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Female Adnexal Tumor of Probable Wolffian Origin (FATWO) With Recurrence 3 Years Postsurgery: *C-kit* Gene Analysis and a Possibility of a New Molecular Targeted Therapy

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Summary

This is the case report of a 38-year-old woman who presented with a mass of the right broad ligament that was diagnosed as a female adnexal tumor of probable Wolffian origin (FATWO). The patient was treated with a simple mass excision. Three years after the excision, the patient presented with uterine bleeding. A total abdominal hysterectomy was advised. Intraoperative histologic consultation showed a poorly differentiated tumor on the surface of the left ovary. After extensive immunohistochemistry analysis and after reviewing the histology slides from the primary tumor, the final diagnosis was concluded to be recurrent FATWO on the surface of the ovary. *C-kit* immunohistochemistry was found to be strongly positive. Polymerase chain reaction amplification of *C-kit* genes on exons 9, 11, 13, and 17 and of *PDGFR* gene on exons 12 and 18 showed no mutational changes. Owing to the limited options in treating recurrent disease and the lack of prognostic factors for recurrence or metastasis, the patient was started on 400 mg of imatinib mesylate therapy for 6 months. In addition, the patient is undergoing continuous follow-up by computed tomographic imaging every 6 months. As chemotherapy and radiation therapy for recurrent or metastatic FATWO are most often unsuccessful, a molecular targeted therapy, such as tyrosine kinase inhibitor, could be considered. However, collective data are needed from multiple centers to determine its effectiveness in these patients.

Keywords

FATWO; Recurrence; *C-kit*; Therapy

Female adnexal tumors of probable Wolffian origin (FATWO) are tumors arising in the leaves of the broad ligament and they are thought to originate from mesonephric remnants. FATWO are rare neoplasms with only 71 cases having been reported. Since their original description by Kariminejad and Scully in 1973 (1), 8 cases with recurrent disease have been identified (2). Although they are considered to be a tumor of low malignant potential, they have the potential to recur and a few cases have been found to metastasize. On account of the small number of reported cases that recur and/or metastasize, no recommendations

regarding initial evaluation, treatment, follow-up, or adjuvant and salvage therapy are available (2,3). As a result, Gleevac (STI 571), a tyrosine kinase inhibitor known to be the treatment of choice against gastrointestinal stromal tumors, was recently proven to be effective for 1 patient diagnosed with metastatic, C-kit-positive, FATWO (4).

Herein, we describe a 38-year-old patient who was diagnosed with FATWO of the right broad ligament. Three years later, the patient developed a left ovarian mass morphologically and immunophenotypically similar to the original tumor. Clinical, morphologic, immunohistochemical, *C-kit* gene mutational analysis of the tumor and treatment options are also discussed.

CASE REPORT

The patient is a 38-year-old White woman who originally presented in 2007 with a right adnexal mass. At laparotomy, she was noted to have a $12 \times 11 \times 10$ cm mass arising from the broad ligament. There was no evidence of any other pelvic or abdominal disease. The mass was surgically removed. After consultation with 2 different external expert pathologists, the mass was suggested to represent a FATWO. The patient had good recovery without complications. In the interim, the patient was diagnosed with invasive breast cancer. In 2010, while on tamoxifen, she experienced abnormal uterine bleeding. As a result, the patient underwent hysterectomy with the removal of bilateral tubes and ovaries. Intraoperatively, the right ovary seemed to be normal and the left ovary showed multiple, small, firm nodules, the largest measuring 1×1 cm. The frozen section diagnosis concluded as a poorly differentiated tumor. Therefore, complete staging was performed, including an omentectomy and bilateral pelvic and para-aortic lymph node dissection. Her postoperative course was uneventful and the patient was discharged 3 days after surgery.

A hysterectomy and bilateral salpingo-oophorectomy with lymphadenectomy and omentectomy specimens were received at the Department of Surgical Pathology at Roswell Park Cancer Institute. The left ovary showed multiple firm nodules on the surface, the largest of which measured $1.9 \times 1.7 \times 0.6$ cm. The right ovary showed multiple benign cysts. The uterus and both fallopian tubes were grossly unremarkable. Microscopic examination of the left ovary showed a tumor proliferation on the surface of the ovary, without invasion of the ovarian parenchyma. The tumor consisted of uniform, medium-sized cells arranged in a sieve-like pattern, with few glandular and solid areas. The neoplastic cells had a small amount of cytoplasm and oval-to-round nuclei. Few cells exhibited longitudinal nuclear grooves (Figs. 1A, B). In some areas, the tumor cells showed minimal cytologic atypia with prominent nucleoli. The uterus, omentum, and lymph nodes were all negative for tumor. Immunohistochemistry (IHC) showed tumor cells to be positive for AE1/3, cytokeratin (CK)7, WT1, calretinin, and α -inhibin and they were negative for epithelial membrane antigen (EMA), CK20, and synaptophysin (Figs. 2, 3). The tumor from the left ovary was compared with the original right adnexal mass from 2007, which showed similar morphology and immunophenotype. Consequently, the tumor on the surface of the left ovary was considered to be recurrent from her primary broad ligament tumor. However, the mitotic rate was higher in the recent tumor (15/10 high-power field) in comparison with the primary tumor (1/10 high-power field).

In addition, tumor cells were immunoreactive for C-kit (CD117). For a molecular study of the *C-kit* gene, DNA was extracted from the formalin-fixed, paraffin-embedded tissue as described earlier (5). A polymerase chain reaction amplification of exons 9, 11, 13, and 17 of the *C-kit* gene and of exons 12 and 18 of *PDGFR* gene was performed using a procedure published earlier (5,6). Sequencing analysis of exons on *C-kit* and *PDGFR* genes showed no mutational changes.

The patient did not have any postoperative complications. Owing to the limited options for treatment, and the minimal side effects of tyrosine kinase inhibitor therapy, the patient was started on 400 mg on imatinib mesylate (Gleevec; Novartis pharmaceuticals, NJ) therapy for 6 months with follow-up set at 6-month intervals.

DISCUSSION

FATWO is a rare neoplasm arising from the remnants of mesonephric/Wolffian ducts. These tumors were originally described in the leaves of the broad ligament. The age of the patients diagnosed with FATWO can range from 18 to 83 years with a median age of 50 years (2). Grossly, they are solid tumors with some tumors showing cystic components. Microscopically, these tumors can sometimes pose diagnostic difficulties and they should be distinguished from sex-cord stromal tumors [granulosa cell tumor (GCT) and Sertoli-Leydig cell tumor], and surface epithelial tumors (papillary serous and endometrioid adenocarcinoma). The characteristic histopathologic features are medium-sized neoplastic cells arranged in a sieve-like, diffuse pattern with tubules and cystic structures. The lack of Leydig cells argues against the diagnosis of Sertoli-Leydig cell tumors. The presence of nuclear grooves is nonspecific (can be seen in both FATWO and GCT), making the differentiation from GCT difficult. The IHC is crucial to make the correct diagnosis. FATWO tumor cells are immunoreactive for pancytokeratin (AE1/3), CAM5.2, CK7, WT1, α -inhibin, calretinin, and vimentin and they are negative for EMA and CK20. In sex-cord stromal tumors, α -inhibin is usually diffusely positive as opposed to focal positivity in FATWO. In addition, GCT is almost always negative for CK7 and positive for AE1/3 in 30% to 37% of cases (7,8). In addition, serous papillary carcinoma and endometrioid carcinoma are immunoreactive with total cytokeratin, EMA, and WT1, but are negative for α -inhibin (9,10). In this case, the original location of the tumor in the broad ligament and the tumor immunoprofile supports the diagnosis of FATWO.

Most FATWO cases are benign; however, a few cases have the potential to recur and metastasize. Metastasis/recurrences have been reported to occur in approximately 11% of cases and they may occur as early as 2 years. The most frequent metastatic sites are the liver and the lung (1,11). In our patient, the tumor recurred within a 3-year period. To the best of our knowledge, there are no histologic characteristics or biomarkers that can predict tumor outcome in patients diagnosed with FATWO.

Owing to the rarity of these tumors, there are no clear recommendations regarding patient treatment. Currently, the main treatment is surgical debulking, including a total abdominal hysterectomy and bilateral salpingo-oophorectomy. However, as chemotherapy and radiation therapy have not proven to be effective in recurrent FATWO tumors, the treatment options

are even more limited (1,4). Recently, C-kit immunoreactivity has been identified in 2 cases; 1 of these 2 cases had a molecular study undertaken and no mutational changes were found by polymerase chain reaction analysis (4,12). In this case, the tumor cells showed strong and diffuse immunoreactivity for C-kit antibody. However, for *C-kit* gene, no activating mutation was detected on exons 9, 11, 13, and 17. The positivity of C-kit by IHC and mutational analysis might be because of the methodology itself in which only limited exons were analyzed; meaning that only 25% of mutant alleles are detected by this method (13). Gleevec (STI 571) is a new type of tyrosine kinase inhibitor known to be effective in treating gastrointestinal stromal tumors. It selectively inhibits various tyrosine kinases including KIT, BCR-ABL, and platelet-derived growth factor. Gleevec is an oral medication with very few side effects including, but not limited to, skin rash, nausea, and vomiting (14). Steed et al. (4) showed that after chemotherapy failure, Gleevec therapy was successful in reducing tumor recurrence size in 1 patient after only 12 weeks of therapy and absence of disease after 10 months of follow-up. However, considering the early recurrence of the tumor (3 y), C-kit positivity and absence of effective systemic therapies, the best therapy that could be offered with no severe side effects was STI 571. Thus, the patient started 400 mg of Gleevec orally, every day for 6 months followed by clinical and computed tomographic imaging assessment of her disease status.

Owing to the small number of recurrent metastatic FATWO cases, there are no clear recommendations regarding treatment options. The therapy of choice for primary FATWO is a total abdominal hysterectomy with bilateral salpingo-oophorectomy. However, the role of chemotherapy and radiotherapy in recurrent disease is unknown and thus, has proven to be unsuccessful. Despite the lack of sufficient data on the effect of Gleevec on these types of tumors, the administration of this target molecular therapy in recurrent, *C-kit*-positive, FATWO could be considered. A multicenter effort to collect and identify those patients with the diagnosis of FATWO with recurrence and metastasis to confirm the value of Gleevec is needed.

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FIG. 1.

(A) Proliferation of tumor cells in a sieve-like pattern is seen (hematoxylin and eosin, 10 ×).

(B) Tumor cells are medium in size and exhibit mild cytologic atypia with few cells with prominent nucleoli.

FIG. 2.
Tumor cells are strongly positive for total cytokeratin (AE1/3) (40 ×), for CK7 (40 ×), calretinin (40 ×), and for WT1 (40 ×).

FIG. 3.
Tumor cells are also positive for C-kit/CD117 (40 ×) and they are negative for epithelial membrane antigen EMA (40 ×).