types of pediatric cancers. Cancer biomarkers are commonly used in pediatrics to monitor cancer progression, recurrence, and prognosis, but pediatric reference value distributions have not been well established so far. The normal range of AFP in an adult is below 20 ng/mL, while CA125 is below 35 U/mL. The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) sought to develop a pediatric database of covariate-stratified reference value distributions. They found the upper limit of the 4-month to 5-year reference interval for CA125 was at 33 U/mL\textsuperscript{19}. In Sonia L. La'ulu’s study\textsuperscript{20}, AFP reference intervals decreased with increasing age and reached adult concentrations by age 3 years.

Under the guidance of ultrasound or via endoscopic examination, a biopsy of the suspicious lesions can be obtained, which can lead to a pathological diagnosis. The
diagnosis of YST should be made prior to initiation of neoadjuvant chemotherapy (NACT), even in unresectable tumors when a biopsy is possible. When it is unsafe to take a biopsy sample, the combination of typical radiological appearance and high levels of conventional tumor markers might be sufficient to make a diagnosis and start neoadjuvant chemotherapy\textsuperscript{21}. In the case series reported by Yan Lu et al.\textsuperscript{22}, the diagnosis prior to surgery in 11 patients of the NACT group was mainly dependent on the clinical features, radiology examination, and extraordinarily elevated serum AFP level. AFP plays a key role in differential diagnosis. Furthermore, exploratory laparoscopy is an effective tool for biopsy and investigation of tumor invasion\textsuperscript{23}.

Immunohistochemistry can serve as a helpful adjunctive tool for the identification of a YST component. SALL4, a pluripotent marker of germ cell differentiation, is expressed in all germ cell tumors except choriocarcinoma and is, therefore, best utilized to identify the presence of a germ cell component but has low overall specificity for YST\textsuperscript{24}. AFP has long been held as the gold standard immunomarker for YST as its specificity is high. Potential exclusionary markers include Keratin 7 and EMA, although yolk sac tumors with a glandular pattern may be focally positive for these markers. PAX-8, Napsin A, and hormone receptors are typically not expressed in YSTs.

To date, no treatment guidelines have been established for extragonadal YST. The therapeutic principles of extragonadal germ cell tumors are the same as those of their
primary gonadal counterparts. A combination of comprehensive surgery and chemotherapy appears to achieve better outcomes. Minimally invasive surgery has been proven to have a better surgical prognosis and faster recovery\textsuperscript{25}. The required components of pediatric surgical staging are a collection of peritoneal fluid or washings for cytology; inspection and palpation of peritoneal surfaces, omentum, retroperitoneal lymph nodes, and a biopsy sample of any areas of abnormality\textsuperscript{21}. There is no consensus about the role of systematic lymphadenectomy, but the omission of staging peritoneal procedures seems to increase the recurrence rate, though without impact on overall survival. Given the very high chemosensitivity of such tumors, potential nodal metastasis should be cured by adjuvant chemotherapy in these patients. Nodal dissection should be carried out only where there is evidence of nodal abnormalities during surgical exploration and/or initial CT scan \textsuperscript{26}. The systematic ovarian biopsy is not necessary when the contralateral ovary is macroscopically normal.

In a case reported by Rudaitis et al.\textsuperscript{27}, NACT with four PEB cycles was chosen as an option to reduce tumor size and minimize the extent of the surgical procedure. In our case, the preoperative histology of the YST was acquired by biopsy. NACT with four PEB cycles was administered before surgery to minimize the size of the tumor. The effects of NACT with PEB combination chemotherapy were favorable. However, the tumor had infiltrated the full thickness of the uterine muscle, a laparoscopic hysterectomy was conducted with informed consent from her parents. Laparoscopic
hysterectomy in young children has rarely been reported. Because of the small size of the uterus, delicate tissue, and limited space of the pelvic and abdominal cavities in children, it is impossible to place the uterine manipulator, which makes the surgery more difficult. The specimen was enclosed in a specimen bag and removed through an umbilical incision.

In conclusion, YST arising in the uterus is a rare malignant neoplasm. Early detection and treatment are key to improving the survival of children. It should be differentially diagnosed from other pelvic malignancies with reference to serum AFP levels and histology. Positive survival can be achieved through PEB chemotherapy and surgery. Further studies are necessary to determine the most effective and appropriate treatments.

Disclosure/conflict of interest
The authors indicate no conflicts of interest.

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References


Table 1 Summary of the reported cases for uterine yolk sac tumor

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<tr>
<th>Authors, Reference</th>
<th>Age (yr)</th>
<th>Initial symptoms</th>
<th>AFP (ng/ml)</th>
<th>Surgery</th>
<th>FIGO stage</th>
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<th>Radiotherapy</th>
<th>Outcome</th>
<th>Follow-up time (mo)</th>
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<td>28</td>
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<td>380</td>
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<td>Yes</td>
<td>No</td>
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<td>87</td>
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<td>71</td>
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**Abbreviations:**
- ABD, abdominal distension;
- ABP, abdominal pain;
- ADM, adriamycin;
- AVB, abnormal vaginal bleeding;
- AVD, abnormal vaginal discharge;
- BEP, bleomycin, etoposide, cisplatin;
- BSO, bilateral salpingo-oophorectomy;
- BVP, bleomycin, vinblastine, cisplatin;
- CTX, cyclophosphamide;
- EP, etoposide, cisplatin;
- MTX, methotrexate;
- NA, not available;
- OMT, omentectomy
- PALND, para-aortic lymph node dissection;
- PLND, pelvic lymph node dissection;
- PT, paclitaxel, carboplatin;
- RH, radical hysterectomy;
- TAH, total abdominal hysterectomy;
- VCR, vincristine;
- VAC, vincristine, actinomycin, cyclophosphamide;
- 5-FU, 5-fluorouracil;
<table>
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<th>COG Germ Cell Tumor Staging</th>
<th>Criteria</th>
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<tr>
<td><strong>I</strong></td>
<td>The tumor has been entirely removed, and tumor markers are normal</td>
</tr>
<tr>
<td><strong>II</strong></td>
<td>Microscopic traces of the tumor are still present after surgery; tumor markers do not return to normal following surgery</td>
</tr>
<tr>
<td><strong>III</strong></td>
<td>Visible traces of tumor are left behind after initial treatment, and the lymph nodes are affected</td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td>The tumor has spread from its original site to other, more distant areas of the body</td>
</tr>
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</table>
Fig. 1: MRI showing a large mass with abnormal signal measuring 6.3×4.7 cm behind the bladder in the pelvic cavity
Fig. 2 A: Laparoscopy showing a yellow tumor approximately 2.5 cm in diameter protruding from the left lower segment of the uterus; B: Specimen showing a smooth uterine cavity and the yellow soft tumor measuring at $2.5 \times 2.0$ cm infiltrating the full thickness of the uterine muscle.

Fig. 3 A: A large number of foam-like cells in the tumor (hematoxylin and eosin, $\times 200$); B: Immunohistochemical staining for CD68($\times 400$). Tumor cells are patchy positive for CD68.