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Case report

Yolk sac tumor of the endometrium in a post-menopausal woman: Case report and review of the literature

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1. Introduction

A yolk sac tumor (YST) is a germ cell tumor (GCT) that primarily arises in the ovary. YST account for 10–20% of all malignant ovarian GCT (Hoffman, et al., 2016). These alpha-fetoprotein (AFP) producing tumors have been reported to also occur in extra-gonadal sites in the pelvis such as the cervix, vagina, vulva, and bladder, as well as extra-pelvic sites such as the mediastinum and ear (Euscher, 2017). Few reports have been published on primary YST of the endometrium, especially in post-menopausal females (Zhang, 2020; Patsner, 2001; Oguri et al., 2006; Damato et al., 2016). We present a case of primary YST of the endometrium in a post-menopausal woman with a review of the literature.

2. Case Presentation

A 73-year-old multiparous post-menopausal female with history of diabetes, hypertension, and hyperlipidemia presented to her gynecologist with complaints of abdominal distension and bloating. She denied vaginal bleeding or discharge. Gynecologic history included a fibroid uterus and normal Pap smears. Pelvic ultrasound imaging revealed a 15.7 × 9.1 × 12.7 cm markedly distended uterus with hypo-echoic material and a 7 × 4.1 × 5.4 cm heterogeneous soft tissue echogenic polypoid mass in the inferior portion of the endometrial cavity. Previous imaging performed eight years prior for history of asymptomatic fibroid uterus showed an 8.3 cm fibroid uterus with mild to moderate retained fluid in the endometrial cavity, bilateral ovaries and fallopian tubes within normal limits. She was referred to a gynecologic oncologist for consultation of the uterine mass and thickened endometrium. Physical exam was notable for an eighteen-week sized uterus with normal appearing cervix and palpably normal parametria on bimanual examination. An endometrial biopsy was inconclusive secondary to insufficient tissue for pathologic evaluation. Serum CA-125 drawn at time of consultation was 13 U/mL.

Soon after initial consultation, she presented to the emergency department with persistent lower abdominal pain. Lab studies were notable for leukocytosis to 23.3 K/uL. She was admitted to rule out pelvic infection and empirically started on Piperacillin/Tazobactam. Abdomen and pelvis computed tomography (CT) imaging confirmed an enlarged uterus with a markedly dilated endometrial cavity, a lower uterine segment mass, and no evidence of extra-uterine disease or lymphadenopathy (Fig. 1). Chest CT was negative for metastatic disease. On hospital day three, her bloodwork revealed persistent leukocytosis despite antibiotic therapy. The decision was made to proceed with surgery for suspicion of uterine malignancy with possible infection.

The patient underwent an exploratory laparotomy, total abdominal

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hysterectomy, bilateral salpingo-oophorectomy with a gynecologic oncologist. Intra-abdominal survey revealed a globular 16 cm, enlarged uterus with grossly normal bilateral fallopian tubes and ovaries. No ascites, carcinomatosis or pelvic or *para*-aortic lymphadenopathy was noted. The remainder of her abdominal survey was within normal limits and without evidence of gross infection. Intra-operative frozen section pathology revealed a high-grade malignant neoplasm, invasive to more than 50% of the myometrium. Decision was made to perform staging with pelvic and *para*-aortic lymph node dissection and omental biopsy. Post-operatively, the antibiotics were discontinued and the patient recovered well. Her WBC count decreased to 14.3 K/uL and she was discharged home on post-operative day three.

3. Pathology

Grossly, the tumor measured 4 cm in the greatest dimension and originated in the lower uterine segment. It was mostly polypoid and located in the endometrial cavity. Focal myometrial invasion of approximately 43% of the myometrial thickness was identified. The tumor had solid and focally tubulo-cystic architecture and the neoplastic cells had clear cytoplasm and high-grade nuclear atypia (Fig. 2). No hyaline globules were identified. No coexisting conventional endometrial carcinoma and no atypical or other endometrial hyperplasia of the background endometrium could be identified. The omentum and pelvic and *para*-aortic lymph nodes were negative for tumor.

Immunostaining showed that the tumor was diffusely positive for cytokeratin AE1/AE3, while only rare cells were positive for epithelial membrane antigen (EMA). The tumor was diffusely positive for AFP, glypican 3 and SALL4, and negative for estrogen receptors, PAX8, napsin A, monoclonal carcinoembryonic antigen (CEA), vimentin, calretinin, inhibin, WT1, CD10, desmin, smooth muscle actin, HMB-45 and melan-A (Fig. 2). There was a minute (approximately 0.01 cm) cluster of atypical clear cells in the right ovarian hilum, which was suspicious for metastatic tumor, but this could not be confirmed with immunohistochemical (IHC) stains, since the focus was exhausted in the immunostained sections.

4. Outcome

Final pathology revealed a stage IIIA endometrial YST due to the suspicious cluster of atypical cells in the right ovarian hilum. Serum AFP drawn one month post-operatively was notably elevated to 10.5 ng/mL (upper normal limit: 8.3 ng/mL). The remainder of her tumor markers, including CA-125, hCG and LDH were within normal limits. Following GOG protocol 78 for ovarian GCT, she completed four cycles of adjuvant chemotherapy with etoposide and cisplatin (EP). She was not a candidate for bleomycin due to abnormal pulmonary function tests. Her AFP levels have since been within normal limits and she was clinically and radiographically disease free at 15 months since surgical diagnosis.

5. Discussion

Our case report adds to the few published cases of primary endometrial YST in post-menopausal women. Careful diagnosis and awareness of endometrial YST as an entity must be accounted for as there is a propensity for these tumors to be mistaken as more commonly encountered carcinomas due to overlapping morphologic and IHC features (Euscher, 2017; Euscher, 2019). Specifically, YST's are most likely to be mistaken for clear cell carcinomas, which express similar epithelial markers as YST (cytokeratin, EMA) but not similar tumor markers (CA-125 vs AFP) (Zhang, 2020; Euscher, 2019).

YST neoplasms are typically tan to gray in color, solid and cystic character with a grossly smooth external surface, unless there is invasion into surrounding structures. They additionally appear with hemorrhage with or without necrosis (Zhang, 2020; Oguri et al., 2006; Euscher, 2019). Several histologic patterns exist, including reticular or micro cystic, mesh-like, endodermal sinus (festoon) with Schiller-Duval bodies, as well as polyvesicular vitelline, enteric, solid, parietal, glandular, endometrioid-like, hepatoid, and mesenchymal. IHC staining of the cytoplasm is typically notable for keratin and AFP, negative for PAX8 and estrogen receptors, and variable staining for EMA (Euscher, 2019).

Ultimately, our gross specimen and IHC results were consistent with a YST and is similar to previously reported IHC profiles of YSTs in older patients. Additionally, our tumor was diffusely positive for p53, consistent with a TP53 mutation. Furthermore, our tumor was negative for napsin A, arguing against clear cell carcinoma, and negative for calretinin and inhibin, arguing against sex cord-stromal-like tumor.

We found eighteen cases (Table 1) of endometrial YST in post-menopausal females in our review of the English literature (**S1**). Of these cases, seven reported pure YST; the remainder coincided with GCT (1/18) or other endometrial pathologies: endometrioid/adenocarcinoma (5/18), undifferentiated or not otherwise specified (4/18), serous carcinoma (3/18), uterine carcinosarcoma/malignant mixed Müllerian tumor (2/18), clear cell carcinoma (1/18), and complex atypical hyperplasia (1/18). Most patients presented with abnormal vaginal

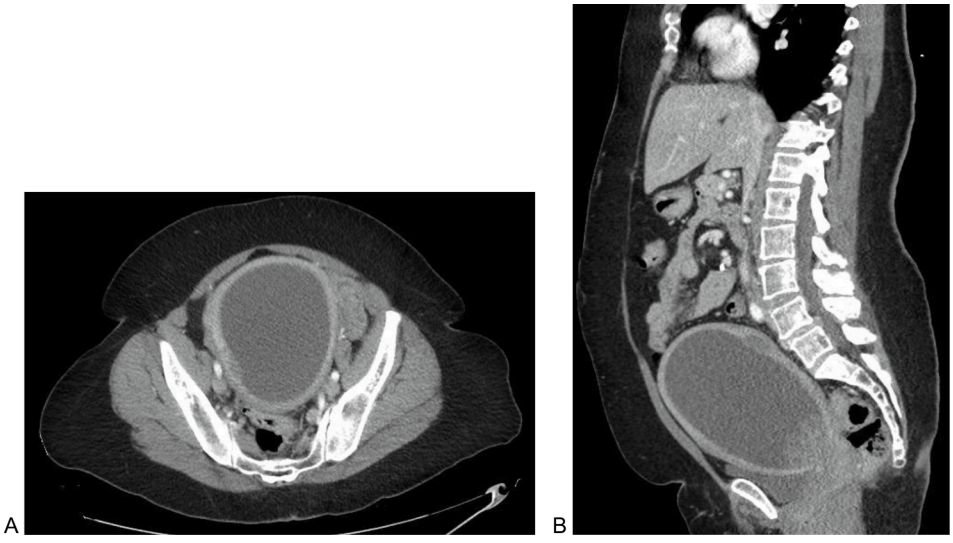

Fig. 1. CT imaging axial [A] and sagittal [B] views of the uterus demonstrating an enlarged uterus with complex mass with cystic and solid component measuring 15 × 8.5 × 9.8 cm.

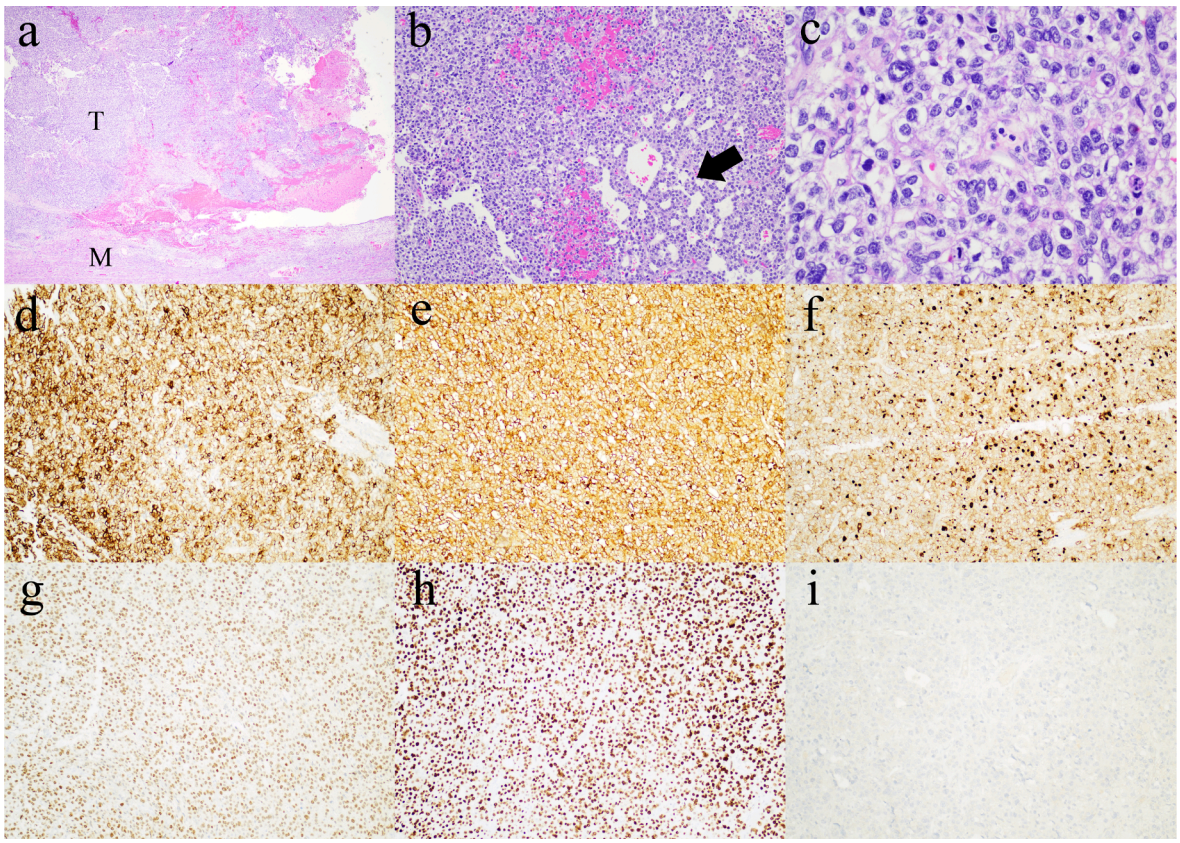

Fig. 2. [a] The tumor (T) is polypoid and mostly distinct from the myometrium (M). Focally, it invaded less than 50% of the myometrial thickness (not shown). Hematoxylin and eosin (H&E), original magnification ×20. [b] The architecture of the tumor is solid and focally tubule-cystic (arrow). H&E, original magnification ×100. [c] Tumor cells have clear cytoplasm and high-grade nuclear atypia. No hyaline globules were identified. H&E, original magnification ×400. [d] The tumor was diffusely positive for cytokeratin AE1/AE3. Immunostain for cytokeratin AE1/AE3, original magnification ×100. [e] The tumor was diffusely positive for alpha-fetoprotein (AFP). Immunostain for AFP, original magnification ×100. [f] The tumor was positive for glypican 3. Immunostain for glypican 3, original magnification ×100. [g] The tumor was positive for SALL4. Immunostain for SALL4, original magnification x100. [h] The tumor showed diffuse, strong positive staining for p53, consistent with a TP53 mutation. Immunostain for p53, original magnification ×100. [i] The tumor was completely negative for PAX8. Immunostain for pAX8, original magnification ×100.

bleeding or discharge of multiple weeks to months duration and AFP level was elevated pre-or postoperatively, when reported. Of the reports that documented the specific procedure, a total or modified radical hysterectomy with bilateral salpingo-oophorectomy was performed in most cases.

YSTs in post-menopausal women, especially primary endometrial YST, are rare and thought to arise from pre-existing somatic epithelial neoplasms. The suggested mechanisms of extra-gonadal YST histogenesis include: (1) misplaced or arrested migration of germ cells during embryogenesis, (2) reverse migration of germ cells, (3) aberrant or *retro*-differentiation of somatic tumor cells to more primitive ones, (4) specialized differentiation from a somatic carcinoma, (5) arising from residual fetal tissue following incomplete abortion, and (6) metastasis from an occult primary germ cell tumor of the gonad (Euscher, 2019). Specifically for patients with uterine YST, the mechanisms regarding somatic carcinoma derived from a pluripotent somatic stem cell, *retro*-differentiation of mature cells to embryonal cells, and stalled migration of pluripotent germ cells have been emphasized in *peri*-menopausal or post-menopausal patients (Simpson et al., 2019).

In our case, any of these possible mechanisms are feasible. The fifth and sixth proposed mechanisms can be applied to our patient with her history of two aborted pregnancies and the minute focus of involvement of the right ovary on pathology that was suggestive of metastatic YST, respectively. Although no adjacent coexisting conventional endometrial carcinoma was identified in our case, the YST had evidence of a mutated TP53 gene which is more consistent with a high-grade endometrial carcinoma than with a germ cell tumor (Liu, 1995). Therefore, it is possible that our YST arose in a pre-existing somatic endometrial neoplasm and overgrew the original carcinoma, thereby supporting the third and fourth proposed mechanisms.

Standard recommended treatment for ovarian GCTs is bleomycin, etoposide, and cisplatin (BEP) following the 1994 GOG study (GOG protocol 78). This study revealed that three courses of adjuvant BEP after completely resected ovarian GCTs nearly always prevented recurrence (Williams et al., 1994). Our review of primary endometrial YST cases which specified treatment with BEP, three of the four cases were NED at more than six months (fifth case with patient expiration secondary to septic shock is not included). However, two instances of progressive (Patsner, 2001) and recurrent cancer (Damato et al., 2016) were reported despite BEP. In the case report with recurrence, the initial stage of disease was IB and that patient received adjuvant vaginal brachytherapy. This further supports adjuvant BEP to prevent disease recurrence.

Ultimately, information regarding primary endometrial YST in post-menopausal women is derived from case reports, such as ours. Although cytoreductive surgery, adjuvant therapy with BEP and active surveillance with trending of AFP appears to be a successful approach to treatment, we recommend continued close follow-up as the rarity of this disease precludes larger studies to predict behavior. Investigation into the particular genetic alterations associated with endometrial YST may further elucidate the histiogenesis of the disease.

Table 1
Cases in the English literature of primary YST of the endometrium in postmenopausal aged patients.

Reference	Age, y	Presentation Initial surgery	Alpha fetoprotein (AFP), pre- or postop	Final pathology	Stage	Adjuvant therapy	Recurrence site and treatment	RFS d = days mo = months	OS, mo
Spatz, 1998	49	Abnormal bleeding TAH, BSO, iliac LND	3.4 μg/L 28mo postop	YST	IA	EBRT	Did not recur	N/A	>28
(Patsner, 2001)	59	Postmenopausal bleeding TAH, BSO, PLND omentectomy	27, 670 IU/mL during 2nd surgery	YST	IB	Brachy-therapy	Liver, diaphragm; AFP 27,670 U/mL intraop -> 8,750 3d postop liver, rectosigmoid, PALN BEP x4, EP x2 Plan for 2nd line CT	89d 16mo	>30
Oguri, 2006	65	Watery discharge MRAH, BSO, PLND; 2nd surgery: PALND	2306 ng/mL preop	YST, UCS	IIIC	TC x5	Did not recur	N/A	NR
Ozler, 2015	57	Abdominal pain TAH, BSO, PPALND, omentectomy	31,844 IU/mL preop	YST	IVB	BEP	Expired due to septic shock in post-op period	N/A	less than1
Damato, 2016	63	Postmenopausal bleeding TAH, LSO, omentectomy, appendectomy	244.6 IU/mL 6w postop -> 101.4 IU/mL 10w postop	YST, focal microscopic G1 endometrioid adenocarcinoma	IVB	BEP x3	Liver, lung, intra-abdomen, progressive	6mo	NR
Ravishankar, 2017	71	NR Surgery	NR	YST, serous endometrioid carcinoma	IIIA	NR	NR	NR	DOD, 19
	55	NR Surgery	NR	YST, complex hyperplasia	II	CT/RT	NR	NR	DOD, 16
	59	NR None	NR	YST	N/A	NR	NR	NR	LTF
	68	NR Surgery	NR	YST	IV	CT	NR	NR	DOD, 14
	77	NR Not available	NR	YST, endometrioid carcinoma, undifferentiated carcinoma	IIIC	CT/RT	NR	NR	LTF
	64	NR Surgery	NR	YST, adenocarcinoma, NOS	IIIA	CT/RT	NR	NR	DOD, 23
	87	NR Surgery	NR	YST, adenocarcinoma, NOS	II	CT	NR	NR	AWD, 7
	61	NR Surgery	NR	YST	IA	CT	NR	NR	AWD, 8
	63	NR Surgery	NR	YST, MMMT	IIIC1	CT/RT	NR	NR	NED, 5
	62	NR Surgery	NR	YST, serous carcinoma	IB	CT	NR	NR	AWD, 30
	77	NR Surgery	NR	YST, serous, clear cell, undifferentiated carcinoma	IIIC2	CT	NR	NR	AWD, 17
Lin, 2019	68	Abnormal bleeding TAH-BSO, PPALND, omentectomy	133.4 ng/mL postop	YST	II	BEP x6	Did not recur	N/A	>6
Zhang, 2020	65	Abnormal bleeding TAB, BSO	359 ng/mL preop	YST, embryonal carcinoma, focal immature teratoma, mature teratoma	IA	BEP x3	Did not recur	N/A	>15
Present case	73	Abdominal distention TAH, BSO, PPALND, partial omentectomy	10.5 postop	YST	IIIA	EP x4	Did not recur	N/A	>14

Key: AWD = alive with disease; BEP = bleomycin, etoposide, cisplatin; BSO = bilateral salpingo-oophorectomy; CT = chemotherapy; DOD = died of disease; EBRT = external beam radiation therapy; EP = etoposide, cisplatin; G1 = FIGO grade 1; LND = lymph node dissection; LTF = lost to follow-up; MMMT = malignant mixed Müllerian tumor; MRAH = modified radical abdominal hysterectomy; NACT = neoadjuvant chemotherapy; N/A = not applicable; NED = no evidence of disease; NR = not reported; OS = overall survival; PALN = *para*-aortic lymph node; PALND = *para*-arotic lymph node dissection; PEV = cisplatin, etoposide, vincristine; PLND = pelvic lymph node dissection; PPALND = pelvic and *para*-aortic lymph node dissection; RFS = recurrence free survival; RT = radiation therapy, TAH = total abdominal hysterectomy; TC = paclitaxel, carboplatin; UCS = uterine carcinosarcoma.

6. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review on request.

Author contributions

R Sinha made contributions to conceptualization, data curation, drafting and revising the manuscript. B Bustamante made contributions to conceptualization, data curation, drafting and revising the manuscript. A Truskinovsky made contributions to pathology analysis and drafting the manuscript. GL Goldberg made contributions to supervision, conceptualization, drafting and revising the report. K Shih made contributions to supervision, conceptualization, patient care, drafting and revising the report. All authors read and approved the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2021.100748.

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