



Case report

Malignant Female Adnexal Tumor of Probable Wolffian Origin (FATWO): A case report and review for the literature

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1. Introduction

Female adnexal tumor of probable Wolffian origin (FATWO) is a rare epithelial neoplasm first identified by Novak et al. in 1954 and further described by Kariminejad and Scully in 1973 (Kariminejad and Scully, 1973). FATWO is typically found as a para-tubal mass within the broad ligament and is thought to arise from mesonephric (Wolffian) remnants (Kariminejad and Scully, 1973; Fleming et al., 2017; Shalaby and Shenoy, 2020). The majority of cases are considered benign, however, late tumor recurrences, metastases and disease related death have been documented (Fleming et al., 2017; Heatley, 2009). A review of the literature previously reported that 11% were recurrent (Heatley, 2009). We present a case of recurrent FATWO and a review of malignant FATWO cases.

2. Case

A 28-year-old multiparous woman presented to the emergency department (ED) with left lower quadrant (LLQ) pain for one day duration, unrelieved by over the counter analgesics. Her last menstrual period was 3 weeks prior to presentation. She had no significant medical history; surgical and social history revealed a prior cholecystectomy, current smoking, and Nexplanon use for contraception. Abdominal and

pelvic exams were notable for LLQ tenderness to palpation. Transvaginal ultrasound revealed a 3.5 cm left soft tissue mass with cystic components, suggestive of a pedunculated ovarian lesion with possible intermittent torsion.

She was taken to surgery for suspected ovarian torsion. Intra-operative laparoscopic findings revealed a left para-tubal cyst, without evidence of torsion. The para-tubal cyst was dissected off the mesosalpinx and removed from the abdomen in a specimen retrieval pouch through the umbilical port site. She was discharged on the day of surgery without complaints. Final pathology returned female adnexal tumor of probable Wolffian origin (FATWO). Her four-week post-operative visit in the office was unremarkable. Work-up for FATWO with computed tomography (CT) of the chest was performed and unremarkable, CA 125 was 12, and inhibin B was 82.

Her post-operative course was notable for multiple ED visits for abdominal pain. Ultrasound and CT imaging were unremarkable during these evaluations. In an ED visit approximately two months after surgery, the patient presented with a malodorous discharge from her umbilicus and peri-umbilical pain radiating to the LLQ. Imaging studies were unremarkable, WBC was 9.12 K/uL, and vital signs were normal. Exam revealed a purulent drainage from the umbilical port site and cultures grew *Proteus mirabilis* and *Streptococcus agalactiae*. She was treated with oral antibiotics with resolution of her symptoms.

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Eight months after initial surgery, she presented to the ED with severe peri-umbilical pain radiating to the LLQ. CT of the abdomen (Fig. 1) now showed multiple, ≤ 9 mm, rounded enhancing lesions in the abdominal wall at the level of the umbilicus, and one 7 mm implant deep to the rectus aponeurosis just below the level of the umbilicus. These findings were concerning for a recurrent neoplasm. Pelvic ultrasound now showed a 3.9 cm simple left ovarian cyst. Physical exam revealed tenderness in the peri-umbilical area and left adnexal and cervical motion tenderness. A superficial 1 cm mass was palpated in the base of the umbilicus just deep to the dermis. She was treated empirically for pelvic inflammatory disease due to physical exam and ultrasound imaging findings. After a short interval, the patient was brought to the operating room for an umbilectomy and left salpingo-oophorectomy. Frozen pathology showed recurrent FATWO in the umbilectomy specimen; the remaining specimens were benign.

3. Pathology.

Pathology (Fig. 2) from the para-tubal cystectomy revealed a smooth tan-white fallopian tube cyst measuring $3.0 \times 2.5 \times 2.0$ cm with previously disrupted cyst structure. The tumor was multifocally positive for cytokeratin AE1/AE3 and cytokeratin 7 (CK7). CD117 (c-Kit) was moderately positive in approximately 7% of the tumor cells. Estrogen receptor (ER) stained strongly positive in approximately 75% and moderately positive in approximately 10% of the tumor cells. Progesterone receptor (PR) stained strongly positive in approximately 40% and moderately positive in approximately 10% of the tumor cells. There was negative staining for epithelial membrane antigen (EMA), PAX8, and p40. The specimen was diffusely positive for calretinin, multifocally positive for inhibin and very focally positive for CD10. The tumor had a wild-type pattern of immunostaining for p53. The Ki67 index of the tumor was moderately increased/positive.

Pathology from the recurrence revealed multiple tan-white, firm, and fleshy nodules ranging from $0.9 \times 0.8 \times 0.8$ cm to $1.4 \times 1.0 \times 0.9$ cm in the umbilectomy specimen. The largest nodule measured 0.7 cm from the epidermal surface. The left fallopian tube and ovary were benign. The morphology of the recurrent sample was almost identical to the initial specimen. Immunohistochemical staining was also similar with Ki67 positive in approximately 10% of tumor cells, c-Kit staining in 5–10% of tumor cells with moderate intensity, ER staining of 80% of tumor cells with strong to moderate intensity, and PR staining 50% of

tumor cells with moderate to weak intensity.

4. Discussion

Less than 100 cases of FATWO have been reported and the majority show benign behavior (Heatley, 2009). However, increasing reports of metastatic and recurrent FATWO support a low malignant potential lesion (Brescia et al., 1985). Based on our literature review (Table 1), upwards of 25% FATWO cases published have recurrence or metastasis, which is significantly higher than the initial report of 11% in 2009 (Heatley, 2009).

FATWO is primarily reported to originate within the broad ligament. Embryologically, under the influence of gonadal hormones, sexual differentiation of the mesonephric (Wolffian) and para-mesonephric (Müllerian) ducts starts at approximately seven weeks gestation. Both ducts become enclosed in peritoneal folds which ultimately become the uterine broad ligaments. The lack of testosterone in the female causes the mesonephric ducts to regress by twelve weeks gestation (Hoffman et al., 2016).

In reviewing malignant FATWO cases (Table 1), age at presentation ranged from 15 to 81. Clinical presentations included abdominal pain, pelvic pain, changes in bowel habits and incidental findings on examination. Initial surgery included exploratory laparotomy, tumor resection with or without hysterectomy, removal of adnexal structures, omentectomy and pelvic and para-aortic lymph node dissection. Operative findings were notable for right laterality being more prevalent than left sided lesions. Tumor size ranged from 2.5 cm to >20 cm in largest dimension. Post-operative adjuvant therapy was typically not recommended. After recurrence and repeat cytoreductive surgery, treatment with standard chemotherapeutic agents, most commonly carboplatin and paclitaxel, or radiotherapy was employed with mixed success. Although many reports suggested positive outcomes with patients being alive at time of publication, several also reported patient death secondary to disease anywhere from four months to eight years after the initial surgery.

The diagnosis of FATWO is challenged by its various morphologies and undefined immunophenotype. Morphologic, immunohistochemical, and molecular analysis of fifteen FATWO cases revealed three major morphologies: tubular, solid and sieve-like (Bennett et al., 2020). In our case, the tumor showed solid and cribriform growth patterns. These morphologies overlap with other commonly encountered gynecologic



Fig. 1. Axial (A) and sagittal (B) computed tomography (CT) imaging showing nodules (arrowheads) concerning for recurrence of FATWO.

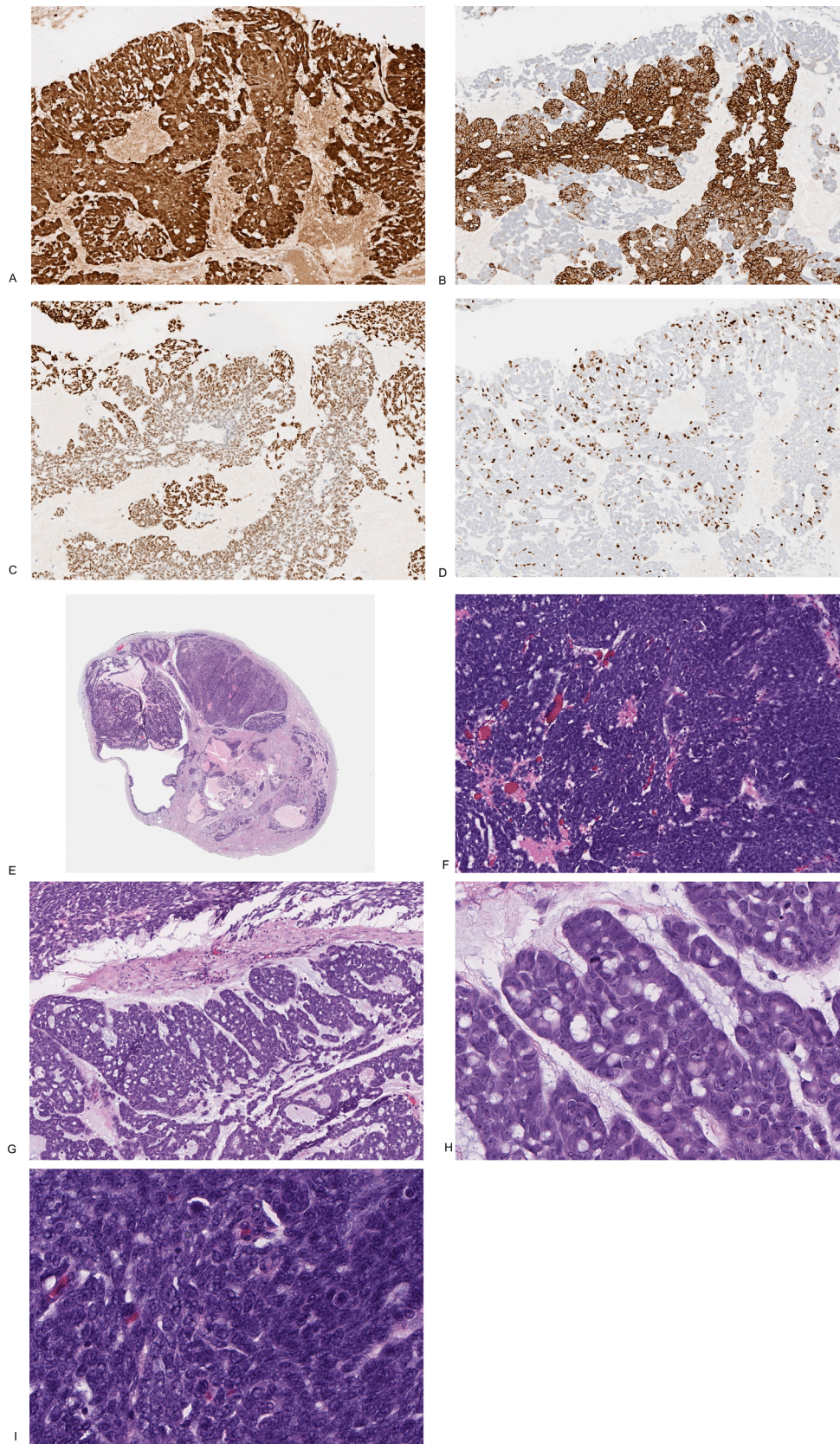


Fig. 2. Immunohistochemical staining showed diffusely positive Calretinin (A) and CK7 (B) in the tumor cells. ER (C) stains roughly 80% of the tumor cells with moderate to strong intensity. KI-67 (D) proliferation index is low and is positive in approximately 10% of the tumor cells. Low-power microscopy of the tumor (E) shows a well-circumscribed partially cystic lesion. F and G represent medium power views of the cribriform architecture/growth (F) and solid growth (G) patterns. H and I show high power views of both architectural components of the tumor (cribriform, H and solid component, I) significant for cuboidal cells with scant cytoplasm and uniform round to ovoid nuclei with mostly low to focally low to intermediate nuclear atypia. Tumor cells showed low proliferative activity manifested with low mitotic activity that was counted as less than two in ten high power fields.

Table 1
Cases in the English literature of malignant FATWO.

Case	Age	Presentation Initial surgery	Origin, w/wo metastasis	Tumor size in greatest dimension, cm	Positive IHC	Adjuvant therapy	Recurrence site	RFS/PFS, mo	Recurrence/Progression treatment	Status
Taxy, 1976	41	Dysfunctional uterine bleeding Hysterectomy	Right broad ligament	8.5	Noncontributory	EBRT	Hepatomegaly	55	Tissue/tumor biopsy	Alive at time of publication
Abbot, 1981	18	Acute abdominal condition Laparotomy, right adnexal cystectomy and removal of portion of right fallopian tube	Right mesosalpinx	8.5	Alcian blue, faint PAS, Reticulin	/	Right adnexa, serosal surfaces of peritoneal cavity -> peritoneum, mesenteries, serosa of bowel L hemidiaphragm	78	BSO, omentectomy, tumor resection (incomplete); Cyclophosphamide, Doxorubicin, Cisplatin -> partial response/ progression , tumor resection, IV/IP 5-FU, Peptichemio, Bleomycin	DOD, 8y s/p initial surgery
Hughesdon, 1982	79	Urinary retention, constipation Removal of bilateral adnexa	Left ovary	14	Alcian blue, PAS	/	Pouch of Douglass	14	None	DOD, 14 m s/p initial surgery
Brescia, 1985	23	Right lower quadrant pain Laparotomy, tumor incision/ drainage, biopsy -> Complete tumor resection, partial cystectomy, vaginectomy, PLND	Retroperitoneum in pararectal space	13	PAS, Reticulin	/	1st: lower pole of surgical incision, omentum, bowel serosa, deep rectal space 2nd: omentum at hepatic flexure 3rd: right liver lobe	1st: 21 2nd: 36 3rd: 84	1st: surgical resection of recurrent tumor, EBRT 2nd: surgical resection of recurrent tumor 3rd: right hepatectomy, partial resection of diaphragm, EBRT	Alive at time of publication
Prasad, 1992	47	Tenesmus TAH-BSO, PLND, partial omentectomy, appendectomy	Right ovary/posterior broad ligament, +peritoneal spread	12	PAS, Reticulin, Cytokeratin, EMA	8 cycles Cisplatin- Cytoxin	N/A	N/A	N/A	Alive at time of publication
Daya, 1993	20	Right lower quadrant pain Resection of paravaginal tumor, in fragments	Right lateral vaginal wall	12	PAS, Reticulin	/	1st: Site of previous surgery 2nd: paravaginal areas	1st: 24 2nd: 12	1st: biopsy, transposition of ovaries -> RT, Cisplatin 2nd: LOA, resection of tumor	Alive at time of publication
Daya, 1994	81	Abdominal distension, weight loss TAH-BSO, omentectomy	Right broad ligament, +omental spread	20	Reticulin	N/A	N/A	N/A	N/A	Died of other causes, 3 m postop Not reported
Sheyn, 2000	60	Abdominal mass TAH, BSO, omentectomy, LAR with primary reanastomosis, appendectomy	Right mesosalpinx, +peritoneal spread	11	CAM 5.2, Vimentin, Type IV collagen	8 cycles Cisplatin- Cytoxin	Surface of liver	61	Surgical resection of liver surface mass	Not reported
Ramirez, 2002	38	Lower abdominal pain, enlarging abdominal mass, constipation Exploratory laparotomy, optimal tumor reductive surgery (LOA, excision of pelvic mass, BSO, omentectomy, excision of perihepatic masses, appendectomy), optimal debulking	Pelvis, +peritoneal spread	17	PR	NR	Right anterior abdominal wall (including subcutaneous tissue), liver parenchyma, left upper quadrant, spleen, pelvis	4	Carboplatin/Paclitaxel, IM Leuprolide, progressive	Alive time of publication
	71	Incidental pelvic mass on exam Exploratory laparotomy, omentectomy, tumor reductive surgery, optimal debulking	Pelvis	16	Calretinin, Cytokeratin, Moc31, CK5/6, ER, PR	NR	Peritoneal implant, liver margin	10	Unsuitable for biopsy, monitor with CT imaging	Alive at time of publication
Atallah, 2004	27	Incidental left adnexal mass on pelvic examination Resection of left adnexal mass	Left broad ligament	11	PAS, Reticulin	NR	Peritoneal implants	27	TAH, BSO, omentectomy, PPALND; Cisplatin/Cyclophosphamide ->	DOD, 2y after temporary

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Table 1 (continued)

Case	Age	Presentation Initial surgery	Origin, w/wo metastasis	Tumor size in greatest dimension, cm	Positive IHC	Adjuvant therapy	Recurrence site	RFS/PFS, mo	Recurrence/Progression treatment	Status
Steed, 2004	15	Abdominal pain	Retroperitoneum, paravaginal, broad ligament	14.2	Cytokeratin 7 and 19, CAM 5.2, Vimentin, EMA	/	broad ligament, uterosacral ligaments, abdominal wall	less than 24	progressive , Paclitaxel/Cisplatin for disease stabilization -> diffuse metastasis Surgical resection of tumor; Cisplatin/ Cyclophosphamide -> progressive , Amifostine, Etoposide, Ifosfamide, Carboplatin, Irinotecan; refused RT -> laparotomy, optimal debulking [uterus and ovaries preserved for future fertility], +c-kit	disease stabilization Alive at time of publication
		Exploratory laparotomy, resection of mass, removal of enlarged PALN [uterus and ovaries preserved for future fertility]					Broad ligament	less than 12	Epithilone B -> progressive , Gleevac -> radical hysterectomy, upper vaginectomy, large and small bowel resections, optimal debulking -> Gleevac	
Halushka, 2004	34	Right sided pelvic pain BSO	Right fallopian tube	5.8	AE1/AE3, CAM 5.2, Calretinin, Inhibin	NR	Number recurrences not reported Inguinal mass	NR 24 from initial surgery	Debulking procedures x2, complete hysterectomy, "standard" chemotherapy Fine needle aspiration	Alive at time of publication
Sivridis, 2005	76	Abdominal pain, urinary retention TAH, BSO	Right broad ligament, +peritoneal spread	20	PAS, Pankeratin, Vimentin, S-100 protein, NSE	/	N/A	N/A	N/A	DOD, 4 m s/p initial surgery
Tamiolakis, 2007	75	Ascites, urinary retention Right ovarian and broad ligament resection	Right broad ligament	4.7	AE1/AE3, CAM 5.2, Calretinin, Inhibin	6 cycles Cisplatin-Cytoxan	Left broad ligament	24	Tumor resection	Not reported
Lesin, 2009	60	Lower abdominal pain TAH, bilateral adnexectomy, omentectomy, pelvic washings	Right broad ligament	8	Not performed	NR	Vaginal cuff	72	LOA, excision of tumor mass; no additional therapy	Alive at time of publication
Syriac, 2011	38	Right adnexal mass Exploratory laparotomy, resection of tumor	Right broad ligament	12	AE1/AE3, CK7, WT1, Calretinin,	/	Left ovary	36	Hysterectomy, BSO, omentectomy, PPALND; +C-kit -> Gleevac	/
Heller, 2011	24	Pelvic pain	Left broad ligament	4	Calretinin, Vimentin, CK7, Inhibin	/	Appendix, small bowel serosa, omentum, posterior bladder peritoneum, broad ligament	1.5	Total omentectomy, appendectomy, PPALND, resection of tumor, optimal debulking [uterus and right ovary preserved for future fertility], Carboplatin/Taxol; + ER, PR, Calretinin, Vimentin, CK7, inhibin	Lost to follow-up
		Exploratory laparotomy, resection of left broad ligament tumor, left distal fallopian tube, omental and peritoneal biopsies					Pelvis, causing large bowel obstruction and hydronephrosis	s/p chemotherapy for recurrence	Recommended large bowel stent, bilateral percutaneous nephrostomy	
Liu, 2011	24	Pelvic pain Resection of tumor, omental biopsy	Left broad ligament	Not reported	ER, Calretinin, Cytokeratin, Vimentin, Inhibin	/	Serosa of appendix	1	Exploratory surgery, resection of left adnexal lesion	/
Deshimaru, 2014	30	Right ovarian mass on pelvic examination and transvaginal ultrasound	Right fallopian tube/ broad ligament, +peritoneal spread	5	Calretinin, Inhibin, CD10, Vimentin, Desmin, CD34	1 cycle Paclitaxel -Carboplatin; 3 cycles Carboplatin	Progression, tumor implants on bowel serosal surface, omentum, left ovary, pouch of Douglas	4	TAH, BO, omentectomy, tumorectomy, PPALND; oral Medroxyprogesterone acetate	DOD, 3y s/p initial surgery
		Exploratory laparotomy, RSO, tumorectomy					Progression, iliopsoas, anterior vaginal wall	3	Vaginal tumor resection, transvaginal tumorectomy; pegylated liposomal doxorubicin, irinotecan, gemcitabine	

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Table 1 (continued)

Case	Age	Presentation Initial surgery	Origin, w/wo metastasis	Tumor size in greatest dimension, cm	Positive IHC	Adjuvant therapy	Recurrence site	RFS/PFS, mo	Recurrence/Progression treatment	Status
							Progression, abdominal cavity	s/p chemotherapy for recurrence #2 7	None	
Deen, 2007	81	Post-menopausal bleeding, pelvic mass on imaging Exploratory laparotomy, TAH, BSO, infracolic omentectomy, peritoneal washings (small amount of cyst wall left behind)	Right ovary	18	Vimentin, Calretinin, / alpha-inhibin, chromogranin A, CD56, MIB1		Right adnexa, paravaginal area	7	RT offered however patient declined	Not reported
Kwon, 2016	52	Pelvic pain TAH, BSO, total omentectomy, PLND, washing cytology	Left ovary hilus	8	D2-40, Calretinin, / CK, CD10, CD56, Vimentin, CK7, mucicarmine		Right sided cul-de-sac Progression, cul-de-sac, hepatic tip	9 s/p chemotherapy for recurrence	Paclitaxel/Carboplatin Recommended additional debulking surgery, chemotherapy	Lost to follow- up
Qiu, 2017	53	Abdominal distention Exploratory laparotomy, hysterectomy, BO, resection of left mesosalpinx tumor and omentum	Left mesosalpinx	10	Inhibin A, Calretinin, NR ER, PR, CD99, Pax2, cytokeratin	NR	Multiple nodules in abdominal and pelvic cavity	24	Laparotomy, resection of pelvic masses and partial resection of omentum, Cisplatin (IP), Docetaxel (IV), Oxaliplatin (IP), progressive	DOD, 83d after 2nd surgery
Wakayama, 2017	37	Lower abdominal pain Laparotomy, LSO, PLND, omental biopsy, tumor resection	Left tubal fimbriae, posterior leaf of broad ligament	7	CK7, Vimentin, Inhibin, Calretinin	NR	Peritoneal implants	17	TAH, RSO, extirpation of disseminated tumors, incomplete debulking, +C-kit, progressive , Gleevac, progressive , incomplete debulking, Paclitaxel/ Carboplatin	Alive at time of publication
Hong, 2018	50	Lower abdominal pain, constipation, increased urinary urgency Exploratory laparotomy, TAH, BSO, mass resection, omentectomy, PPALND	Left ovary, +peritoneal spread	17	ER, PR, CK7, EMA, CD10	NR	N/A	N/A	N/A	Alive at time of publication
Present case	28	Left lower quadrant pain Laparoscopic left paratubal cystectomy	Left mesosalpinx	3	AE1/AE3, CK7, CD10, Calretinin, Inhibin, ER, PR, C-kit	NR	Seeding vs recurrence at umbilical port site	8	Umbilectomy, LSO; recommended treatment with Gleevac	Alive at time of publication

BSO = bilateral salpingo-oophorectomy; BO = bilateral oophorectomy; cm = centimeters; d = day; DOD = died of disease; EMA = epithelial membrane antigen; EBRT = external beam radiation therapy; ER = estrogen receptor; IHC = immunohistochemistry; IP = intraperitoneal; LAR = low anterior resection; LOA = lysis of adhesions; LSO = left salpingo-oophorectomy; m = month; MRI = magnetic resonance imaging; N/A = not applicable; NR = not recommended; PALN = para-aortic lymph node; PAS = periodic acid Schiff; PFS = progression free survival; PLND = pelvic lymph node dissection; PPALND = pelvic and para-aortic lymph node dissection; PR = progesterone receptor; RFS = recurrence free survival; RSO = right salpingo-oophorectomy; RT = radiation therapy; s/p = status post; TAH = total abdominal hysterectomy; y = year; / = not reported; + = positive or present.

neoplasms such as endometrioid carcinoma and sex cord stromal tumors (e.g., Sertoli-Leydig cell tumors, granulosa cell tumors) (Shalaby and Shenoy, 2020; Bennett et al., 2020).

Although there is no single specific immunohistochemical stain for FATWO and patterns are not entirely reproducible between FATWO specimens, immunohistochemistry can help narrow the differential diagnosis. Endometrioid carcinoma typically has diffuse staining of EMA, PAX8, CK7, ER and vimentin. In Wolffian tumors, EMA and PAX8 are typically negative, as was in our case (Bennett et al., 2020). Distinguishing FATWO from sex cord stromal tumors provides a pathological challenge. Overlapping stains include calretinin, inhibin, and CD10 (Hoffman et al., 2016). However, sex-cord stromal tumors are typically diffusely positive for inhibin, whereas FATWO may have focal staining, as was in our case. Additional stains include CK7 and pancytokeratin (AE1/3), for which FATWO is reportedly immunoreactive, again seen in our case. CK7 is not seen and AE1/3 is rarely seen (33–37%) in granulosa cell tumors. Variable expression of ER, PR, and c-Kit is reported in FATWO (Shalaby and Shenoy, 2020). Moderate to strong staining of ER, PR, and c-Kit were seen in both the original paratubal and recurrence specimens for our patient.

Very little information regarding the optimal management of FATWO is known. Surgical management is the primary approach to treatment. Treatment for recurrence with standard chemotherapy and other hormonal approaches, targeted therapy, or radiation therapy have been published with relatively short progression free and overall survival. Reports of targeted therapy with Imatinib mesylate (Gleevec) in the setting of c-Kit positivity first suggested by Steed et al. in 2004 has been used to some degree of success (Steed et al., 2004; Harada et al., 2006). Due to the variable outcomes of FATWO, the recommendation for close clinical follow-up is suggested.

It remains unclear whether our case is one of true recurrence or surgical port site seeding during extraction of the specimen. However, there was no reported gross spillage of tissue or fluid at the initial surgery and a specimen retrieval pouch was used. Tumor dissemination and wound seeding, as elaborated in C.G. (Thomas, 1961) article in the Annals of Surgery, can be “enhanced” during specimen extraction and “direct dissemination of surface tumors (Thomas, 1961).” We are additionally intrigued by her multiple post-operative ED presentations. Although imaging at earlier post-operative visits were negative for abdominal pathology and cultures grew bacteria known to inoculate the genitourinary and intestinal tracts, the possibility of an inflammatory element from seeded FATWO is presented.

The ideal management of FATWO remains elusive due to its rarity and variation in invasive potential and multiple clinical presentations.

4.1. 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.

CRedit authorship contribution statement

Risha Sinha: Conceptualization, Data curation. **Bethany Bustamante:** Conceptualization, Data curation. **Farnaz Tahmasebi:** . **Gary L. Goldberg:** Supervision, Conceptualization.

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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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. F Tahmasebi made contributions to pathology analysis and drafting the manuscript. GL Goldberg made contributions to supervision, conceptualization, drafting and revising the report.

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