

Case Report

Endometrial yolk sac tumors: a case report

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Abstract: A yolk sac tumor (YST) is a malignant tumor originating from germ cells. YST mainly arises from the gonads, rarely occurring in extragonadal sites. Endometrial yolk sac tumors are rare. In this study, a case involving a 36-year-old female with a history of irregular vaginal bleeding and elevated alfa-fetoprotein levels is presented. Multi-disciplinary clinical, laboratory, and pathological investigations contributed to the diagnosis of an unusual case of an endometrial yolk sac tumor. The patient was treated with surgery, followed by postoperative chemotherapy. Serum levels of alfa-fetoprotein were restored to normal and the patient remained free of disease for 15 months.

Keywords: Yolk sac tumor, endometrium, alfa-fetoprotein

Introduction

Yolk sac tumors (YST), also known as endodermal sinus tumors, are malignant germ cell tumors (GCT) that usually arise in the gonads, such as the testis or ovaries. Although most YSTs occur in the gonads, about 10-20% of cases arise in extragonadal sites including the mediastinum, sacrococcygeal region, retroperitoneum, cervix, vulva, pelvis, lung, head, neck, and stomach [1-5]. Patient serum levels of alfa-fetoprotein (AFP) are elevated. Primary YSTs of the endometrium are extremely rare. Currently, surgery and chemotherapy are the major treatments for such tumors. Herein, we described a case of endometrial YST in a young woman and discussed the clinical, morphological, and immunohistochemistry (IHC) features.

Case presentation

Clinical history

A 36-year-old married Chinese woman was presented in October 2014 with a 2-month history of irregular vaginal bleeding. The patient underwent a cesarean section in May 2011, from that point she was on barrier contraception. Gynecological examination showed that her enlarged cervix was characterized by grayish-

white necrotic tissues and contact bleeding. The uterus was slightly enlarged without any distinct abnormalities palpable in the bilateral adnexa. An abdominal ultrasonography also did not show any abnormalities in the liver, gallbladder, spleen, pancreas, kidneys, ureter, or urinary bladder. Magnetic resonance imaging (MRI) revealed enlarged uterine volume and a soft tissue mass measuring 8.4 × 6.3 × 6 cm³ in the cervical canal and anterior wall of the lower segment of the uterus. This mass protruded into the uterine cavity. On October 23, 2014, a biopsy specimen of the cervix excrescence revealed "clear cell adenocarcinoma". The laboratory tests detected a serum alfa-fetoprotein (AFP) level of 4597 ng/mL (reference value: 0-20 ng/mL). Serum levels of CEA, CA153, CA125, CA199, and β-HCG were within normal range. A chest computed tomography (CT) scan was negative. Frozen biopsy from an endometrial mass revealed "adenocarcinoma". Subsequently, the patient underwent surgery including total abdominal hysterectomy, bilateral salpingo-oophorectomy with pelvic lymphadenectomy, omentectomy, and appendectomy without visible residual metastases. One day post-surgery, serum AFP levels decreased dramatically to 3,008 ng/mL and 1 week after surgery AFP levels were 1,147 ng/mL. Six cycles of

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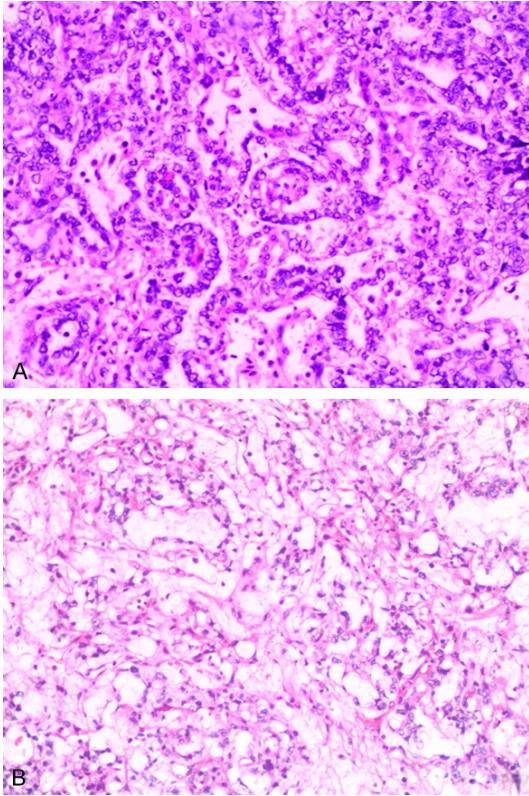


Figure 1. Histopathologic features of yolk sac tumor component: A. Yolk sac tumor (YST) with a typical Schiller-Duval body. B. Yolk sac tumor (YST) with microcapsule structures. (H&E staining, original magnification $\times 100$ magnification).

intravenous chemotherapy with docetaxel 75 mg/m² and nedaplatin 80 mg/m² were administered every 21 days. After one course of chemotherapy, the serum AFP level reached 152.9 ng/mL that further returned to normal range after two courses of chemotherapy. The patient is still alive and has remained free of disease for 22 months.

Histology and immunohistochemistry

The uterus, measuring approximately 13 \times 11 \times 3 cm³ in volume, was filled with a cauliflower-shaped tumor, measuring 5 \times 3.5 \times 3 cm³, with areas of hemorrhage and necrosis. This solid tumor presented a grayish-yellow and grayish-white cut surface with fuzzy margins. The texture of the tumor was brittle. This tumor infiltrated $>2/3$ rd of the myometrial thickness and serosa of the corpus uteri. Moreover, it invaded the cervical canal stroma but not the bilateral adnexa.

Histologically, the tumor areas presented an endodermal sinus with glandular, papillary, and

solid patterns. Typical Schiller-Duval (SD) bodies (**Figure 1A**) and microcapsule structures (**Figure 1B**) were also observed in the local area. The stroma was hypocellular, loose, and myxoid. A systematic examination of the bilateral adnexa and pelvic lymph nodes did not reveal any neoplastic transformation.

Furthermore, immunohistochemistry analysis revealed a diffused and intense positive staining of AFP, SALL4, and Glypican-3 in the focal area (**Figure 2A-C**). Her tumor did not express ER, PR, vimentin, CK20, CD30, PAX-8, WT-1, P53, β -HCG, and EMA.

Discussion

YSTs are rare malignant tumors originating from germ cells, first described by Teilmann in 1959 [1]. Nearly 85-90% of YSTs occur in reproductive organs and the remaining in other areas [2]. Some studies have reported that primary extragonadal YSTs occur in the mediastinum, sacrococcygeal region, retroperitoneum, cervix, vulva, pelvis, lung, head, neck, and stomach [3-7]. Although the histogenesis of extragonadal YSTs remains controversial, two main theories have been proposed to explain the extragonadal site [8]. The first theory is that the tumor originates from aberrant differentiation of somatic cells, which might explain occurrence of YST in the endometrium and stomach. Another hypothesis is that the tumor appears to arise from germ cells misplaced during embryogenesis and malignant transformation leads to primary germ cell tumors at extragonadal sites [9]. YSTs that originated in the endometrium are extremely rare. To the best of our knowledge, only 13 cases of primary YSTs of the endometrium have been reported in the literature [10-21] including 10 patients with pure YSTs and 3 co-existing with other endometrial malignancies (endometrial adenocarcinoma and carcinosarcoma). Herein, we reported the fourteenth case of primary YST of the endometrium. The majority of patients manifest the disease in their second and third decades of life, although there have been case reports of malignant germ cell tumors occurring in infancy as well as postmenopausal women [22, 23].

Intraoperative frozen diagnosis of YSTs without any information regarding serum levels of AFP is rather challenging. If the pathologist is equipped with this information, YSTs could have been included in differential diagnosis. In the present case, a preoperative biopsy speci-

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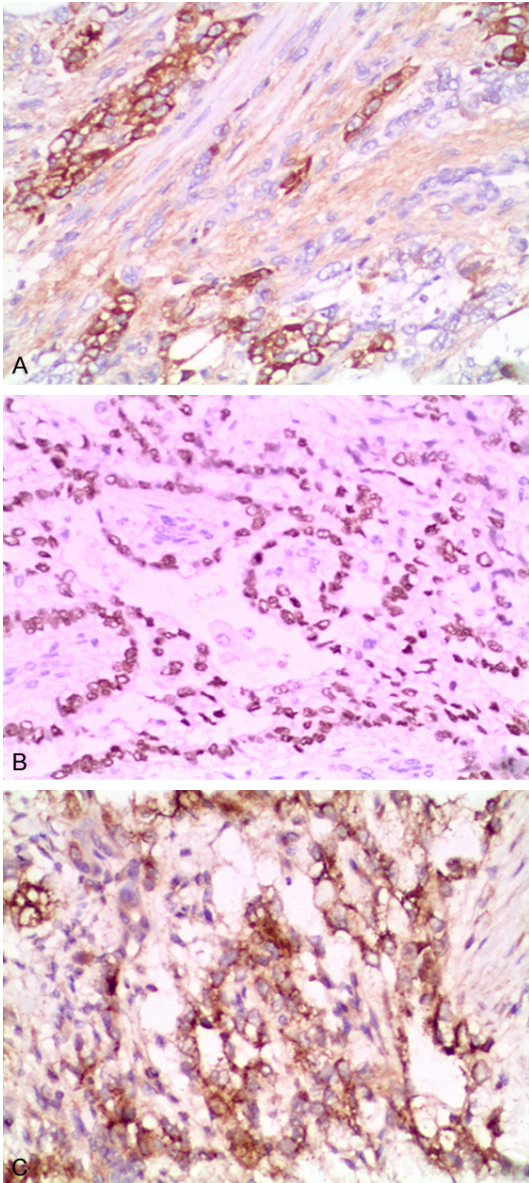


Figure 2. Envision immunohistochemical analysis: A. AFP positive expression in the yolk sac tumor component. B. SALL4 positive expression in the yolk sac tumor component. C. Glypican-3 positive expression in the yolk sac tumor component (EnVision immunohistochemistry, original magnification $\times 200$).

men of the cervix and intraoperative frozen diagnosis of endometrium were misdiagnosed as clear cell adenocarcinoma. The common histological pattern of YST is reticular, involving a labyrinth of channels lined by primitive cells focally expanded to form microcysts lined by clear or flattened and atypical epithelial cells. The stroma is hypocellular, loose, and myxoid. In classic growth, these are papillary fibrovascular structures wherein a central blood vessel is mantled by tumor cells and projected into

space lined by tumor cells (endodermal sinuses and S-D bodies). Fewer patterns include solid, tubular, glandular, and polyvesicular structures, which usually exist in different combinations and histological variants. Schiller-Duval bodies are characteristic and valuable in identification of YST. However, this structure occurs in only 20% of YST cases [8]. In this case, tumor tissues manifested the characteristics of abundant papillary and glandular structures and less S-D bodies interfered with our diagnosis.

Compared to gonadal site YSTs, accurate diagnosis of endometrial YSTs by hematoxylin-eosin (HE) staining alone would be relatively difficult, due to nonspecific clinical symptoms and imaging characteristics. Thus, immunohistochemistry staining occupies a critical role in accurate histological diagnosis of YST. PLAP, CD117, AFP, and β -HCG are routine immunohistochemistry markers for diagnosis and differential diagnosis of gonadal GCTs. AFP staining is positive in most cases of YST, however, an immunohistochemistry assay might be negative for AFP in some cases [8].

Thus, we investigated the recently described GCT markers including OCT3/4, CD117, CD30, PLAP, AFP, Glypican-3, SALL4, and β -HCG together with CK and EMA. We found that GCT markers AFP, Glypican-3, SALL4, PLAP, and CD117 showed positive expression to different degrees. Although AFP staining is strongly positive in most YST cases, AFP was positively expressed in the local area in the current case while SALL4 was expressed extensively and diffusely, but robust. Cao et al. found that SALL4 is one of the new indicators that can identify YSTs of the ovary with increased sensitivity and specificity [24]. Therefore, we speculated that, due to the lack of sensitivity and specificity of these germ cell tumor markers, combining the use of a variety of germ cell tumor markers, especially SALL4, was essential in YST cases.

Assessment of serum AFP levels is useful in diagnosing YSTs and also in monitoring response to therapy and prognosis [25]. Serum AFP levels decrease after treatment, within 2-3 weeks. In this case, the patient presented an extremely high level of serum AFP at 4597 ng/mL before the operation, decreasing rapidly postoperative. Thus, pathologists and physicians are obligated to evaluate serum tumor

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markers, including AFP, prior to operations on primary external genital tumors. In cases where tumors display epithelioid features similar to adenocarcinoma, primary YSTs of external genitals should be considered.

Surgical treatment alone is quite unsuccessful in eradicating these tumors. Improved efficiency of chemotherapy has led to better prognosis in patients with YSTs. Furthermore, cisplatin-based combination chemotherapy that includes cisplatin, etoposide, and bleomycin has been identified as the optimal regimen of adjuvant treatment for germ-cell tumors. Patients with GCT, sensitive to cisplatin-based chemotherapy, have resulted in gradual restoration of AFP to normal levels. In our current case, the morphological and immunohistochemistry pattern, elevated levels of serum AFP, and rapid decrease of AFP levels in clinical treatment were in agreement with characteristics of an endometrial YST.

Conclusion

In summary, we presented an unusual case of endometrial carcinoma with YST. Multidisciplinary clinical, laboratory, and pathological investigations contributed to diagnostic accuracy. Notably, higher serum AFP levels were gradually reduced to normal as a result of chemotherapy. However, additional molecular genetic studies will be essential in deciphering the clinical and pathophysiological mechanisms underlying these tumors.

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Disclosure of conflict of interest

None.

Abbreviations

YST, Yolk sac tumor; AFP, Alfa-fetoprotein; SD, Schiller-Duval; CK, Cytokeratin; PLAP, Placental alkaline phosphatase; ER, Estrogen receptor; PR, Progesterone receptor; EMA, Epithelial membrane antigen.

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References

- [1] Teilum G. Endodermal sinus tumor of the ovary and testis. Comparative morphogenesis of the so-called mesoepithelioma ovarii (Schiller) and extraembryonic (yolk sac-allantoic) structures of the rat's placenta. *Cancer* 1959; 12 : 1092-1105.
- [2] Nerli RB, Ajay G, Shivangouda P, Pravin P, Reddy M, Pujar VC. Prepubertal testicular tumors: our 10 years experience. *Indian J Cancer* 2010; 47: 292-295.
- [3] Sakaguchi M, Maebayashi T, Aizawa T, Ishibashi N, Fukushima S, Saito T. Successful radiotherapy in postoperative recurrence of a primary mediastinal yolk sac tumor: a case report. *Thorac Cancer* 2016; 7: 358-362.
- [4] Akasbi Y, Najib R, Arifi S, Lakranbi M, Smahi M, Mellas N, ELMesbahi O. Complete histologic response to chemotherapy in a patient with a mediastinal yolk sac tumor: a case report. *BMC Res Notes* 2014; 7: 803.
- [5] Choi JE, Choe AR, Yoon SE, Nam EM, Park H, Lee KE. Germ cell tumor targeting chemotherapy in gastric adenocarcinoma with an endodermal sinus tumor component: a case report. *Chemotherapy* 2017; 62: 54-57.
- [6] Arumugam D, Thandavarayan P, Chidambaram L, Boj S, Marudasalam S. Primary nasopharyngeal yolk sac tumor: a case report. *J Clin Diagn Res* 2016; 10: ED06-7.
- [7] Sakamoto Y, Nagaoka T, Tamura K, Kaneko H. A case report of a metastatic yolk sac carcinoma in the pulmonary artery of a young female Sprague-Dawley rat. *Toxicol Pathol* 2016; 29: 269-273.
- [8] Kim SW, Park JH, Lim MC, Park JY, Yoo CW, Park SY. Primary yolk sac tumor of the omentum: a case report and review of the literature. *Arch Gynecol Obstet* 2009; 279: 189-192.
- [9] Yao XD, Hong YP, Ye DW, Wang CF. Primary yolk sac tumor of seminal vesicle: a case report and literature review. *World J Surg Oncol* 2012; 10: 189.
- [10] Abhilasha N, Bafna UD, Pallavi VR, Rathod PS, Krishnappa S. Primary yolk sac tumor of the endometrium: a rare entity. *Indian J Cancer* 2014; 51: 446.
- [11] Pileri S, Martinelli G, Serra L, Bazzocchi F. Endodermal sinus tumor arising in the endometrium. *Obstet Gynecol* 1980; 56: 391-396.
- [12] Clement PB, Young RH, Scully RE. Extraovarian pelvic yolk sac tumors. *Cancer* 1988; 62: 620-626.

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- [13] Ohta M, Sakakibara K, Mizuno K, Kano T, Matsuzawa K, Tomoda Y, Nakashima N, Ogawa T. Successful treatment of primary endodermal sinus tumor of the endometrium. *Gynecol Oncol* 1988; 31: 357-364.
- [14] Joseph MG, Fellows FG, Hearn SA. Primary endodermal sinus tumor of the endometrium. A clinicopathologic, immunocytochemical, and ultrastructural study. *Cancer* 1990; 65: 297-302.
- [15] Spatz A, Bouron D, Pautier P, Castaigne D, Duvillard P. Primary yolk sac tumor of the endometrium: a case report and review of the literature. *Gynecol Oncol* 1998; 70: 285-288.
- [16] Patsner B. Primary endodermal sinus tumor of the endometrium presenting as "recurrent" endometrial adenocarcinoma. *Gynecol Oncol* 2001; 80: 93-95.
- [17] Oguri H, Sumitomo R, Maeda N, Fukaya T, Moriki T. Primary yolk sac tumor concomitant with carcinosarcoma originating from the endometrium: case report. *Gynecol Oncol* 2006; 103: 368-371.
- [18] Rossi R, Stacchiotti D, Bernardini MG, Calvieri G, Lo Voi R. Primary yolk sac tumor of the endometrium: a case report and review of the literature. *Am J Obstet Gynecol* 2011; 204: e3-4.
- [19] Wang C, Li G, Xi L, Gu M, Ma D. Primary yolk sac tumor of the endometrium. *Int J Gynaecol Obstet* 2011; 114: 291-293.
- [20] Ji M, Lu Y, Guo L, Feng F, Wan X, Xiang Y. Endometrial carcinoma with yolk sac tumor-like differentiation and elevated serum β -hCG: a case report and literature review. *Onco Targets Ther* 2013; 6: 1515-1522.
- [21] Qzler A, Dogan S, Mamedbeyli G, Rahatli S, Haberal AN, Dursun P, Ayhan A. Primary yolk sac tumor of endometrium: report of two cases and review of literature. *J Exp Ther Oncol* 2015; 11: 5-9.
- [22] Thiele J, Castro S, Lee KD. Extragenital endodermal sinus tumor (yolk sac tumor) of the pelvis. *Cancer* 1971; 27: 391-396.
- [23] Oh C, Kendler A, Hernandez E. Ovarian endodermal sinus tumor in a postmenopausal woman. *Gynecol Oncol* 2001; 82: 392-394.
- [24] Cao D, Guo S, Allan RW, Molberg KH, Peng Y. SALL4 is a novel sensitive and specific marker of ovarian primitive germ cell tumors and is particularly useful in distinguishing yolk sac tumor from clear cell carcinoma. *Am J Surg Pathol* 2009; 33: 894-904.
- [25] Yang LG, Ying LZ, Jian QZ. Prognostic value of serum α -fetoprotein in ovarian yolk sac tumours: a systematic review and meta analysis. *Mol Clin Oncol* 2015; 3: 125-132.