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Case report

Somatic yolk sac differentiation in tumors of the gynecologic tract: A report of two cases and review of the literature

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1. Introduction

Yolk sac tumor (YST) is a type of malignant germ cell tumor (GCT) that morphologically recapitulates the fetal yolk sac (Rutgers, 1987). YSTs typically present in younger women (frequently younger than 20) as a pure YST or part of a mixed GCT (Rutgers, 1987; Skala, 2020). YST differentiation (YSTd) was first reported in association with an ovarian epithelial carcinoma (ovarian endometrioid carcinoma) by Rutgers *et al* (Rutgers, 1987). The authors describe an ovarian mass in a 50-year-old woman showing an endometrioid carcinoma (EC) containing foci of YST. Trophoblastic differentiation in somatic neoplasms ranges from hormonal secretion only, hormonal secretion with syncytiotrophoblast-like giant cells, to areas morphologically indistinguishable from a GCT (Rutgers, 1987). The authors proposed the term neometaplasia to describe the process of germ cell differentiation in a carcinoma and hypothesized a somatic/carcinomatous origin for the germ cell components (Rutgers, 1987).

We report two cases of malignant ovarian tumors associated with somatic YSTd. Case 1 is a patient with an ovarian EC with somatic YSTd. Case 2 is a patient with sarcomatous overgrowth (SO) of an ovarian adenosarcoma with focal somatic YSTd. Somatic YSTd arising from an adenosarcoma has not previously been reported.

2. Case 1

2.1. Case presentation:

A 65-year-old nulliparous woman was referred to our center for a large pelvic mass. She complained of abdominal bloating, discomfort, and distention for one year. Contrast-enhanced computed-tomography (CT) scan (Fig. 1) showed a pelvic mass measuring 28.9 × 20.4 × 26.5 cm with solid components and a small amount of ascites. There was a 2.2 cm ill-defined expansile sclerotic lesion in the manubrium and a borderline enlarged left retropectoral lymph node. Serum tumor markers showed: CA125 = 716 U/mL, CA19-9 = 480 U/mL, carcinoembryonic antigen (CEA) = 2.7 ug/mL, and lactate dehydrogenase (LDH) = 249 U/L. Her past medical history was significant for osteoarthritis, high body mass index (BMI) (40 kg/m2), cholecystectomy, and remote measles and mumps infection. She quit smoking more than 30 years ago. Her family history was insignificant for malignancy. Menarche was at the age of 13 and menopause at age 55. She had lifelong regular menstrual cycles and never used oral contraceptive pills (OCP) or hormone replacement therapy (HRT).

The patient underwent a midline total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH BSO), and staging, which included bilateral pelvic lymph node dissection, infracolic omentectomy, appendectomy, small bowel resection, and pelvic washing. There was a 20 cm mass arising from the right ovary adherent to the sigmoid

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colon. Frozen histological assessment reported an EC. The patient was discharged home post-operative day 4.

2.2. Pathology:

The final pathology showed ovarian EC (FIGO grade 1) with somatic YSTd arising in the right ovary with areas suspicious for surface involvement (Fig. 1). The somatic YSTd comprised 36 % of the tumor and was discrete from the EC areas. Endometriosis was present on both ovaries, uterine serosa, and small bowel serosa. The pelvic fluid cytology and pelvic lymph nodes were negative for malignancy. The mismatch repair (MMR) immunohistochemistry (IHC) profile was normal. On IHC staining, the YST component was positive for Glypican 3 and CDX2 and negative for ER and PAX8. The EC component was positive for ER, p16 (mosaic pattern), and PAX8 and negative for Glypican 3 and CDX2. Both components were negative for WT1 and showed wild-type staining with p53.

2.3. Outcome:

Tumor board review recommended six cycles of Carboplatin AUC 5 and Paclitaxel 175 mg/m^2 every-three weeks. Chemotherapy was started nine weeks after the surgery. The treatment was delayed for one week after cycle four due to neutropenia. A follow-up CT scan showed no evidence of residual disease. The left retropectoral lymph node had decreased in size and the bony lesion remained unchanged. Serum tumor markers reverted to normal after chemotherapy. The patient was in remission during her last follow-up nine months after chemotherapy treatment.

3. Case 2

3.1. Case presentation:

A 75-year-old woman (G3P2A1) was referred to our center for a large pelvic mass and ascites. Fifteen years previously, she had an abdominal TAH BSO and staging for postmenopausal bleeding, thickened endometrial lining, and a large complex adnexal cyst with normal serum tumor markers. The previous pathology was reported as an ovarian serous cystadenofibroma and endometrial hyperplasia without atypia, hence, she was discharged from gynecologic oncology clinic.

Menarche commenced at age 11 and menopause at age 58 with regular menstrual periods. She used an OCP for two years and had never used HRT. She quit smoking more than 55 years ago. Her mother was diagnosed with breast cancer at age 65 and her grandmother had pancreatic cancer at age 80.

A large pelvic mass with ascites was present on CT scan (Fig. 2). Core biopsy showed a high-grade malignant tumor, unable to further classify. Her serum CA125 was elevated (589 U/L), whereas serum CEA, CA 19–9, and LDH were normal. She underwent debulking surgery and was found to have two large masses in the pelvis with ascites. Both masses were resected without residual disease. Her postoperative period was unremarkable.

3.2. Pathology:

The first mass was received in two fragments (23 cm and 17 cm in largest dimension) and the second mass measured 18 cm is largest dimension. The first mass was an adenosarcoma and the second mass was an adenosarcoma with SO and focal somatic YSTd (Fig. 2). The area of somatic YSTd comprised less than 5 % of the overall tumor volume and was enveloped within the SO. The SO was homologous, monomorphic, and mitotically active with areas of necrosis. IHC showed the SO was positive for WT1, PR (focal), CyclinD1 (focal), and CD117 (focal) and negative for cytokeratin AE1/3, PAX8, CD10, ER, Desmin, Caldesmon, and Myogenin. ARID1B, INI1, BRG1, MSH6, and PMS2 were intact (normal). Glypican 3 and CDX2 highlighted the small focus of somatic YSTd (Fig. 2). p53 was wild type in both components. Custom panel based RNA fusion analysis that included nearly all previously reported genetic fusions in ovarian and uterine tumors was negative for genetic

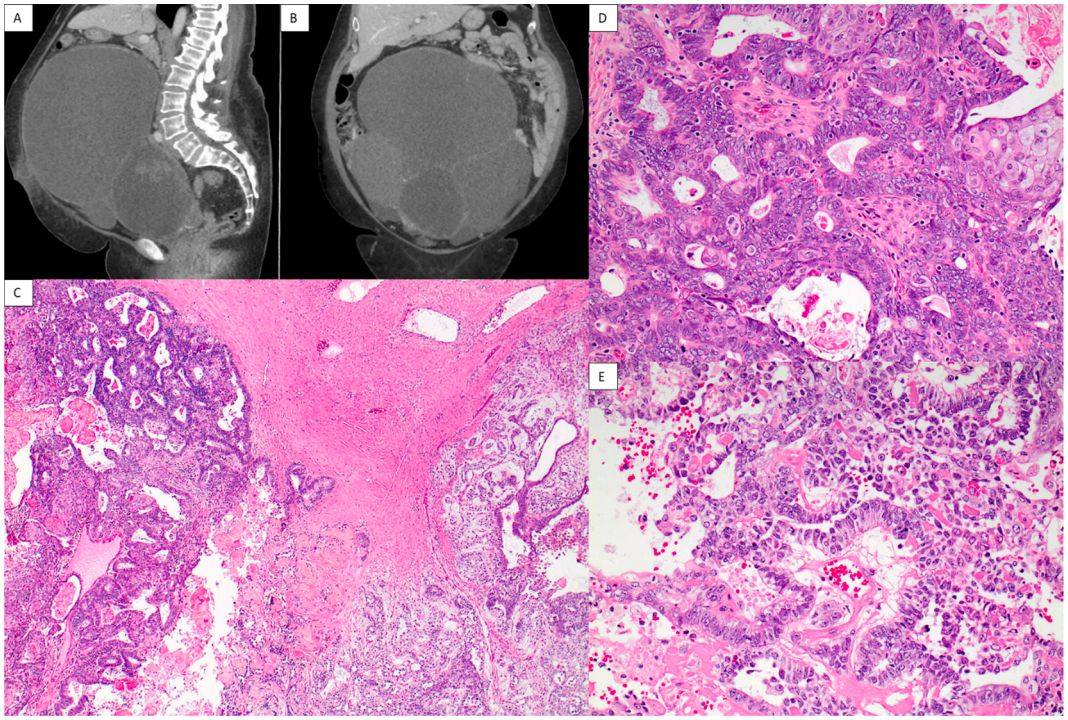

Fig. 1. Preoperative CT scan, sagittal view (A) and coronal view (B), showing a large complex multiloculated mixed cystic/solid mass in the pelvis measuring 28.9 × 20.4 × 26.5 cm. Representative images from the ovarian mass showing the endometrioid carcinoma with somatic yolk sac tumor differentiation at 4x magnification (C), endometrioid carcinoma at 20x magnification (D), and yolk sac tumor at 20x magnification (E).

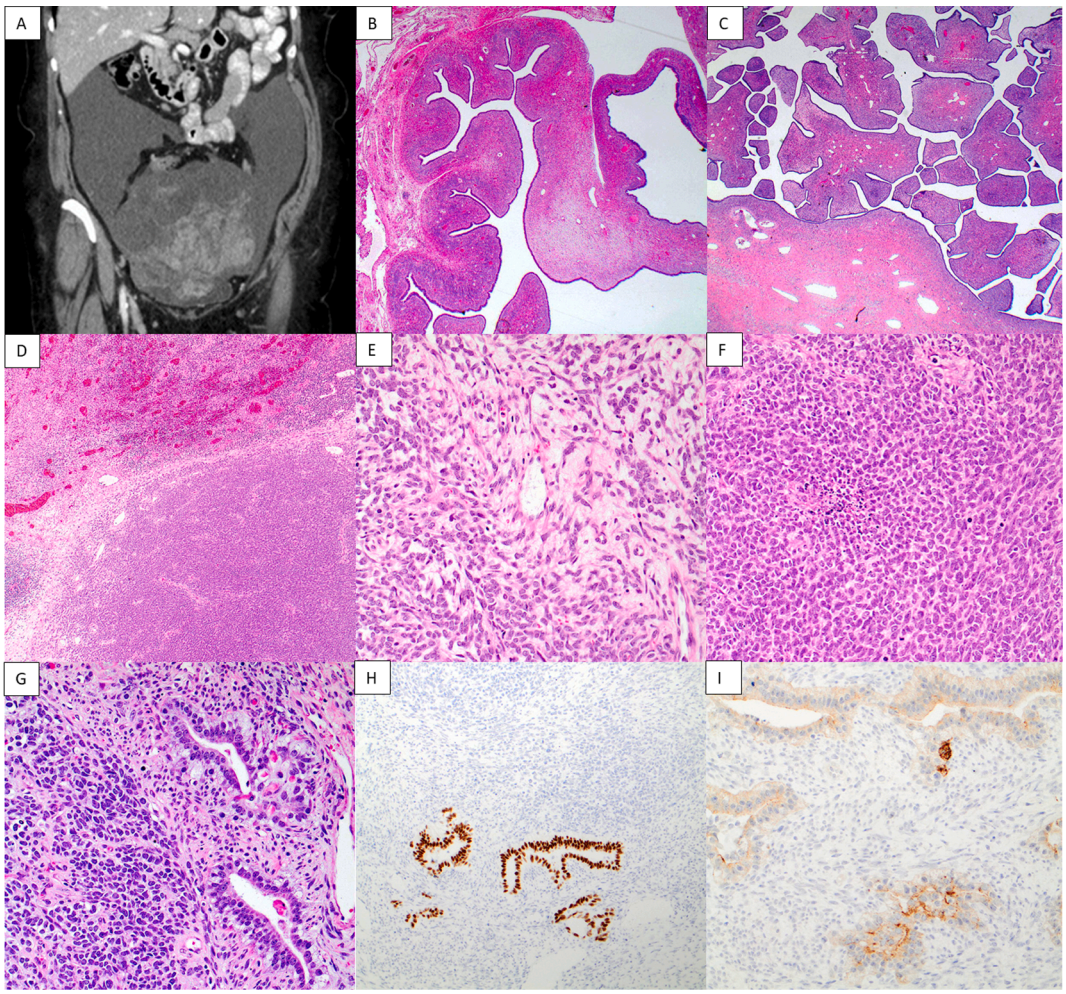

Fig. 2. Preoperative CT scan, coronal view, showing a large pelvic mass measuring 20.1 × 16.7 cm (A). Representative images from the previously resected ovarian tumor at 2x magnification (B) and recurrent tumor showing the adenosarcoma at 2x magnification (C). Representative images from the sarcomatous overgrowth at 4x magnification (D) and 20x magnification (E, F). Sarcomatous overgrowth with somatic yolk sac tumor differentiation 20x magnification (G), CDX2 immunohistochemistry 10x magnification (H), Glypican 3 immunohistochemistry 20x magnification (I).

fusions.

3.3. Outcome:

Tumor board review recommended dual platinum-based chemotherapy. She declined further treatment and follow-up.

4. Discussion

Since the initial report by Rutgers *et al*, multiple case reports and series describing germ cell differentiation associated with carcinomas have been published. Skala *et al* described eight YSTs (six arising in the ovary and two in the endometrium) in patients over the age of 35; six cases were associated with an epithelial component (Skala, 2020). The YST components harbored similar mutations to their respective epithelial carcinomas: *PTEN, PIK3CA, FGFR2, CTNNB1* in those associated with ECs and *TP53* and *PIK3CA* in those associated with high-grade carcinomas, supporting the theory that YSTd is somatically derived from the carcinoma component (Skala, 2020). Of note, isochromosome 12p (i(12p)), a genetic abnormality associated with malignant GCTs arising in younger patients, was found in three cases associated with high-grade carcinomas (in addition to *TP53* and *PIK3CA* mutations). In these cases, i(12p) was postulated to be secondary to chromosomal instability and aneuploidy; most cases had a poor prognosis (Skala, 2020). Acosta *et al* tested nine tumors of the gynecologic tract (six ovarian and three uterine) with epithelial and germ cell/trophoblastic components (seven with YSTd, one with choriocarcinoma differentiation, and one with epithelioid trophoblastic tumor differentiation) and demonstrated shared mutations between the epithelial and germ cell/trophoblast components (Acosta, 2020). Similar to Skala *et al*, the shared mutations were driver mutations typically described for the respective epithelial components (Acosta, 2020). In contrast to Skala *et al*, none of the YST components showed i(12p), however, four of the cases showed aneuploidy of chromosome 12 (Acosta, 2020). All of the tumors tested showed high copy number variations (CNVs), suggesting that germ cell/trophoblastic differentiation may reflect genomic instability (Acosta, 2020). The largest case series described 18 cases of YST in women over 40; seventeen cases were ovarian primaries and one was a uterine primary (McNamee, 2016). A total of 31 cases of ovarian carcinoma with somatic YSTd including outcomes have been reported to date (McNamee, 2016; Abe, 2008; Lopez, 2003; Wang, 2018; Ahn, 2020; McCarthy, 2016; Roth, 2011; Nogales, 1996; Hodgson, 2020; Roma and Pryzybycin, 2014). Twelve cases of pure ovarian YST (10/12 patients $\geq$ 50 years old) have also been reported (McNamee, 2016; Wang, 2018; Roth, 2011; Roma and Pryzybycin, 2014). Somatic YSTd occurs with variable epithelial components. 28 % (12/43) occurred with EC (one had EC, immature teratoma, and carcinoid), 28 % (12/43) as pure somatic YST (two cases had concurrent endometriosis), 21 % (9/43) with high-grade serous carcinoma (HGSC) (one with serous tubal intraepithelial carcinoma), 9 % (4/43) with clear cell carcinoma (CC) (one borderline clear

cell adenofibroma), 5 % (2/43) with low-grade serous carcinoma (LGSC), 5 % (2/43) with large cell neuroendocrine carcinoma (LCNEC), and 2 % (1/43) with carcinosarcoma (CS). In one case, the epithelial carcinoma was reported as an adenocarcinoma, not further specified (Wang, 2018). Table 1 lists previously reported cases with clinical follow-up (36 cases) grouped according to the epithelial component. In cases of ovarian EC with somatic YSTd, 43 % (3/7) of stage I cases died of disease and 100 % (4/4) cases > stage I died of disease. In cases of pure ovarian somatic YST in older patients (youngest age 40), 25 % (1/4) of stage I patients died of disease and 60 % (3/5) cases > stage I died of disease. In cases where the epithelial component was non-endometrioid, only 20 % (3/15) were stage I and 60 % (9/15) patients had either recurred and were alive with disease or had died of disease.

The cases reported are associated with poor outcomes, even in patients with stage I disease, all of whom received adjuvant chemotherapy. In contrast, classic GCTs arising in young patients typically have a good prognosis and excellent response to chemotherapy (Acosta, 2020). Diagnostic nomenclature should highlight that germ cell/trophoblastic differentiation associated with a carcinoma has a poor prognosis compared to classic GCTs (Acosta, 2020). It is uncertain if germ cell/

Table 1
Summary of previously reported cases of ovarian carcinoma with somatic yolk sac tumor differentiation with outcomes.

Reference	Patient age	Histotype	Stage	Treatment	Outcome
Roth (Roth, 2011)	48	EC, CC and YST	IA	Chemo NOS × 5 cycles	NED at 24 months
Nogales (Nogales, 1996)	71	EC and YST	IA	Chemo NOS × 6 cycles	NED at 12 months
Nogales (Nogales, 1996)	64	EC and YST	IA	Chemo NOS × 3 cycles	Recurrence at 8 months, DOD at 14 months
Abe (Abe, 2008)	52	EC and YST	IC	BEP × 3 cycles, CT × 3 cycles	NED at 20 months
Rutgers (Rutgers, 1987)	50	EC and YST	IC	VDC × 5 cycles	Recurrence at 7 months, DOD
Lopez (Lopez, 2003)	51	EC and YST	IC	CEB × 4 cycles	Recurrence at 10 weeks, DOD at 10 months
Hodgson (Hodgson, 2020)	27	EC and YST	IC	BEP × 3 cycles	NED at 15 months
Nogales (Nogales, 1996)	31	EC and YST	III	Chemo NOS × 6 cycles	Recurrence at 1 month, DOD at 8 months
Nogales (Nogales, 1996)	71	EC and YST	III	Chemo NOS × 1 cycle	DOD at 3 months
Nogales (Nogales, 1996)	40	EC and YST	IV	Chemo NOS × 3 cycles	DOD at 5 months
McNamee (McNamee, 2016)	63	EC and YST	IVB	n/a	DOD at 10 months
McNamee (McNamee, 2016)	50	YST and EM	IC	n/a	NED at 22 months
McNamee (McNamee, 2016)	60	YST	IC	n/a	NED at 22 months
Roth (Roth, 2011)	60	YST	IC	CT	NED at 14 months
Wang (Wang, 2018)	55	YST	IC	BEP × 6 cycles	DOD at 30.8 months
Wang (Wang, 2018)	60	YST	IIC	BEP × 4 cycles	NED at 40.6 months
Wang (Wang, 2018)	55	YST	IIC	BEP × 5 cycles	DOD at 18.5 months
McNamee (McNamee, 2016)	40	YST	IIIB	n/a	DOD at 27 months
Roma (Roma and Pryzybycin, 2014)	70	YST and EM	IIIC	Chemo NOS × 6 cycles	Recurrence at 7 months, AWD
McNamee (McNamee, 2016)	42	YST	IVB	n/a	DOD at 8 months
Wang (Wang, 2018)	50	YST	n/a	DDP × 3 cycles, FP × 1 cycle	DOD at 8.5 months
McCarthy (McCarthy, 2016)	62	HGSC and YST	IC3	Chemo NOS	NED
Wang (Wang, 2018)	77	HGSC and YST	IIIC	NACT × 3 cycles, CT a 1 cycle	NED at 7 months
McNamee (McNamee, 2016)	68	HGSC and YST	IIIC	n/a	NED at 1 month
Roma (Roma and Pryzybycin, 2014)	61	HGSC and YST	IIIC	Chemo NOS × 6 cycles	Recurrence at 7 months, AWD
McNamee (McNamee, 2016)	56	HGSC and YST	IIIC	n/a	DOD at 4 months
McNamee (McNamee, 2016)	62	HGSC and YST	IIIC	n/a	DOD at 20 months
Nogales (Nogales, 1996)	73	CS and YST	III	None	AWD at 2 months
Wang (Wang, 2018)	61	LGSC and YST	IIIB	BEP × 2 cycles, PEV × 1 cycle, CT × 1 cycle	Recurrence at 8 months, AWD at 23 months
Roth (Roth, 2011)	67	LGSC and YST	IIIC	None	Died of post-op complications
McNamee (McNamee, 2016)	79	BCCAF and YST	IA	n/a	NED at 21 months
Wang (Wang, 2018)	58	CC and YST	IC	BEP × 3 cycles	NED as 12 months
Roth (Roth, 2011)	49	CC and YST	IIIA	Chemo NOS	Recurrence at 3 months, DOD at 15 months
McNamee (McNamee, 2016)	48	CC and YST	IIIC	n/a	DOD at 12 months
McNamee (McNamee, 2016)	59	LCNEC and YST	IIB	n/a	DOD at 21 months
Ahn (Ahn, 2020)	82	LCNEC and YST	IIIC	None (patient choice)	Recurrence at 9 months

EC: Endometrioid carcinoma.
CC: Clear cell carcinoma.
YST: Yolk sac tumor.
HGSC: High grade serous carcinoma.
YST: Yolk sac tumor.
CS: Carcinosarcoma.
LGSC: Low grade serous carcinoma.
BCCAF: Borderline clear cell adenofibroma.
CC: Clear cell carcinoma.
LCNEC: Large cell neuroendocrine carcinoma.
EM: Endometriosis.
Chemo NOS: chemotherapy with no further details provided.
BEP: Bleomycin, etoposide, platinum.
CT: Carboplatin and paclitaxel.
VDC: Vincristine, dacrinomycin, cyclophosphamide.
CEB: Cisplatin, etoposide, bleomycin.
DDP: Cisplatin, adriomycin, 5-fluorouracil.
FP: 5-fluorouracil and cisplatin.
NACT: Neoadjuvant chemotherapy.
PEV: Cisplatin, epirubicin, vinorelbine.
NED: No evidence of disease.
DOD: Dead of disease.
AWD: Alive with disease.

trophoblastic differentiation is an independent predictor of poor prognosis (Acosta, 2020). Serum AFP levels are elevated in the majority of cases and can be helpful to monitor treatment response and disease recurrence (Wang, 2018). Somatic YSTd has been reported in tumors arising at other sites including the bladder (Collins, 2022), vulva (Kolin, 2022), cervix (Liu, 2022) and colorectum (Takashi, 2020) and is also reported to have poor outcomes.

To the best of our knowledge, case two is the first reported case of adenosarcoma with SO showing somatic YSTd. It is unclear whether the YSTd is clonally related to the SO. El Hallani *et al* described cases of mixed mullerian adenosarcoma and EC in which the EC is clonally related to the sarcoma (El Hallani, 2021). It is thus plausible that adenosarcoma may give rise to the component of YSTd observed here either directly or indirectly through an unsampled EC component.

Malignant tumors associated with somatic YST differentiation are uncommon. They are understudied and the optimal treatment (germ cell chemotherapy protocol versus chemotherapy directed to the somatic component) is uncertain. Based on studies showing the molecular alterations in the GCT components match the common driver mutations in the corresponding epithelial component, most authors suggest treatment regimens directed towards the epithelial component. To the best of our knowledge, this is the first report of somatic GCT differentiation in a non-epithelial malignancy in the gynecologic tract. Pathologists and clinicians should be aware of these rare cases, which arise predominantly in post-menopausal patients and show aggressive behavior compared to GCTs arising in younger patients.

5. Author contributions:

Dr. A Bassi: First author, helped write the paper (clinical case presentations), edit the paper and provided CT images for Figs. 1 and 2. Obtained consent from both patients for the case report.

Dr. G Nelson: Assisted Dr. Bassi with obtaining consent and edited the paper.

Dr. CH Lee: Gynecologic and sarcoma pathologist who was consulted on the adenosarcoma case and edited the paper.

Dr. T Ogilvie: Gynecologic and breast pathologist reporting part of the pathology from case 2 (adenosarcoma with sarcomatous overgrowth and somatic yolk sac tumor differentiation).

Dr. A Cota: Pathologist reporting the pathology of case 1 (ovarian endometrioid carcinoma with yolk sac tumor differentiation).

Dr. S Lee: Gynecologic pathologist reporting the final pathology for case 2, tumor board review pathologist for case 1, selected the two cases for the case report and helped write and edit the paper.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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