

Case report

Malignant recurrence of Female Adnexal Tumor of Probable Wolffian Origin (FATWO)

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1. Introduction

Wolffian tumor, also referred to as a female adnexal tumor of Wolffian origin (FATWO), is an extremely rare extraovarian, extratubal tumor of distinctive epithelial form originating from mesonephric remnants (Bennett et al., 2020). FATWOs are found in the paraovarian region within the leaves of the broad ligament and less frequently within the fallopian tubes, ovaries, retroperitoneum, pelvic wall and paravaginal region (Mirkovic et al., 2018; Rosen et al., 2019). Of about 100 reported cases worldwide, most Wolffian tumors are benign. However, the National Comprehensive Cancer Network (NCCN) defines FATWO as borderline tumors with uncertain malignant potential (Network and Clinical Practice Guidelines, 2020). About 10–20% of cases have been reported as malignant and/or recurrent (Hubner et al., 2019; Syriac et al., 2011). Recurrence is rare; the reported median time of tumor recurrence after initial resection is 48 months (Syriac et al., 2011; Hong et al., 2017). Most frequent sites of metastasis are liver and lung (Hubner et al., 2019; Syriac et al., 2011; Sheyn et al., 2000; Shalaby and Shenoy, 2020).

Symptoms are variable and non-specific, making clinical diagnosis of Wolffian tumors difficult. Patients often report lower abdominal pain, distension, abnormal vaginal bleeding, and/or pelvic masses. A pelvic ultrasound demonstrating a semi-solid, vascularized mass can suggest further workup to rule out Wolffian tumor. Computed tomography (CT) can determine anatomic features and origin of tumor (Shalaby and Shenoy, 2020). Immunohistochemical features and mutation analyses

may aid in differentiating a FATWO tumor from other ovarian tumors, but are not diagnostic as can be seen in Table 1 (Hubner et al., 2019; Syriac et al., 2011; Hong et al., 2017).

Due to the rarity, currently there is no established standard of treatment. However, suggested therapy is tumor resection with total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). In some cases of malignant Wolffian tumors, adjuvant chemotherapy and radiotherapy have demonstrated promising results with platinum and taxane based regimens (Shalaby and Shenoy, 2020; Network and Clinical Practice Guidelines, 2020; Hubner et al., 2019; Syriac et al., 2011).

2. Case presentation

We present a 47-year-old female (Gravida 2, Para 2) with a recurrent Wolffian tumor. At age 45, the patient presented with infrequent right lower quadrant pain and pressure for a few months. Pelvic exam revealed a non-tender mass in the right adnexal region. Pelvic ultrasound demonstrated a solid, complex right adnexal mass measuring 10 × 9 × 9 cm and normal tumor markers (CA-125, AFP, and HCG). Evaluation by gynecologic oncology recommended surgical intervention for diagnostic and therapeutic purposes.

During the procedure, the mass was adherent to the anterior abdominal wall, lower uterine segment, and cardinal ligament. However, it did not directly involve any of these structures, the fallopian tubes, ovaries, uterus or cervix. Dissection of the mass resulted in

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rupture, displacement down the paravesical space, and gross spillage with 200 mL of blood, which resulted in conversion to an open laparotomy. The mass was sent for frozen section, which revealed possible Granulosa cell or Wolffian duct origin tumor. Due to its benign appearance and the patient's age, the left ovary was left in-situ. The patient's complete procedure was a laparoscopy with conversion to laparotomy, TAH, right salpingo-oophorectomy (RSO), left salpingectomy (LS), pelvic tumor debulking, right pelvic node dissection, pelvic peritoneal biopsies and omentectomy.

Final pathology of the mass revealed low mitotic rate and a lack of cytological atypia. No malignant cells were identified in peritoneal washings and immunohistochemical marker, PAX8, was negative. In addition, no significant diagnostic abnormalities were appreciated in specimens of surrounding structures. The diagnosis of a low-grade

Wolffian tumor required no need for further therapy. The patient continued to follow up for the remainder of that year with no evidence of recurrence in that time.

Two years after the initial occurrence and resection, the patient presented to her primary care physician with complaints of generalized abdominal pain, hematuria, dysuria, and perianal pain. Urological workup revealed no significant findings. However during gynecologic evaluation, she additionally reported: incomplete voiding, right pelvic pain with radiation to right flank and rectum, vaginal spotting, and dyspareunia. She also noted a 20-pound weight gain and chronic constipation since her surgery two years prior. Physical exam demonstrated no significant findings, however pelvic ultrasound revealed: a midline, complex pelvic mass with punctate calcifications measuring 3.5 × 3.5 × 4.3 cm with surrounding free fluid, an additional mass on the right

Table 1

Summary of literature reports including: diagnosis, tumor markers, immunohistochemistry, hormone receptors, treatment, recurrence/metastasis, and surveillance.

Author	Diagnosis	Tumor marker	Immunohistochemical markers	Hormone receptors	Treatment	Recurrence/ Metastasis	Surveillance
Rosen et al., 2019	Benign FATWO (incidental)	NA	inhibin, calretinin, pancytokeratin, and CD10 (+) PAX-8, CD34, actin, desmin, S100, EMA, and HMB45 (-)	ER/PR (-)	Pelvic wall mass removal ONLY	NA	1 month follow up
Ramirez et al., 2002	FATWO with 3 yr recurrence	Elevated CA-125 = 286 > 46 (recurrence)	inhibin, calretinin, and focally for cytokeratin 7 (+) epithelial membrane antigen (EMA) (-)	PR (+) ER, c-kit and Her2/neu (-)	Ex lap and tumor reductive surgery – BSO, omentectomy, perihepatic mass excision carboplatinum/paclitaxel, leuprolide – progressive disease	First – 3 y post op Second – 4 mos after excision of secondary	NA
Case 1							
Case 2	Recurrent FATWO	CA-125 = 13 CEA = 1.5	calretinin, cytokeratin, and Moc31 (+) focally positive for CK5/6. negative for inhibin, B72.3, CK20, S-100 protein, EMA, and p53.	ER/PR (+) c-Kit and Her-2/neu (-)	Exploratory laparotomy, omentectomy, and tumor reductive surgery	New nodules in LU pelvis	10 and 17 months
Sheyn et al., 2000	Metastatic FATWO	CA-125 wnl	cytokeratin CAM5.2 and vimentin (+) EMA, S100, and a-inhibin (-)	NA	TAH, BSO, omentectomy, low anterior resection of rectosigmoid with primary anastomosis, and appendectomy cysplatin-cytoxan chemotherapy	Recurrence 5 years	followed up by serial CT, chest x-ray films, and cancer antigen 125 levels every 6 months.
Hong et al., 2017	Malignant FATWO	CA-125 = 70.3 HE4 = 147 CEA = 4.3	CD10, CK7, and EMA (+) CEA, inhibin, CD99, Calretinin, CK20, WT-1, and PAX8 (-)	ER/PR (+)	TAH, BSO mass resection, omentectomy, and left iliac and paraaortic lymphadenectomy.	NA	“close monitoring”
Syriac et al., 2011	Recurrent FATWO	NA	C-kit (CD117), AE1/3, cytokeratin (CK)7, WT1, calretinin, and α-inhibin (+) EMA CK20, and synaptophysin (-)	NA	TAH, BSO, omentectomy and bilateral pelvic and para-aortic lymph node dissection Imatinib mesylate therapy for 6 months	3 year recurrence	follow-up by CT every 6 months
Hubner et al., 2019	Benign FATWO	Ca-125 = 23.1 CEA = 0.3	CD10 and cytokeratins (the pancytokeratin antibodies AE1/3, Cam5.2, cytokeratin 7) Inhibin (+) irregular, diffuse reactivity for SF1 partial positivity for calretinin and CD56. FOXL2 (-)	PR (+) ER (-)	laparoscopic tumor removal and chromopertubation.	NA	NA
Bennett et al., 2020	15 cases	NA	Pankeratin, EMA,GATA3, and PAX8 (+)	NA	NA	1 patient with recurrence	6 patients followed ranging 1 to 14 years
Review of 15 cases	Mostly benign FATWOs		TTF-1 (-) CD10, SF-1, calretinin, inhibin, ER/PR, cytokeratin 7, and WT1 variably expressed.				

measuring $1.9 \times 1.7 \times 1.7$ cm, and a complex left adnexal mass measuring $5.0 \times 3.3 \times 2.7$ cm. A small amount of peripheral and internal flow on Doppler interrogation was noted in each mass. CT of the abdomen and pelvis confirmed the presence of a left complex ovarian cyst and left pelvic mass above the vaginal cuff, anterior and contiguous to the ventral aspect of the rectum [Fig. 1]. In correlation with ultrasound findings and history of prior FATWO occurrence, the masses were likely recurrent tumors.

After extensive counseling, the patient underwent an exploratory laparotomy, left oophorectomy, excision of pelvic masses and rigid protoscopy. Intraoperatively, a 3 cm cyst arising from the left ovary with attachments to the left pelvic sidewall and a 5 cm complex mass between the vaginal cuff and the rectum were seen and removed. Due its friable nature, the larger mass ruptured during dissection. Frozen section of the mass was consistent with a Wolffian tumor.

Final pathology confirmed the recurrence of Wolffian tumor. The tumor was composed of epithelioid and spindle cells in solid growth pattern with scattered tubules, and focal areas of “sieve-like” pattern. Due to the recurrence with malignant concern, immunohistochemical studies were conducted and extramural consultation was obtained. The tumor cells were positive for AE1/3, CD10, PAX-8, CK19, CD56, calretinin (focal), BerEP4 (focal), p16 (focal), and WT1 (patchy). They were negative for EMA, inhibin, melanin A, chromogranin and synaptophysin. Atypical features of the tumor included brisk mitoses, hypercellular, prominent nuclear pleomorphism and prominent nucleoli. The proliferative index was reported to be 20% on Ki-67 immunostain [Fig. 2].

Due to the immunohistochemical nature of the tumors and presence of high mitoses, the patient elected to receive adjuvant therapy with carboplatin and taxol every 3 weeks for 4 cycles. She is currently undergoing this treatment.

3. Discussion

Wolffian tumors are often diagnosed with presentation of compressive symptoms or incidental physical exam findings (Rosen et al., 2019). Compressive genitourinary and gastrointestinal symptoms, as seen in our patient, are suspicious for recurring tumors similar to presentation of other female reproductive tumors.

Wolffian tumors pose a diagnostic challenge due to the variability in immunohistochemical, molecular, and genetic findings (Table 1) (Hong et al., 2017; Bennett et al., 2020; Mirkovic et al., 2018). Bennett, et al reviews the immunohistochemical profile of 15 cases, as well as reported FATWOs, and indicates there is no definitive diagnostic marker for a

Wolffian tumor. However, immunohistochemistry can aid in distinguishing Wolffian tumors from other reproductive origins. For example, the presence of CD10 staining distinguishes Wolffian tumors from sex cord stromal tumors and lack of epithelial membrane antigen (EMA) differentiates from epithelial tumors (Bennett et al., 2020; Mirkovic et al., 2018; Rosen et al., 2019; Sheyn et al., 2000; Shalaby and Shenoy, 2020; Ramirez et al., 2002). Our case demonstrates similar findings. Positive CD10 combined with negative PAX8 markers are suggested to distinguish a Wolffian tumor from a tumor of Mullerian origin (Rosen et al., 2019; Hong et al., 2017). While the first occurrence of the benign Wolffian tumor in our patient was identified as PAX8 negative, the malignant recurrence was determined to be PAX8 positive. Our case reflects a deviation from the noted pattern and supports limitation on the diagnostic immunohistochemical markers (Shalaby and Shenoy, 2020; Ramirez et al., 2002).

Malignant diagnosis is determined by clinical recurrence and spread, with cautious interpretation of molecular and immunohistochemical markers (Rosen et al., 2019). Although patients may benefit from additional molecular genomic testing if actionable mutations are identified, not enough data is available to recommend specific targeted therapies for FATWOs in general. As more data becomes available, treatment can be tailored to each case.

Defining therapeutic standards for managing malignant Wolffian tumors has been challenging due to limited FATWO reports on malignancy and recurrence (Rosen et al., 2019; Ramirez et al., 2002). In absence of additional data, lymph node evaluation and omentectomy are suggested for staging of FATWO. If fertility is not desired, suggested management is tumor resection with TAH, BSO, and tumor debulking (Shalaby and Shenoy, 2020; Hubner et al., 2019; Syriac et al., 2011). Fertility-preserving approaches may be taken for younger patients; however, these therapeutic measures may increase the risk of recurrence and malignancy (Hubner et al., 2019; Syriac et al., 2011). During our patient's initial surgical management, her left ovary was spared to prevent the need for hormone replacement therapy given the patient's age. However, we discovered no evidence that sparing her left ovary caused her recurrence. For recommendations on surveillance, exams, and follow up, we extrapolate from ovarian cancer surveillance data as recommended by NCCN guidelines (Network and Clinical Practice Guidelines, 2020). If fertility-sparing procedures were performed, it is reasonable to obtain imaging every 3–6 months for at least 2 years. When checking tumor markers, if elevated pre-operatively, then it is reasonable to re-evaluate tumor markers following the same schedule as exams.

The literature suggests benefits from adjuvant chemotherapy, with limited information regarding adjuvant radiation therapy (Table 1). Three cases in the literature cite therapy with radiation, of which one had a recurrence (Ramirez et al., 2002). There is also limited evidence supporting use of hormonal targeted therapy as FATWOs have variable expression of hormone receptors (Hubner et al., 2019; Shalaby and Shenoy, 2020; Ramirez et al., 2002).

4. Conclusion

Due to the rarity of the Wolffian tumor, diagnostic and therapeutic standards for Wolffian tumors are limited. Our case contains many concordances with the literature with a few unique features. While immunohistochemical markers can aid in differentiating tumor origin, our case supports that these markers are inconsistent and must be interpreted cautiously. Compression symptoms involving the genitourinary and gastrointestinal tract should raise suspicion of recurrence.

Author Contribution

Author 1: Amal Amir

Compiled information, curated data, acquired consent, wrote original draft, and edited final draft.

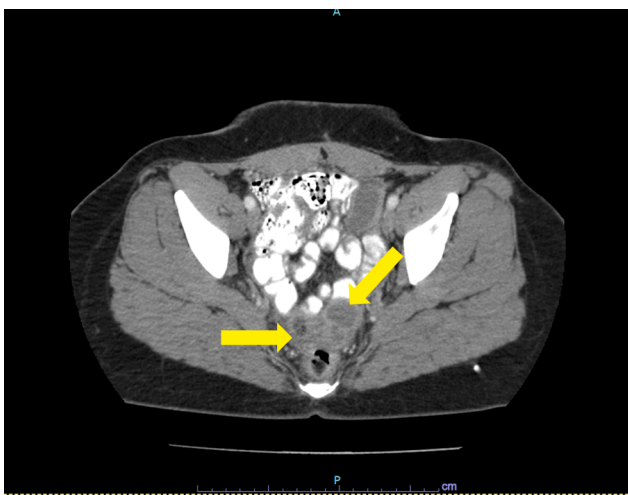


Fig. 1. Computed tomography (CT) of the abdomen and pelvis with contrast depicting multiple masses in the pelvis. There is a complex mass near the left ovary and left abdominal mass located anteriorly to the rectum.

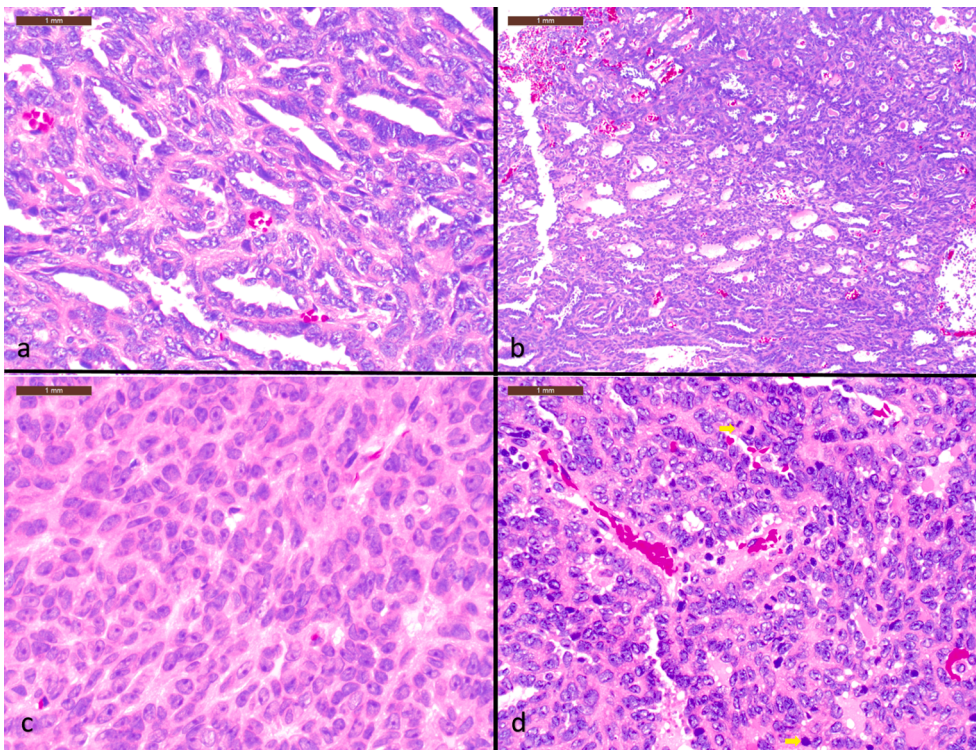


Fig. 2. a: This hematoxylin and eosin (H&E) stain demonstrates Wolffian tumor visualized on low magnitude (10x). This slide shows tubular pattern. b: (H&E stain) Wolffian tumor visualized on low magnitude (10x). This slide shows mixed sieve-like pattern. c: (H&E stain) Wolffian tumor visualized on high magnitude (40x). This slide shows mixed epithelioid and spindled components with cytologic atypia. d: (H&E stain) Wolffian tumor visualized on high magnitude (40x). This slide shows scattered mitotic figures (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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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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