Case report

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

Risha Sinha a, Bethany Bustamante a, Alexander Truskinovsky b, Gary L. Goldberg a, Karin K. Shih a,*

a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Zucker School of Medicine at Hofstra/Northwell, Northwell Health, 270-05 76th Avenue, Suite C-221, New Hyde Park, NY 11040, United States

b Department of Pathology, Northwell Health, 6 Ohio Drive, Suite 202, Lake Success, NY 11042, United States

ARTICLE INFO

Keywords:
Extragonadal germ cell tumor
Yolk sac tumor
Endometrial cancer
Postmenopausal

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...
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 tumor had solid and focally tubulo-cystic architecture and the neoplastic approximately 43% of the myometrial thickness was identified. 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.

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, serum 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 (festival) 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.](image-url)
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 second 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.

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.
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 – 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 | 89d | >30 |
| Oguri, 2006 | 65     | Watery discharge | MRAH, BSO, PLND; 2nd surgery: PALND | 2306 ng/mL preop | YST, UCS | IIC | 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 0w 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      | Surgery | NR | YST, serous endometrioid carcinoma, undifferentiated carcinoma | IIA | NR | NR | NR | DOD, 19 |
| 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 | IIA | 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-aortic 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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