Female Adnexal Tumor of Probable Wolffian Origin

A Review

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Context.—Female adnexal tumor of probable Wolffian origin (FATWO) is an extremely rare gynecologic neoplasm of low malignant potential. Fewer than 90 cases of this entity have been described in the English-language literature. It is presumed to be derived from mesonephric (Wolffian) duct remnants in the upper female genital tract. We provide a literature review to increase awareness of this extremely uncommon entity.

Objectives.—To review the clinical and pathologic findings of FATWO and to discuss common entities in the differential diagnosis.

Data Sources.—The study involved PubMed (National Center for Biotechnology Information, Bethesda, Maryland) searches, including multiple review articles, case reports, retrospective studies, selected book chapters, and University of Mississippi Medical Center cases.

Conclusions.—FATWO can affect patients from a wide age range and present with a nonspecific clinical presentation. It typically presents as solid tumors with occasional nodular, lobulated, or cystic appearances. FATWO can show a variety of histologic patterns which may result in diagnostic difficulties for pathologists. There is no single specific immunohistochemical stain for FATWO, and the pathogenesis and molecular alterations are not yet well understood. Although it is generally considered a benign entity, recurrent and metastatic cases have been reported. There are no current recommendations regarding the optimal clinical management of FATWO.

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Female adnexal tumor of probable Wolffian origin (FATWO) was first described in 1973 by Kariminejad and Scully.1 They designated this tumor as female adnexal tumor of probable Wolffian origin because of its location in the broad ligament in which Wolffian remnants are abundant and because it lacks resemblance to tumors of müllerian origin.1 The mesonephric (Wolffian duct) system traverses numerous female reproductive organs, including the broad ligament, mesosalpinx, fallopian tubes, ovaries, and peritoneum, and is believed to be the origin of FATWO. This is a rare gynecologic neoplasm of low malignant potential with fewer than 90 cases being reported worldwide in the English language literature.2 The rarity of reported cases, the nonspecific clinical manifestations, the variable histologic patterns, and the poorly defined radiologic features make the diagnosis of FATWO very challenging.

CLINICAL FEATURES

Patients with FATWO often present with vague abdominal symptoms, such as abdominal pain or a palpable mass if the tumor is large enough.3,4 Many patients remain asymptomatic, and the tumors are discovered incidentally during physical examination or abdominal surgeries performed for other pathologies.2 The age of patients diagnosed with FATWO ranges from 15 to 83 years. The mean age at diagnosis is reported to be 50 years.5 The most frequent location of FATWOs is in the broad ligament, but they can also be found in the ovary, fallopian tube, paravaginal area, or the retroperitoneum.6 Preoperative serum cancer antigen 125 (CA-125) levels are typically within reference range in FATWO7 and currently there are no serum biomarkers that are directly associated with the development of the disease.5

RADIOLOGIC FINDINGS

In patients with FATWO who present with symptoms, pelvic ultrasound is commonly used as the initial diagnostic imaging technique. Ultrasound typically demonstrates a semisolid, well-vascularized mass, which leads to further imaging. Computed tomography scans demonstrate lesions that are solid, cystic, or heterogeneously enhanced and are more accurate than ultrasounds in determining the origin of the lesion and the tumor’s anatomic features and possible metastatic implants.2,6 Matsuki et al8 reported that magnetic resonance imaging is often nonspecific because FATWOs are typically described as slightly hyperintense adnexal masses with cystic degeneration, which is very difficult to differentiate from subserosal leiomyomas and ovarian tumors such as thecomas.
GROSS PATHOLOGY

In addition, FATWOs vary widely in size, with reported cases ranging from 0.8 to 25 cm in diameter. On gross examination, the tumors are typically sharply demarcated and encapsulated. The cut surface is gray-yellow or light brown, often solid, but also sometimes nodular, lobulated, or cystic with a smooth, glistening appearance. Focal hemorrhage and cystic necrosis can be seen in the mostly solid tumors.9,10

MICROSCOPIC FEATURES

Moreover, FATWOs can show high intratumor and intertumor variability and exhibit a variety of architectural patterns.9 Histologic patterns may include (1) solid (consisting of sheets of fusiform to spindle cells), (2) tubular (with closely packed, winding, branching, and anastomosing slender tubules; Figure, A through C), or (3) sievelike (with hollow tubules varying in size and shape with cyst formation). Rare trabecular or micropapillary patterns may also be seen. In most instances, it is the mixture of patterns that is diagnostic and distinguishes FATWOs from other tumors such as Sertoli cell tumors, adenomatoid tumors, and clear cell carcinomas.11,12 Cytologically, these tumors are characterized by stratified or simple flattened epithelium with small- to medium-sized round, ovoid, or spindle-shaped nuclei, inconspicuous and occasionally prominent nucleoli, and variable but typically low mitotic rate and minimal atypia (Figure, D).11,13 Homogenous periodic acid–Schiff–positive eosinophilic secretions may be seen within the lumens of some of the tubules, particularly those that are cystic. The stroma varies from a delicate network of reticulin fibers separating the solid tubules to large areas of hyalinized collagen.11

IMMUNOHISTOCHEMISTRY

There is no single specific immunohistochemical (IHC) stain for FATWOs. However, the use of IHC panels is crucial in making the diagnosis and differentiating FATWOs from other similar entities. FATWOs have been reported to be immunoreactive for pancytokeratin (AE1/3; 100%), CAM 5.2 (100%), cytokeratin 7 (88%), keratin 903 (17%), CK8, CK18, CD10, calretinin (91%; Figure, E), inhibin-A (68%; Figure, F), and vimentin (100%).11,5,7,14 They are typically negative for epithelial membrane antigen (EMA), S100, actin, CD15, human bone marrow endothelial marker-1 (HBME-1), and CK20.5,7,15 Staining with chromogranin, synaptophysin, and neuron-specific enolase is usually weakly positive.2 Variable expression of estrogen receptor, progesterone receptor, androgen receptor, Wilms tumor 1 (WT1), and CD117 (c-Kit) has been reported.11

MOLECULAR FEATURES

The pathogenesis and molecular alterations of FATWO are not well understood. Mirkovic et al11 used a 300-gene panel on a limited series of 7 cases to identify driver mutations in FATWOs and to identify possible genetic differences between FATWO and other pathologically related entities using massively parallel sequencing. A few nonrecurrent molecular aberrations, which are significantly different from those found in entities in the differential diagnosis, were identified. FATWO was characterized by a low mutational burden and by the absence of KRAS/NRAS mutations (characteristic of mesonephric carcinoma), the absence of DICER1 mutations (characteristic of Sertoli-Leydig cell tumor), the absence of PTEN, PIK3CA, KRAS, and CTNNB1 mutations (characteristic of endometrioid carcinoma), and frequent KMT2D mutations of uncertain biologic significance.11 Larger gene panels, whole exome sequencing, or alternative molecular methods may be helpful to further characterize the molecular pathogenesis of FATWOs. Additionally, several IHC investigations on FATWOs demonstrated strong or weak expression of the c-Kit protein (CD117); nevertheless, cases without CD117 immunostaining have also been described.9 Harada et al16 performed polymerase chain reaction and sequencing analyses for exons 9 and 11 of the c-Kit gene on a FATWO case that was immunohistochemically positive for c-Kit and revealed no mutation in either exons 9 or 11. It still remains unclear whether c-Kit gene mutations are essential to FATWOs.16

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of FATWO (Table) includes endometrioid adenocarcinoma of the fallopian tube, Sertoli-Leydig cell tumor, and broad ligament granulosa cell tumor (GCT). Endometrioid carcinomas arise from the fallopian tube, whereas FATWO is extratubal and usually arises within the broad ligament and ovary. Moreover, endometrioid carcinoma occasionally presents focal squamous differentiation and intraluminal mucin, which have not been reported in FATWO cases. Nuclear atypia and mitoses are much more common in endometrioid adenocarcinoma than they are in FATWO. Endometrioid carcinoma staining is positive for EMA and negative for calretinin and inhibin-α, but EMA negativity and calretinin and inhibin-α positivity are in line with FATWO. Sertoli-Leydig cell tumors may bear a strong morphologic resemblance to FATWO, but the presence of a sievelike pattern and the absence of Leydig cells may be useful in the diagnosis of FATWO. Additionally, Sertoli-Leydig cell tumors typically exhibit endocrine symptoms that are absent in FATWO. Moreover, Sertoli-Leydig cell tumors have not been observed in the paratubal area or in the broad ligament. GCTs are also important to consider in the differential diagnosis because of their morphologic and immunophenotypic features that occasionally mimic FATWOs. Grooved nuclei, scant cytoplasm, and endocrine manifestations are traits of GCTs that resemble Wolffian duct tumors pathologically.2,7,9,11,16 Recent studies suggest that steroidogenic factor-1 (SF-1) may be helpful in the distinction of FATWOs from Sertoli-Leydig cell tumor, Sertoli cell tumor, and adult GCT because FATWOs are consistently negative for this marker which is positive in most sex cord-stromal tumors; however, only a few cases have been studied.11 In sex cord-stromal tumors, inhibin-α is usually diffusely positive as opposed to the focal positivity in FATWO.15 In addition, GCTs are almost always negative for CK7 and are positive for AE1/3 in 30% to 37% of cases. In addition, endometrioid carcinoma is immunoreactive with a broad spectrum cytokeratin, EMA, and WT1 but are negative for inhibin-α.15 However, Kommos et al17 demonstrated positive staining for inhibin-α in 90% of tumors of probable Wolffian origin as well as in a range of sex cord-stromal tumors of the ovary. These findings may indicate that inhibin-α is not sufficient to distinguish between Sertoli cell and Wolffian tumors and that additional immunostains should be used as well.17

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Review of Pathologic Features of FATWO—Shalaby & Shenoy
Microscopic appearance of female adnexal tumor of probable Wolffian origin. A, Tumor shows closely packed branching tubules. B, Tumor shows tubules of varying shapes and sizes giving a glandular appearance. C, Tumor shows solid architectural growth pattern. D, High-power view shows tumor cells with a moderate amount of eosinophilic cytoplasm, round to ovoid nuclei and prominent nucleoli. E, Calretinin stain shows strong and diffuse positivity in tumor cells. F, Inhibin stain shows patchy positive tumor cells (hematoxylin-eosin, original magnifications ×100 [A through C] and ×400 [D]; original magnification ×200 [E]; original magnification ×200 [F]).
TREATMENT AND PROGNOSIS

Although most cases of FATWO exhibit benign clinical behavior, a few cases behave aggressively. In recent years, some recurrent and metastatic cases have been described. Metastases and recurrences have been reported to occur in approximately 11% of cases and they may occur as early as 2 years after diagnosis. Liver and lung were the most frequent metastatic sites. Median time for recurrences was 48 months with a range of 13 to 96 months and in some cases recurrences occurred a long interval after the diagnosis. Most recurrent tumors have developed in patients that were initially treated with tumor resection alone. The prognosis of FATWOs has not been found to correlate with its clinical presentation or histopathologic features, and recurrence can occur in the absence of aggressive histopathologic findings. However, the presence of necrosis, capsular invasion, a high number of mitoses, cellular pleomorphism, immunohistochemical positivity for CD117 and, probably, overexpression of Ki-67 are currently known properties of FATWOs with malignant potential. The presence of these findings should warrant careful evaluation of the patient with full investigation and appropriate follow-up. Because of the few reported cases, there are no comprehensive recommendations regarding initial evaluation, treatment, follow-up, or adjuvant and salvage therapy for FATWO. Various therapeutic options have been discussed in the literature. Complete surgical resection with hysterectomy, bilateral adnexitomy, and debulking of the tumor is considered to be the most effective therapy for primary FATWO. Chemotherapy and radiation therapy have a controversial role in the treatment of recurrent and malignant FATWO. The most commonly used chemotherapeutic regimen in malignant cases is paclitaxel and carboplatin. Tyrosine kinase inhibitors such as imatinib were also used in some patients with c-Kit+ tumors. However, to determine the effectiveness of this option, collective data are needed from multiple centers.

CONCLUSIONS

Female adnexal tumor of probable Wolffian origin is an extremely uncommon gynecologic neoplasm that is thought to derive from the mesonephric remnants in the upper female genital tract. It can exhibit different growth patterns and architectural features. Recognizing the variable morphology and the appropriate use of immunohistochemical stains is recommended to make the diagnosis of FATWO and to differentiate it from the more common similar entities. A few studies have investigated the molecular abnormalities seen in FATWO. More studies are needed to further characterize the molecular mechanisms underlying the pathogenesis of FATWO. There are currently no specific histologic criteria or serum biomarkers that can predict prognosis in patients with FATWO. This tumor generally exhibits a benign clinical behavior; however, recurrent and metastatic cases have been reported.

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