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Original Article

Value of PAX-8 and SF-1 Immunohistochemistry in the Distinction Between Female Adnexal Tumor of Probable Wolffian Origin and its Mimics

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Summary: Female adnexal tumors of probable wolffian origin (FATWOs) are rare. They can closely mimic endometrioid adenocarcinomas with a prominent spindle cell component and Sertoli cell tumors (SCTs). To further define their immunohistochemical profile and origin, we investigated the expression of PAX-8, PAX-2, and GATA binding protein 3 (GATA-3) (wolffian markers) and of steroidogenic factor-1 (SF-1) (sex-cord stromal marker) in FATWOs. We also studied the expression of PAX-8 and PAX-2 in endometrioid adenocarcinomas; of SF-1 in Sertoli-Leydig cell and SCTs; and of PAX-8, PAX-2, GATA-3, and SF-1 in rete ovarii—a proposed site of origin for FATWOs. A database search yielded 8 FATWOs, 18 ovarian/tubal/paraovarian endometrioid adenocarcinomas, and 8 ovarian Sertoli-Leydig cell and SCTs. Eleven cases with rete ovarii sections were included. Of the FATWOs studied, all were negative for PAX-8, PAX-2, GATA-3, and SF-1. Of the endometrioid adenocarcinomas studied, PAX-8 was positive in all and PAX-2 was positive in 57%. Of the Sertoli-Leydig cell and SCTs, all were positive for SF-1 except one. The rete ovarii were positive for PAX-8, weakly positive for SF-1, and negative for PAX-2 and GATA-3. Our study suggests that PAX-8 and SF-1 can be helpful in the distinction between FATWOs and endometrioid adenocarcinomas and SCTs, respectively. Our results do not support a Mullerian or sex-cord stromal or rete ovarii origin for FATWOs. It is curious, however, that FATWOs do not express wolffian markers—it is possibly related to their origin from a distinctive portion of the wolffian duct. **Key Words:** FATWO—Endometrioid—Sertoli cell—PAX-8—SF-1—FATWO-like.

Female adnexal tumors of probable wolffian origin (FATWOs) are rare epithelial neoplasms that are thought to arise from the remnants of the mesonephric (wolffian) duct (1,2). They are primarily located in the broad ligament, mesosalpinx, or ovary and are rarely seen in a paravaginal location (1,3,4). Most tumors have a benign outcome; however, occasionally they may recur and rare tumors may metastasize distantly (5–8).

The diagnosis of FATWOs is essentially based on morphology (with their characteristic diffuse, sieve-like, and tubular patterns) in conjunction with the anatomic location of the tumor (1). Immunohistochemistry is helpful as an adjunct, however, the results are variable (2,9,10). FATWOs can be mimicked to a great extent by endometrioid adenocarcinomas with spindled areas and by sex-cord stromal tumors, especially Sertoli cell tumors (SCTs). These tumors can exhibit FATWO-like areas and can also have immunohistochemical (IHC) overlap with FATWOs (11–15). Hence, there is a need for IHC

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markers that can further aid in this differential diagnosis.

Paired box proteins PAX-8 and PAX-2 are established useful markers for Mullerian tumors. In addition, they are also expressed in tumors of wolffian origin (16–19). GATA binding protein 3 (GATA-3) is another transcription factor that plays an important role in the morphogenesis of the wolffian duct (20). Also, steroidogenic factor-1 (SF-1) is an IHC marker that is specific for sex cord stromal tumors (21). To our knowledge, the expression of the aforementioned markers has not been evaluated in FATWOs previously. To better define their IHC profile and origin, we have investigated the expression of PAX-8, PAX-2, GATA-3, and SF-1 in FATWOs. In addition, we studied the expression of PAX-8 and PAX-2 in FATWO-like endometrioid adenocarcinomas, of SF-1 in Sertoli-Leydig cell tumors (SLCTs) and SCTs and of PAX-8, GATA-3, and SF-1 in rete ovarii—one of the proposed sites of origin of FATWOs.

MATERIALS AND METHODS

Following approval by the Institutional Review Board at the Cleveland Clinic, a database search was conducted (from January 1990 to November 2014) for cases of FATWO, ovarian SLCTs and SCTs, and of endometrioid adenocarcinomas that are ovarian or tubal in origin or those that originated from foci of endometriosis in the pelvis. The slides and paraffin-embedded blocks (if available) were retrieved from the archives of the Pathology Department, Cleveland Clinic, Cleveland, Ohio. The hematoxylin and eosin-stained slides were reviewed for all cases.

IHC staining for PAX-8 (rabbit polyclonal, 1:200; ProteinTech Group, Chicago, IL) was performed on all cases of FATWO and endometrioid adenocarcinomas. PAX-2 (rabbit monoclonal, EP3251, 1:50; Epitomics, Burlingame, CA) was performed on FATWOs and endometrioid adenocarcinomas, and GATA-3 (mouse monoclonal, L50-823, 1:100; Biocare Medical, Concord, CA) and SF-1 (mouse monoclonal, N1665, 1:100; R&D Systems, Minneapolis, MN) were performed on FATWOs in cases with available unstained slides or blocks. SF-1 was performed on all cases of SLCTs and SCTs. In addition, slides with rete ovarii from 11 oophorectomy specimens (for benign disease) were stained with PAX-8, PAX-2, GATA-3, and SF-1.

Epitope retrieval was performed using low pH citrate retrieval buffer for PAX-8 for 44 min, high pH EDTA retrieval buffer for PAX-2 for 60 min, high pH EDTA retrieval buffer for GATA-3 for 32 min, and high pH retrieval buffer for SF-1 for 10 min. The antibody incubation times at room temperature were 32 min for PAX-8, 60 min for PAX-2, 24 min for GATA-3, and 30 min for SF-1. The IHC staining for PAX-8 and PAX-2 was detected using the ultra-View DAB polymer-based detection kit (Ventana Medical Systems). For GATA-3, the staining was detected using the optiView DAB IHC detection kit (Ventana Medical Systems), whereas for SF-1, Bond Polymer Refine Detection kit (Leica Biosystems) was used. Positive controls included renal cell carcinoma for both PAX-8 and PAX-2, adrenal cortex for SF-1, and benign breast tissue for GATA-3. Positive and negative controls (without the primary antibody) were included with each run.

The immunostaining results were recorded as positive and negative staining patterns. For all stains, only nuclear staining was considered to be positive. The nuclear staining was recorded as focal ($<50\%$ cells) or diffuse ($\geq 50\%$ cells) with the intensity as weak, moderate, or strong. Negative staining patterns included cases with total absence of any staining as well as cases with only rare ($<5\%$) positive cells. Clinicopathologic information was obtained from the patients' electronic medical record and surgical pathology reports.

RESULTS

FATWOs

Pathologic Findings

Eight cases of FATWO from 7 patients were retrieved. The tumor locations were as follows: ovary (2 cases), paraovarian (2 cases), broad ligament (1 case), mesosalpinx (1 case), and paratubal (1 case). The tumor size was known in 4 cases, it ranged from 6 to 18 cm in size (average, 11.2 cm) in greatest dimension. The gross features were known in 4 cases—cystic and solid mass with tan-yellow to orange solid areas.

Microscopically, the tumors exhibited a combination of histologic patterns with varying proportions of solid, tubular, sieve-like, retiform, and spindled patterns (Figs. 1A, B). Six of the 8 tumors had no significant cytologic atypia, lacked necrosis, and had absent to rare mitotic figures. The remaining 2 tumors belonged to the same patient (with multiple recurrences) and depicted moderate to severe cytologic atypia, foci of necrosis, and mitotic figures up to 15 per 10 high-power fields.

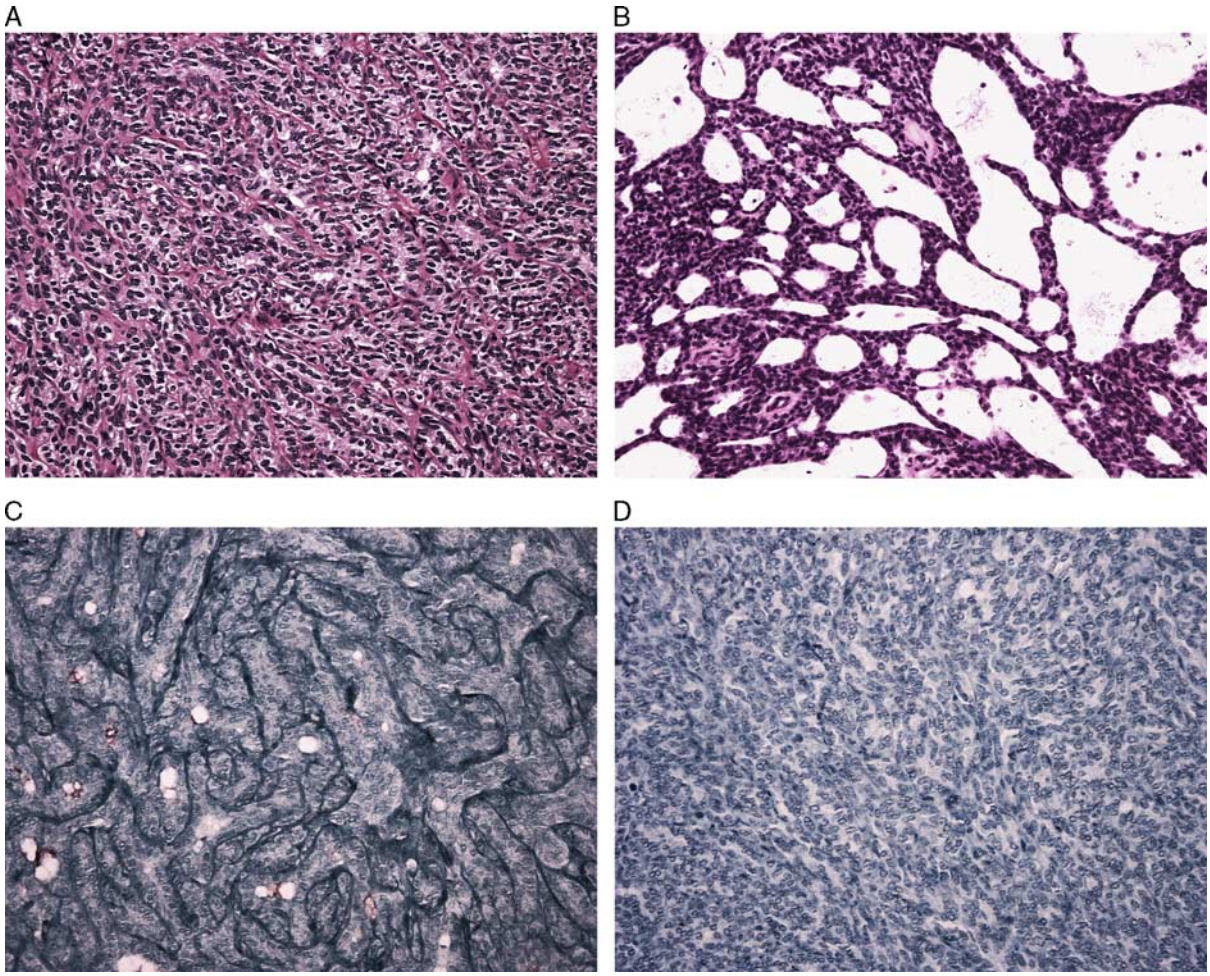

FIG. 1. Morphologic and immunohistochemical features of female adnexal tumors of probable wolffian origin (FATWOs). FATWO with typical histologic patterns—tubular (A) and sieve-like patterns (B) and lined by cytologically bland epithelium (hematoxylin and eosin; magnification: 200 ×). FATWOs were uniformly negative for PAX-8 (C), and steroidogenic factor-1 (SF-1) (D) (magnification: 200 ×).

IHC Findings

PAX-8 was uniformly negative in all the 8 cases of FATWO (Fig. 1C). PAX-2 immunostain could be evaluated in 5 cases and was negative in all of them. The staining patterns of GATA-3 and SF-1 (Fig. 1D) were studied in 5 cases—they were negative in all cases.

In 4 of these 8 cases, additional immunostains had been previously performed to support a diagnosis of FATWO. All 4 cases were positive for AE1/3 and for CD10 and were negative for epithelial membrane antigen (EMA). Three of the 4 cases showed focal reactivity with calretinin and 2 were focally positive for inhibin. CAM5.2 and CK7, each evaluated in 2 cases, were positive. Wilms tumor 1 protein (WT-1) was positive in 2 of the 3 cases that were evaluated and both estrogen and progesterone receptors were positive in one of the 2 cases that were stained.

Endometriod Adenocarcinomas With FATWO-like Areas

Pathologic Findings

Eighteen cases of endometrioid adenocarcinoma arising in ovary, fallopian tube, or pelvic endometriosis were retrieved. Of these, 3 cases showed foci resembling FATWO—the pathologic features of which are described further. The tumor locations were: fallopian tube, ovary (size, 13 cm), and pelvic mass adjacent to the ureter (size, 3.2 cm). The tumor mass in the fallopian tube occupied the lumen. The gross features were known in 2 cases—solid (tan-white) and cystic mass and solid mass with tan cut surface.

Microscopically, the striking feature in all cases was the presence of a prominent spindle cell

component. These spindle cells formed whorls and also merged with the glandular component (Fig. 2A). The glandular component was lined by cuboidal epithelium with cystically dilated glands imparting a sieve-like appearance in 2 cases. One case had conspicuous retiform areas. Foci of typical endometrioid adenocarcinoma were identifiable in 1 case. Two tumors showed moderate cytologic atypia, whereas one exhibited moderate to marked cytologic atypia (Fig. 2B). Mitotic activity was pronounced in 2 cases (up to 11 and 15 per 10 high-power fields). Focal necrosis was identified in 1 case. The pelvic mass showed possible foci of endometriosis from which the tumor likely originated. Interestingly, the latter case had been diagnosed as FATWO on frozen section during intraoperative consultation.

IHC Findings

All 3 tumors with FATWO-like areas revealed diffuse staining with PAX-8—moderate to strong intensity in both the glandular and the spindled areas in 2 cases (Fig. 2C) and weak to moderate intensity in the glandular areas with weak intensity in the spindled areas in the remaining case. PAX-2 was evaluated in 2 cases and showed strong and diffuse staining both in the glandular and in the spindled areas in 1 case (Fig. 2D) and was negative in the other case.

All 15 cases of conventional endometrioid adenocarcinoma were diffusely positive for PAX-8 with strong intensity. PAX-2 staining was analyzed in 12 of these—7 were positive, 2 with strong intensity, and 5 with moderate intensity. The remaining 5 cases were negative.

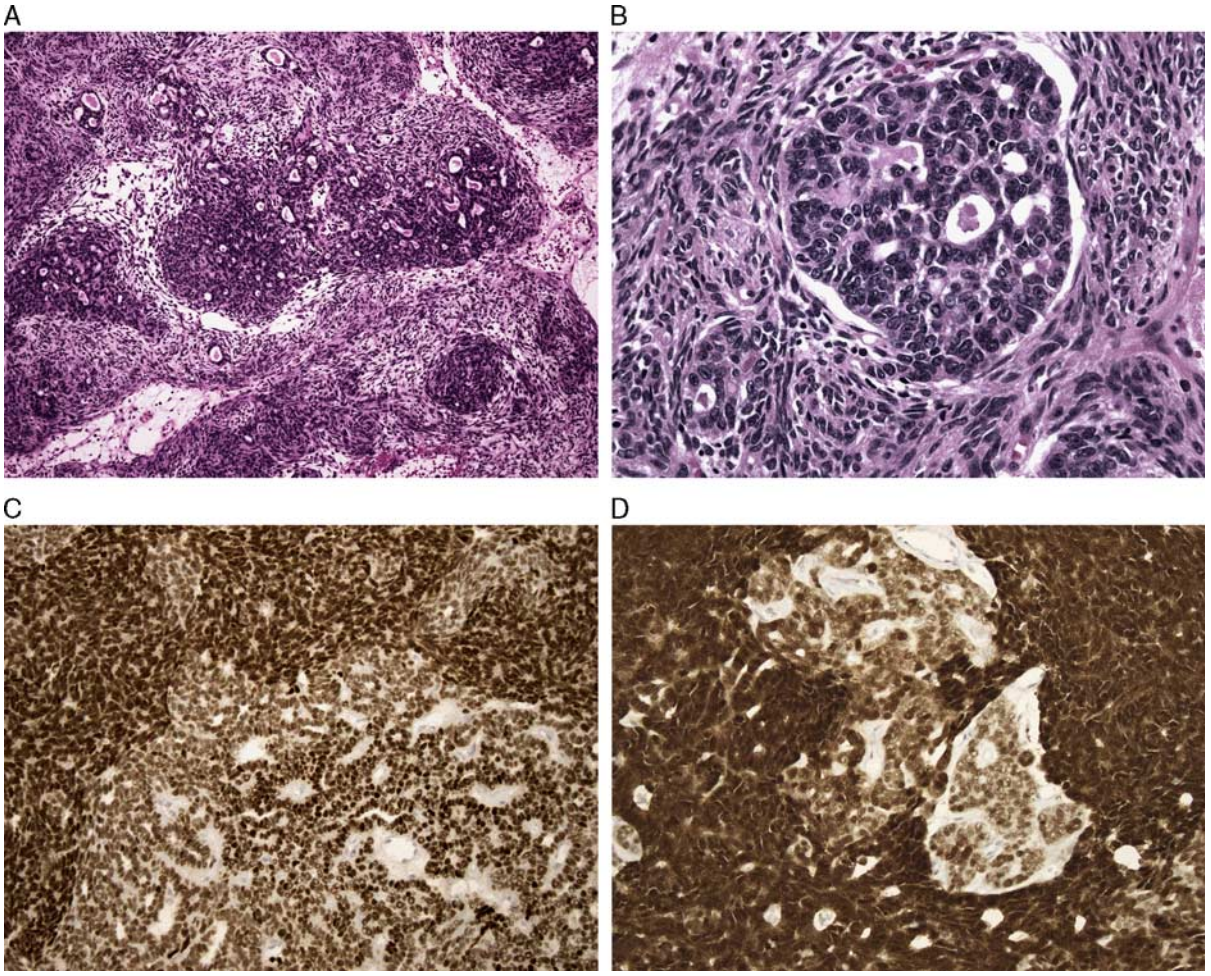

FIG. 2. Morphologic and immunohistochemical features of endometrioid adenocarcinomas. Endometrioid adenocarcinoma with a prominent spindle cell component, merging with the glandular areas (A) [hematoxylin and eosin (H&E); magnification: 100 ×]. Another case with typical foci of endometrioid adenocarcinoma and moderate cytologic atypia (B) (H&E; magnification: 400 ×). PAX-8 showed diffuse positivity—strong intensity in both the glandular and the spindled areas (C); PAX-2 was evaluated in 2 cases and showed strong and diffuse staining both in the glandular and in the spindled areas in 1 case (D) (magnification: 200 ×).

SLCTs and SCTs

Our study included 3 SCTs and 5 SLCTs. Tumors with more than rare Leydig cells were classified as SLCTs. The 3 SCTs included a well-differentiated tumor, a poorly differentiated tumor, and a retiform tumor with intermediate differentiation. The SLCTs included 2 poorly differentiated tumors, 2 cases with intermediate differentiation and 1 well-differentiated tumor.

IHC Findings

All 3 SCTs exhibited diffuse expression of SF-1—2 with moderate intensity and 1 with strong intensity (Figs. 3A, B). Of the 5 SLCTs, 4 tumors expressed SF-1—3 with strong and diffuse staining and 1 with focal moderate staining. SF-1 was also expressed in the Leydig cell component of the positive SLCTs (Figs. 3C, D). The remaining case of SLCT was negative for SF-1.

Rete Ovarii

The rete ovarii (Fig. 4A) in all the 11 cases stained diffusely and strongly with PAX-8 (Fig. 4B) while being negative for PAX-2 and GATA-3. All cases showed diffuse weak nuclear staining with SF-1 (Fig. 4C).

The key IHC findings are summarized in Table 1.

DISCUSSION

Because of their rarity and variety of histologic appearances, FATWOs can pose a diagnostic

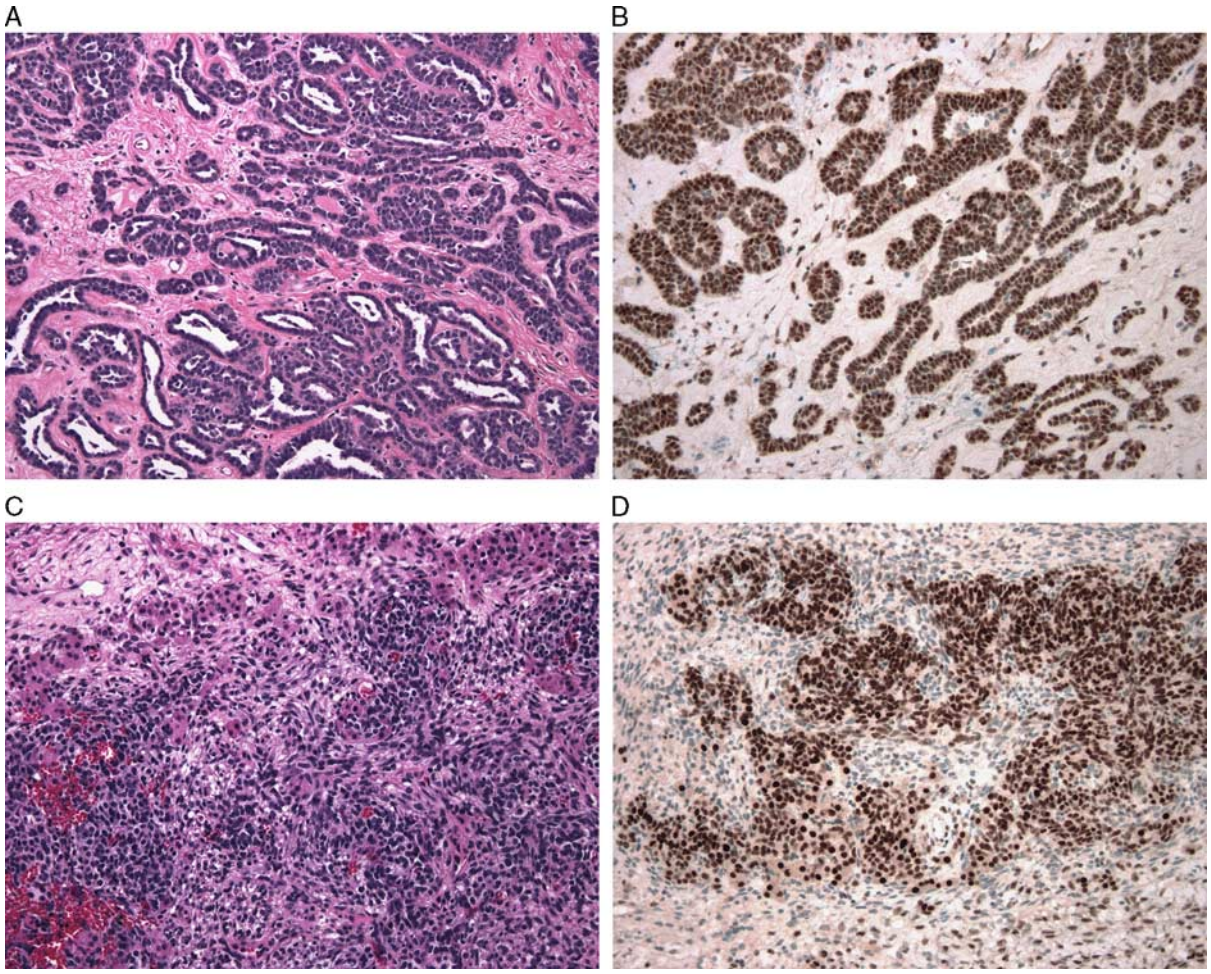

FIG. 3. Immunohistochemical features of Sertoli-Leydig cell and Sertoli cell tumors. Retiform Sertoli cell tumor with branching slit-like spaces (A) [hematoxylin and eosin (H&E); magnification: 200 ×]. The tumor exhibited diffuse and strong positivity for steroidogenic factor-1 (SF-1) (B) (magnification: 200 ×). Sertoli-Leydig cell tumor with intermediate differentiation with nests of Sertoli cells admixed with Leydig cells (C) (H&E; magnification: 200 ×). Both the Sertoli cell and Leydig cell components were strongly and diffusely positive for SF-1 (D) (H&E; magnification: 200 ×).

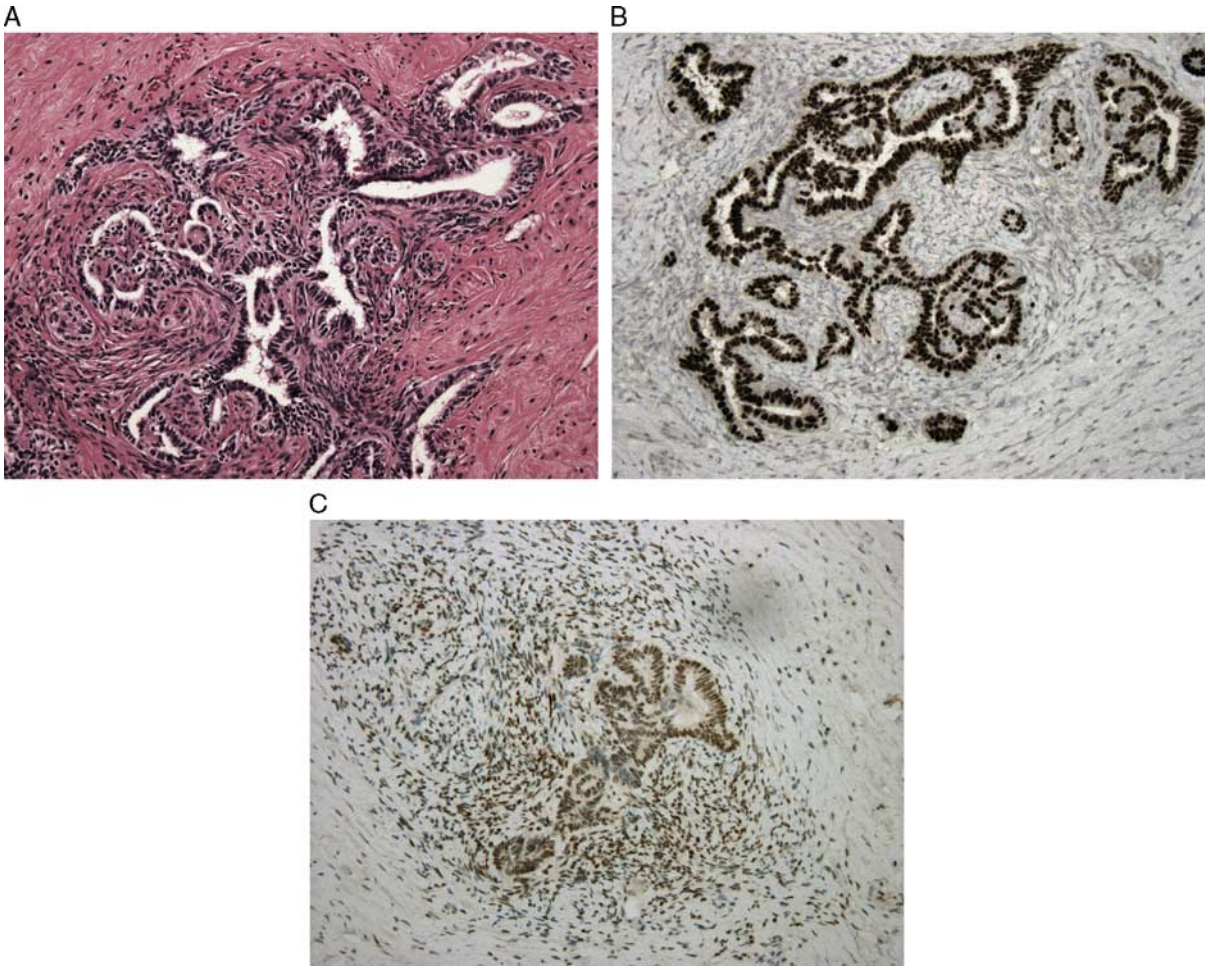

FIG. 4. Immunohistochemical features of rete ovarii. A network of tubules lined by bland cuboidal epithelium characterizes the rete ovarii (A) (hematoxylin and eosin); magnification: 200 ×]. The rete ovarii showed strong and diffuse positivity with PAX-8 (B) and were weakly positive for steroidogenic factor-1 (SF-1) (C) (magnification: 200 ×).

challenge. Two tumors that can closely simulate FATWOs are endometrioid adenocarcinomas with a prominent spindle cell component and well-differentiated SCTs. The former is an important differential diagnosis for tumors located in the fallopian tube or the ovary and the latter is a diagnostic consideration in the context of an ovarian tumor. Endometrioid adenocarcinomas mostly form an intraluminal mass in the fallopian tube rather than being paratubal in location like FATWOs. They usually exhibit areas of typical endometrioid adenocarcinoma, have more cytologic atypia and mitotic activity, may contain mucin and foci of squamous differentiation, and may be associated with endometriosis or an adenofibromatous component in the ovary (11,12). SCTs may lack the characteristic histologic patterns of FATWOs and may be associated with hormonal manifestations (1,14). Although there may be morphologic/anatomic/clinical clues, one often has to resort to immunohistochemistry to reach the correct diagnosis.

FATWOs typically express cytokeratins AE1/3 and CAM5.2 and vimentin (2,9). Focal CK7 reactivity has been reported in up to 88% of FATWOs. They are negative for monoclonal carcinoembryonic antigen and mostly negative for EMA with focal staining seen in 12% of cases. A good proportion of these tumors may be positive for calretinin, inhibin, and androgen receptor—91%, 68%, and 78%, respectively. Immunoreactivity may be seen with estrogen and progesterone receptors in up to 28% and 24% of cases, respectively (2). Also, FATWOs are usually positive for CD10 (22). These IHC features are nonspecific and overlap with those of its close differential diagnoses. Endometrioid adenocarcinomas are typically positive

TABLE 1. *Key immunohistochemical findings of FATWO and its mimics*

	Immunohistochemical stains			
Tumor types	PAX-8	PAX-2	GATA-3	SF-1
FATWO	Negative (8)	Negative (5)	Negative (5)	Negative (5)
Endometrioid adenocarcinoma	Positive (18)	Positive (8) Negative (6)	NA	NA
Sertoli-Leydig cell tumor	NA	NA	NA	Positive (4) Negative (1)
Sertoli cell tumor	NA	NA	NA	Positive (3)

FATWO indicates female adnexal tumors of probable wolffian origin; GATA-3, GATA binding protein 3; SF-1, steroidogenic factor-1.

for cytokeratins AE1/3 and CAM5.2, CK7, EMA, vimentin, and estrogen and progesterone receptors and may express calretinin and CD10 (23). SCTs are mostly positive for inhibin, calretinin, vimentin, and cytokeratins AE1/3 and CAM5.2 and are negative for EMA (14).

Considering the probably wolffian origin of FATWOs, we investigated the expression of PAX-8, PAX-2, and GATA-3 in these tumors. PAX-2 and PAX-8 are members of the PAX family of transcription factors that play an important role during embryogenesis in the development of organs derived from the Mullerian duct and from the mesonephric (wolffian duct) (18,24–27). GATA-3 is another transcription factor that plays a key role in the regulation of the wolffian duct morphogenesis and guidance in the developing kidney (20). PAX-8 and to a lesser extent, PAX-2 are expressed in tumors of wolffian derivation namely, renal cell carcinomas and nephrogenic adenomas (16,17,19). Regarding the mesonephric proliferations of the cervix, PAX-8, PAX-2, and GATA-3 have shown to be expressed in mesonephric remnants and hyperplasias as well as in malignancies including mesonephric carcinosarcomas (28–31). It is interesting that of the cases of FATWO analyzed in our study, all lacked the expression of PAX-8, PAX-2, and GATA-3.

The other important application of PAX-8 and PAX-2 immunohistochemistry is the recognition of tumors or lesions of Mullerian derivation. As compared with PAX-2, PAX-8 is expressed in a higher percentage of Mullerian tumors and therefore, has proven to be a superior IHC marker for these tumors (18). In terms of endometrioid adenocarcinomas of the ovary, PAX-8 and PAX-2 are reported to be expressed in 38% to 92% and 40% of these tumors, respectively (16,17). We analyzed the expression of PAX-8 and PAX-2 in endometrioid adenocarcinomas—both conventional type and those with a distinctive spindle cell component originating in the ovary, fallopian tube, and pelvic endometriosis. PAX-8 was positive in all the cases and PAX-2 in 57% of cases analyzed. These results are in contrast to that obtained with FATWOs and suggest that PAX-8 and to a lesser extent, PAX-2, can be employed as useful tools in this challenging differential diagnosis of FATWO versus endometrioid adenocarcinoma with FATWO-like areas.

SCT is another tumor that may enter into the differential diagnosis of FATWO in the ovary. SF-1, also known as adrenal 4-binding protein, is a nuclear transcription factor that regulates genes involved in steroidogenesis, development of gonads and adrenal glands, reproduction, sexual differentiation, and metabolism (32–35). It was identified as an important transcription factor regulating transcription of genes encoding for cytochrome P450 steroid hydroxylases (36,37). SF-1 has been shown to be a specific marker for sex-cord stromal tumors including SCTs (21). All the cases of FATWO in our study were negative for SF-1 as compared with the tumors with Sertoli cell differentiation, most of which (88%) were positive for SF-1. These results indicate the potential utility of SF-1 in the differentiation between ovarian FATWOs and SCTs.

Recently, somatic 402C→G missense mutation in the Forkhead box protein L2 (FOXL2) has been shown to be characteristic for adult granulosa cell tumors; being identified in 90% to 97% of these tumors (38). Almost all of these tumors also show IHC expression of FOXL2. FOXL2 immunostaining has also been detected in the Sertoli cell component of SLCTs and in FATWOs. Importantly, all the FATWO cases and most of the SLCTs with positive staining lacked FOXL2 mutation (39). The significance of this staining pattern in the absence of a FOXL2 mutation is not clearly known.

Another prevailing issue with FATWOs is defining their exact origin. Kariminejad and Scully initially described the clinicopathologic features of FATWO. They considered it to be wolffian in origin essentially based on its locations (that harbor mesonephric

remnants), the microscopic features and the exclusion of other diagnostic possibilities. They acknowledged that in some areas the tumor resembled sex cord stromal tumors. They argued that it is unlikely to be sex cord stromal in origin due to its extragonadal location and lack of association with hormonal manifestations (1).

Nogales (40) has conceptualized 2 different zones of the wolffian system—the upper zone including the rete ovarii and the lower zone including the mesonephric remnants in the lateral wall of the uterine corpus, cervix, and vagina. He has favored that FATWOs arise from the upper zone of the wolffian system. Devouassoux-Shisheboran and colleagues performed a detailed IHC comparison of FATWOs with the rete ovarii and the mesonephric remnants. They found that the IHC profile of the FATWOs (including immunoreactivity with inhibin and calretinin) was very similar to that of the rete ovarii and suggested that the FATWOs were derived from the upper zone of the wolffian system, that is, the rete ovarii (2). Tiltman and Allard showed in their study that the IHC expression of glutathione S-transferase μ (GSTμ), a marker expressed in the mesonephric duct remnants but negative in Mullerian duct derivatives, may be seen in FATWOs. They supported a mesonephric origin for the FATWOs (9). Zheng and colleagues, however, have expressed a different viewpoint regarding the origin of FATWOs. They have suggested that FATWO may represent an extraovarian form of sex cord stromal tumors as it shares IHC features with the latter (15).

To a certain extent, the IHC features of FATWOs help us understand their origin. In our study, the FATWOs not only lacked the expression of Mullerian and mesonephric markers, PAX-8 and PAX-2 and the mesonephric marker GATA-3. but also did not express the sex cord stromal marker SF-1. These findings do not support a Mullerian or a sex cord stromal origin of FATWOs. It is well acknowledged that the different parts of the wolffian duct exhibit differences in morphology as well as their IHC profile (40). The rete ovarii in our study had a different IHC profile from the FATWOs—they were strongly and diffusely positive for PAX-8, weakly positive for SF-1, and were negative for PAX-2 and GATA-3. Interestingly, in the male genital tract, wolffian adnexal tumor of the seminal vesicle, that shares morphologic and IHC features with FATWO, has been reported to be diffusely positive for PAX-8 and PAX-2 (41). In a nutshell, our study demonstrates that the FATWOs do exhibit some IHC features different from other structures/tumors that are thought to be wolffian in origin, suggesting its origin from a distinctive portion of the wolffian duct. However, our results are based on a limited number of cases—a larger study may be helpful for a better understanding of the IHC features and origin of FATWOs.

In conclusion, our study shows that PAX-8 and SF-1 can serve as useful IHC markers in the distinction between FATWOs and tumors with FATWO-like areas, that is, endometrioid adenocarcinomas with a prominent spindle cell component and SCTs, respectively. In addition, our work also provides new insights regarding the likely origin of FATWOs from the wolffian duct.

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