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Original Article

SF-1 is a Diagnostically Useful Immunohistochemical Marker and Comparable to Other Sex Cord-Stromal Tumor Markers for the Differential Diagnosis of Ovarian Sertoli Cell Tumor

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Summary: Immunohistochemistry can be an important part of the diagnosis of Sertoli cell tumor of the ovary, including distinction from non-sex cord-stromal tumors such as the sertoliform variant of endometrioid carcinoma and carcinoid. Several good markers for this differential diagnosis have been identified, particularly inhibin, Wilms tumor 1 gene product (WT1), epithelial membrane antigen, and chromogranin; however, many available markers have limitations to some degree. Steroidogenic factor 1 (SF-1; adrenal 4-binding protein; Ad4BP) is a nuclear transcription factor involved in gonadal and adrenal development. In the testes, SF-1 is expressed in Sertoli cells. Immunohistochemical expression of this marker in ovarian sex cord-stromal tumors, including utility for differential diagnosis, has not been rigorously evaluated. As an extension of our previous immunohistochemical studies of ovarian Sertoli cell tumor, expression of SF-1 and comparison with WT1 and inhibin were assessed in 111 primary ovarian tumors: 27 Sertoli cell tumors, 60 endometrioid tumors (including borderline tumors, conventional well-differentiated carcinomas, and sertoliform variants of carcinoma), and 24 carcinoids. SF-1 was expressed in 100% of Sertoli cell tumors but not in endometrioid tumors or carcinoid. WT1 was expressed in 100% of Sertoli cell tumors and 17% of endometrioid tumors; all carcinoids were negative. Inhibin was expressed in 96% of Sertoli cell tumors and 2% of endometrioid tumors (4% of conventional well-differentiated carcinomas); all carcinoids were negative. The extent of expression of all 3 markers was similar in Sertoli cell tumor but greatest for WT1: 63%, 96%, and 78% of cases showed expression of SF-1, WT1, and inhibin, respectively, in more than 50% of tumor cells. Immunohistochemical composite scores combining both extent and intensity of staining in positive cases were calculated for Sertoli cell tumor (possible range: 1–12). Combined extent/intensity of immunostaining was similar for all 3 markers, but WT1 showed the most robust immunoreactivity in positive cases (mean immunohistochemical composite scores for SF-1, WT1, and inhibin: 6.1, 10.8, and 7.8, respectively). We conclude that for the differential diagnosis with endometrioid tumors and carcinoid of the ovary, SF-1 is a sensitive and specific immunohistochemical marker for Sertoli cell tumor and that SF-1 is diagnostically comparable with other good sex cord-stromal markers. **Key Words:** Ovary—Sertoli cell tumor—SF-1—Steroidogenic factor 1—Ad4-binding protein.

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The diagnosis of ovarian Sertoli cell tumor and distinction from other non-sex cord-stromal tumors in the differential diagnosis, such as endometrioid tumors (borderline and sertoliform carcinoma) and carcinoid, can be difficult on occasion. Most cases can be distinguished based on traditional clinicopathologic features. In problematic cases, immunohistochemistry may be necessary. Numerous studies have evaluated various markers in the ovarian tumors mentioned above. Immunohistochemical markers with relative specificity in that differential diagnosis include inhibin, calretinin, and Wilms tumor 1 gene product (WT1) for sex cord-stromal lineage, CK7 and epithelial membrane antigen for epithelial lineage, and chromogranin and synaptophysin for neuroendocrine lineage. For example, pure Sertoli cell tumors express inhibin, calretinin, and WT1 in 82% to 98%, 50% to 60%, and 96% of cases, respectively (1–3). Optimal use of these markers requires evaluating them together in the context of a panel because any of the individual markers can yield deviant results and potentially may create diagnostic confusion. For instance, endometrioid carcinomas can express inhibin or calretinin in up to 25% to 36% of cases and WT1 in 13% to 25% of cases (2–21). Likewise, a subset of several different types of carcinomas from various nonovarian sites can variably express inhibin (15).

Much of the literature on diagnostic immunohistochemistry of ovarian sex cord-stromal tumors has been written during the last 15 years. As newer markers become available, the literature will continue to evolve. One molecule that is not new but which has diagnostic potential and has not been rigorously studied for the distinction of Sertoli cell tumor from non-sex cord-stromal tumors, such as endometrioid tumors and carcinoid, is steroidogenic factor 1 (SF-1; adrenal 4-binding protein; Ad4BP). SF-1 is a nuclear transcription factor that regulates genes which control steroidogenesis, development of the gonads and adrenal glands, sexual differentiation, reproduction, and metabolism (22–30). It is expressed in the testes, ovaries, adrenal glands, pituitary gland, and placenta. Interestingly, this distribution among these organs is similar to that of inhibin. Although the complex interaction between SF-1 and inhibin at the molecular level in different normal organs is not entirely understood, it is thought that, in general, SF-1 regulates the gene for the α subunit of inhibin (29). In the developing testes, SF-1 is expressed in Sertoli cells and Leydig cells, raising the question of whether it may be of immunohistochemical value for the diagnosis of ovarian Sertoli cell tumor.

This study is an extension of our previous immunohistochemical investigations on the ovarian tumors in the above differential diagnosis (2,3,31). The goals were to characterize expression of SF-1 in ovarian Sertoli cell tumor, endometrioid tumors (borderline tumor, conventional well-differentiated endometrioid carcinoma, and the sertoliform variant of carcinoma), and carcinoid and compare the diagnostic utility of immunohistochemical staining for SF-1 with that of other highly sensitive Sertoli cell tumor markers (inhibin and WT1) for this differential diagnosis.

MATERIALS AND METHODS

Case Selection

Primary ovarian pure Sertoli cell tumors, endometrioid borderline tumors, conventional well-differentiated endometrioid carcinomas, the sertoliform variant of endometrioid carcinoma, and carcinoids were retrieved from the files of the Armed Forces Institute of Pathology from 1970 to 2004 after Institutional Review Board approval, and these cases were reviewed by the authors.

Immunohistochemistry

Immunohistochemical stains for SF-1, WT1, and inhibin were performed in 111 ovarian tumors: 27 pure Sertoli cell tumors, 25 endometrioid borderline tumors, 23 conventional well-differentiated endometrioid carcinomas, 12 sertoliform endometrioid carcinomas, and 24 pure carcinoid tumors (18 insular type, 6 trabecular type). Endometrioid tumors with obvious squamous differentiation were not selected for this study. Endometrioid carcinomas were classified as being of the sertoliform type when composed of predominant areas showing architectural features commonly seen in pure Sertoli cell tumor, such as small round open or solid tubules, elongated solid tubules with the paired cell arrangement typically seen in Sertoli cell tumor, and thin cords of cells; these were cases that created strong consideration of pure Sertoli cell tumor in the histologic differential diagnosis but which had other areas with histologic features of conventional endometrioid carcinoma. Most of the sertoliform endometrioid carcinomas were positive for epithelial membrane antigen and CK7, and all were negative for inhibin and calretinin (2).

TABLE 1. *Details for antibodies used in this study*

Antigen	Clone	Dilution	Source	Pretreatment	Detection method/ chromogen	Autostainer
SF-1	N1665	1:100	R&D Systems; Minneapolis, Minnesota	TRS* pH 6.0 steamer 30 min	Envision + /DAB (Dako)	Dako
WT1	6F-H2	Prediluted	Cell Marque; Hot Springs, Arkansas	Protease 3-4 min, plus CC1 mild	Amplification Kit, *i*VIEW/DAB (Ventana)	BenchMark XT
Inhibin	R1	1:25	Dako; Carpinteria, California	CC1 standard	*i*VIEW/DAB (Ventana)	BenchMark XT

* Target retrieval solution (Dako).
DAB indicates 3,3′ diaminobenzidine; SF-1, steroidogenic factor 1; WT1, Wilms tumor 1 gene product.

Formalin-fixed, paraffin-embedded tissue sections were deparaffinized, and immunohistochemical staining was performed using protocols optimized for each antibody. The antibody clone names, sources, dilutions, antigen pretreatments, and immunostaining protocols are listed in Table 1. After pretreatment, primary antibody for SF-1 was applied to respective sections and incubated for 60 minutes at room temperature. Antibody localization was achieved by incubating slides for 30 minutes at room temperature in Envision + labeled polymer (DakoCytomation, Carpinteria, California) using a Dako Autostainer. After pretreatment, primary antibodies for WT1 and inhibin were applied to respective sections and incubated at 37°C for 36 minutes (WT1) and 60 minutes (inhibin). The antigen-antibody complexes were then detected with the *i*VIEW/DAB detection system (Ventana; Tucson, Arizona) using a Ventana automated stainer (Benchmark XT); the amplification kit was used as part of the protocol for WT1. Immunohistochemical staining for all 3 antibodies were performed in the Magee-Womens Hospital Immunohistochemical Laboratory. The results for WT1 for 21 of the Sertoli cell tumors, all endometrioid tumors, and 22 carcinoids are from our previous study of WT1 (3) (also performed in the Magee-Womens Hospital Immunohistochemical Laboratory using the same testing conditions specified above).

Interpretation and Scoring of Immunohistochemical Preparations

Nuclear expression of SF-1 and WT1 and cytoplasmic expression of inhibin in tumor cells were considered positive immunostaining. Expression within tumor stroma was not specifically recorded.

For overall positivity, immunostaining in $>5\%$ of cells was considered positive, and $\leq 5\%$ positive cells was considered negative. Additionally, both extent (based on the percentage of positive cells) and intensity of immunostaining were evaluated by a semiquantitative system. Extent was scored as: 0, $\leq 5\%$; 1 + (1 point), 6% to 25%; 2 + (2 points), 26% to 50%; 3 + (3 points), 51% to 75%; and 4 + (4 points), 76% to 100%. Intensity was arbitrarily scored as: weak (1 point), moderate (2 points), or strong (3 points). Intensity was designated as weak when immunostaining was present but only barely detectable. To correlate extent and intensity of immunostaining in Sertoli cell tumor, these values in positive cases were converted into composite immunohistochemical scores by multiplying the individual scores of extent by intensity (possible range of values from 1 to 12). For example, a case with 3 + extent (3 points) and moderate intensity of immunostaining (2 points) would have an immunohistochemical composite score of $3 \times 2 = 6$.

Statistical Analysis

The differences of the mean immunohistochemical composite scores between SF-1, WT1, and inhibin in Sertoli cell tumor were statistically analyzed using the Student t-test (2-tailed). All P values <0.05 were considered statistically significant.

RESULTS

Overall positivity for SF-1, WT1, and inhibin in all categories of tumors is listed in Table 2. Representative examples of immunoreactivity in Sertoli cell tumor are shown in Figures 1 to 3. All Sertoli cell tumors were positive for SF-1. Expression in $>50\%$

of tumor cells were seen in 17 of 27 (63%) Sertoli cell tumors, and 18 cases (67%) showed moderate or strong intensity. All 60 cases of endometrioid tumors and 24 cases of carcinoid were negative for SF-1. All Sertoli cell tumors were positive for WT1. Expression in $>50\%$ of tumor cells was seen in 26 of 27 Sertoli cell tumors (96%), and all cases showed moderate or strong intensity. Of all endometrioid tumors, WT1 was positive in 10 of 60 (17%) cases. A variable proportion (13%–25%) of all categories of endometrioid tumors showed expression, with the most frequently positive category being the sertoliform endometrioid carcinomas. In positive cases, the majority showed 2+ expression (Table 2). WT1 was negative in all 24 carcinoid tumors. Inhibin was positive in 26 of 27 (96%) Sertoli cell tumors and negative in all 24 carcinoids. Only one of 60 endometrioid tumors showed focal expression of inhibin (Table 2).

The comparison of the extent, intensity, and composite scores of immunohistochemical staining for SF-1 with WT1 and inhibin in Sertoli cell tumor is shown in Table 3. SF-1 and inhibin showed similar extents, intensities, and immunohistochemical composite scores for Sertoli cell tumor. WT1 showed a greater extent and intensity of immunostaining compared with SF-1 and inhibin. The difference in the mean immunohistochemical composite scores for Sertoli cell tumor between SF-1 and inhibin was not statistically significant ($P=0.148$), and the differences for WT1 versus SF-1 and WT1 versus inhibin were statistically significant ($P<0.0001$ and $P=0.001$, respectively).

Structures in normal ovaries (eg, follicles and normal stroma) could not be fully evaluated as in most cases only sections of tumor were used for immunohistochemistry. The stromal cells (tumor stromal cells or non-neoplastic stromal cells) in some cases of Sertoli cell tumor, endometrioid tumors, and carcinoid showed variable expression of SF-1, but those data were not specifically recorded as that was not the goal of this study.

DISCUSSION

The differential diagnosis of ovarian Sertoli cell tumor, which includes non-sex cord-stromal tumors such as endometrioid tumors (borderline tumor and the sertoliform variant of carcinoma) and carcinoid tumors, can be facilitated based on traditional clinicopathologic features. Patients with Sertoli cell tumor may have hormonal manifestations (when present, usually estrogenic but occasionally androgenic); however, estrogenic manifestations can be present in patients with ovarian endometrioid carcinoma. Sertoli cell tumors typically are unilateral and have distinctive open and closed tubular patterns with bland round nuclei. In tubules with elongated solid profiles, the nuclei frequently have a "paired cell" arrangement. Endometrioid tumors, especially carcinoma, may be bilateral, and advanced stage disease suggests endometrioid carcinoma as opposed to Sertoli cell tumor or primary ovarian carcinoid. They may display other growth patterns such as villoglandular forms, confluent glandular appearances, and infiltrative growth with stromal desmoplasia. Their nuclei may be bland, but in endometrioid carcinomas, they can be more atypical and mitotically active than in Sertoli cell tumors. Also, the glandular lumens can contain mucinous secretions. Other characteristic features, which are not present in all cases, include squamous metaplasia, endometriosis, and a background of borderline tumor or adenofibroma. Primary carcinoid tumor is usually unilateral. Distinctive insular, trabecular, or strumal patterns may be appreciated, and the periphery of cells may show fine, granular, and

TABLE 2. *Overall positivity for SF-1, WT1, and inhibin*

Antigen	Sertoli cell tumor (n = 27)*	Endometrioid borderline tumor (n = 25)	Sertoliform endometrioid carcinoma (n = 12)	Well-differentiated endometrioid carcinoma (n = 23)	Carcinoid (n = 24)
SF-1	27 (100%)	—	—	—	—
WT1	27 (100%)	4 (16%)†	3 (25%)‡	3 (13%)§	—
Inhibin	26 (96%)	—	—	1 (4%)‖	—

* For extent of expression, see Table 3.
†Extent of expression: 1+ (n = 0), 2+ (n = 3), 3+ (n = 1), 4+ (n = 0).
‡Extent of expression: 1+ (n = 1), 2+ (n = 1), 3+ (n = 1), 4+ (n = 0).
§Extent of expression: 1+ (n = 0), 2+ (n = 3), 3+ (n = 0), 4+ (n = 0).
‖Extent of expression: 1+ (n = 1), 2+ (n = 0), 3+ (n = 0), 4+ (n = 0).
SF-1 indicates steroidogenic factor 1; WT1, Wilms tumor 1 gene product; –, Negative.

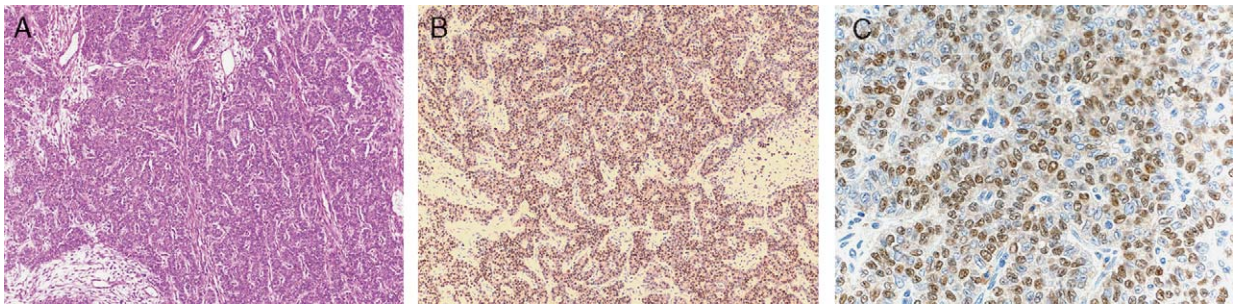

FIG. 1. Sertoli cell tumor: steroidogenic factor 1. A, Hematoxylin and eosin; B, diffuse (3+) extent of expression; and C, nuclear staining with moderate intensity.

eosinophilic granules. The nuclei are bland and uniform, and characteristically, they are round and stippled with a "salt and pepper" appearance. They usually are less atypical and mitotically active than in endometrioid carcinomas. A background of a teratoma is frequently evident, and the carcinoid syndrome may be present in some patients.

In cases in which there is substantial overlap of clinicopathologic features, immunohistochemistry may be necessary. Several different immunohistochemical markers have been assessed in the literature for this differential diagnosis, including inhibin, calretinin, CK7, epithelial membrane antigen, chromogranin, and synaptophysin. In this study, we evaluated whether or not SF-1 has any diagnostic value. SF-1 was a sensitive and specific immunohistochemical marker for ovarian Sertoli cell tumor (Table 2). It was expressed in all cases of Sertoli cell tumor and none of the endometrioid tumors or carcinoids. It had comparable sensitivity and specificity to inhibin. In a prior study, we showed that WT1 was a good immunohistochemical marker for the distinction of Sertoli cell tumor in this differential diagnosis (3). SF-1 was more discriminative than WT1 for a diagnosis of Sertoli cell tumor in the current study. However, the extent of expression of WT1 in Sertoli cell tumor tended to be diffuse whereas the extent in non-Sertoli cell tumors that were positive (endometrioid borderline tumor, conventional well-differentiated endometrioid carcinoma, and the sertoliform variant of endometrioid carcinoma) tended to be less (usually, focal to patchy in endometrioid tumors). We also specifically compared SF-1, inhibin, and WT1 in detail with each other in Sertoli cell tumor (Table 3). Among all 3 markers, WT1 was the one, which most frequently showed diffuse expression, but the extent of expression of SF-1 was comparable with that of inhibin. As a function of combined extent and intensity of staining for assessing the overall immunoreactivity in Sertoli cell tumor (immunohistochemical composite score), SF-1 was comparable with inhibin, but WT1 had the highest composite score.

It is not exactly clear why SF-1 is expressed in ovarian Sertoli cell tumor. SF-1 is a transcription factor that regulates genes involved in steroidogenesis

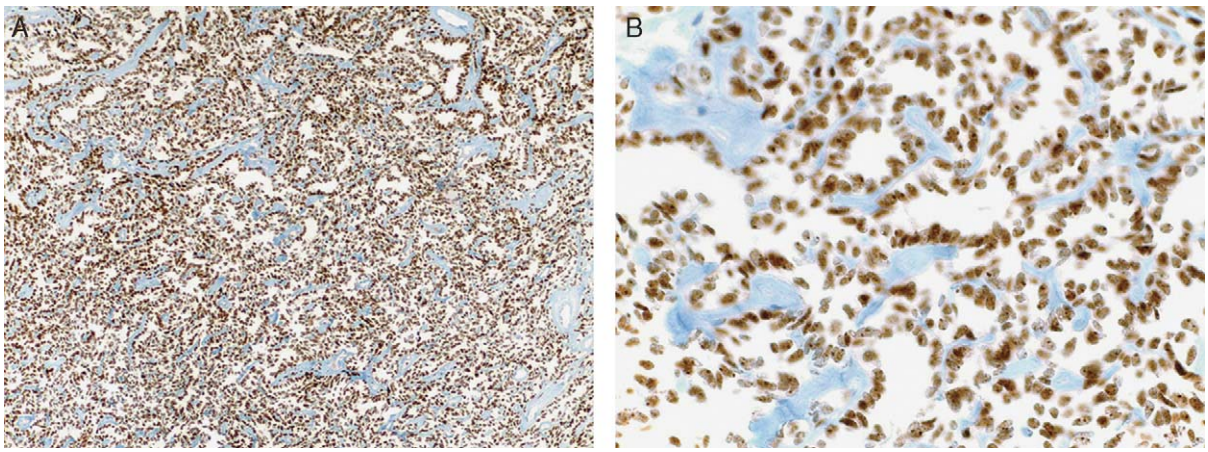

FIG. 2. Sertoli cell tumor: Wilms tumor 1 gene product. A, Diffuse (4+) extent of expression and B, nuclear staining with strong intensity.

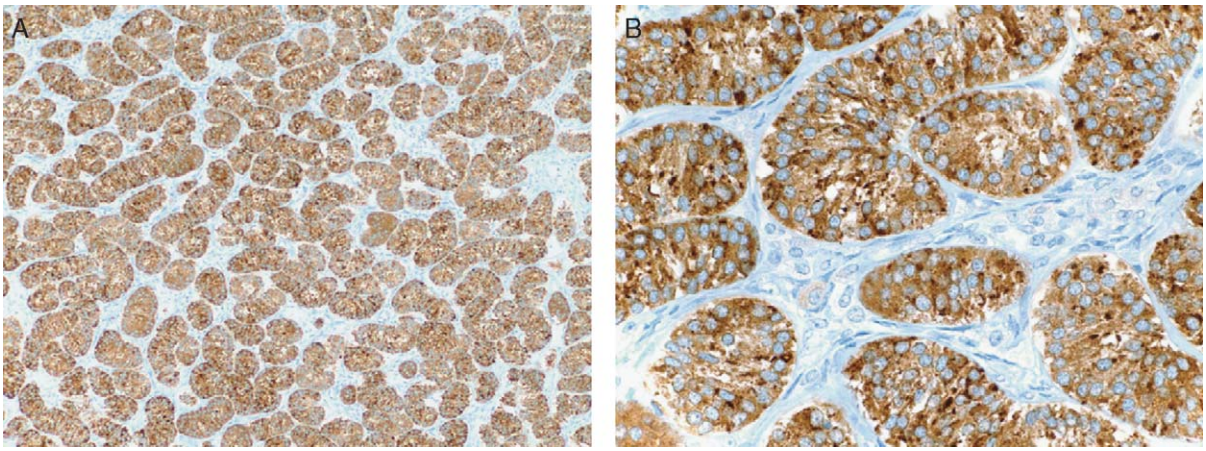

FIG. 3. Sertoli cell tumor: inhibin. A, Diffuse (4+) extent of expression and B, cytoplasmic staining with strong intensity.

and development of the adrenal and pituitary glands. Therefore, it is not surprising that expression of this protein has been described in adrenocortical adenoma/carcinoma, pituitary adenoma, and choriocarcinoma (23,24,32). A subset of ovarian Sertoli cell tumors in the literature is of the lipid-rich type, which could presumably be one explanation for SF-1 expression and might indicate steroid production. However, only 3 Sertoli cell tumors in this study exhibited this morphology, and there was no apparent difference of SF-1 expression between Sertoli cell tumors with and without lipid-rich change (Table 3). Although, the fact that Sertoli cell tumors of the ovary can be associated with hormonal manifestations (typically estrogenic) (1) could be consistent with SF-1 playing a role in steroidogenesis in these tumors. On the other hand, SF-1 is expressed in Sertoli and Leydig cells of the developing testes (25,27,29), and it is known that SF-1 regulates genes involved in gonadal development and sexual differentiation. Thus, another possible explanation could be that SF-1 is expressed in ovarian Sertoli cell tumor simply because it is involved in the control of other genes related to sertoliform differentiation rather than steroidogenesis. Further molecular studies would be necessary to clarify the specific role of SF-1 in ovarian Sertoli cell tumor.

Other studies have not sufficiently assessed expression of SF-1 in ovarian Sertoli cell tumor. In a study of SF-1 expression in a small number of different ovarian sex cord-stromal tumors by Takayama et al (33), only 1 Sertoli cell tumor was tested and found to be negative. In 3 of 5 Sertoli-Leydig cell tumors, expression was present in the Leydig cell component but negative in the Sertoli cell component. Of note, the technical aspects and antibody used in that study were substantially different from those in our study.

It is also of interest that SF-1 is expressed in the normal ovary. Levels fall during embryogenesis but become elevated during adulthood. Expression is restricted primarily to the granulosa and theca cells of the follicles, and the levels progressively increase in these cell types with maturation of the follicles (26,28–30). Additionally, expression of SF-1 has been noted in granulosa cell tumors in some but not all studies. In the same study by Takayama et al (33) mentioned above, all 4 granulosa cell tumors were negative; however, in another study of 80 granulosa

TABLE 3. *Extent, intensity, and immunohistochemical composite scores for Sertoli cell tumor (n = 27)*

	Extent of expression					Intensity of expression			Immunohistochemical composite score*	
Marker	0	1+	2+	3+	4+	Weak	Mod†	Strong	Mean	Range
SF-1‡	—	3 (11%)	7 (26%)	9 (33%)	8 (30%)	9 (33%)	10 (37%)	8 (30%)	6.1	1-12
WT1	—	—	1 (4%)	2 (7%)	24 (89%)	—	6 (22%)	21 (78%)	10.8	4-12
Inhibin	1 (4%)	1 (4%)	4 (15%)	6 (22%)	15 (56%)	6 (22%)	9 (33%)	11 (41%)	7.8	1-12

* Immunohistochemical composite score (calculated only for positive cases).
†Moderate.
‡3 Sertoli cell tumors exhibited lipid-rich change (2 diffuse, 1 focal); all showed 3+ extent of SF-1 expression with moderate intensity of staining.
SF-1 indicates steroidogenic factor 1; WT1, Wilms tumor 1 gene product.

cell tumors, 74% of cases showed immunohistochemical expression of SF-1 in $\geq$20% of tumor cells (22). Thus, SF-1 has the potential to be a valuable immunohistochemical marker in the diagnosis of sex cord-stromal tumors other than Sertoli cell tumor. SF-1 was not evaluated in adult granulosa cell tumors in the current study as they were not the diagnostic focus of this investigation; however, we are assessing expression of SF-1 along with other sex cord-stromal tumor markers in adult granulosa cell tumors, Sertoli-Leydig cell tumors, and steroid cell tumors as part of a separate study (34).

Expression of SF-1 was not observed in the endometrioid tumors in this study; although, some but not all studies have noted expression in epithelial tumors of the ovary. In one study of 82 tumors, including primary ovarian epithelial tumors (various histologic types of cystadenomas, borderline tumors, and carcinomas) and metastatic carcinomas involving the ovary (gastric and breast), expression was not observed in the neoplastic epithelial cells; however, expression was present within intratumoral stromal cells (35). That finding is not unexpected as various non-sex cord-stromal tumors of the ovary may have steroid-producing or hormonally functional stromal cells. However, in a study of 115 primary ovarian epithelial tumors (various histologic types of cystadenomas, borderline tumors, and carcinomas) by Abd-Elaziz et al (36), SF-1 expression was observed within the neoplastic epithelial cells in 40% of cystadenomas, 60% of borderline tumors, and 47% of carcinomas. That study used the so-called *H*-score to calculate the degree of immunoreactivity, but the *H*-scores for each of those 3 categories of tumors might correspond to relatively low levels of immunoexpression. An important finding in that study was that the *H*-scores for the neoplastic epithelial cells were substantially lower than those for intratumoral stromal cells. Expression of SF-1 within the neoplastic epithelial cells could simply reflect intrinsic low-level steroid production (in our study, all endometrioid tumors and carcinoids had an SF-1 score of 0, but none of these were noted to have greater than 0% and less than 6% positive cells). Moreover, differences between their results for epithelial tumors versus ours may have been due to either different antibodies, minor differences in the technical procedure, or selection of different histologic types and categories of epithelial ovarian tumors. Regardless, the important finding in our study was the notable difference in immunoreactivity for SF-1 between Sertoli cell tumor and all categories of endometrioid tumors, making SF-1 a good marker for this differential diagnosis.

The focus of this study was ovarian Sertoli cell tumor and 2 non-sex cord-stromal ovarian neoplasms that frequently enter the differential diagnosis—endometrioid tumors and carcinoid. Female adnexal tumor of probable wolffian origin is another pelvic tumor that may be in the histologic differential diagnosis of ovarian pure Sertoli cell tumor. Female adnexal tumor of probable wolffian origin was not included in the current analysis because of its relative rarity, that it typically arises in paraovarian locations such as the broad ligament, and that the focus of this study was tumors arising in the ovary. Although, female adnexal tumor of probable wolffian origin hasbeen described in the ovary (37), and it may be of interest for future studies to evaluate expression of SF-1 in that type of tumor for purposes of differential diagnosis.

We conclude the following: SF-1 is a sensitive and specific immunohistochemical marker for ovarian Sertoli cell tumor in the context of the differential diagnosis with endometrioid tumors and carcinoid. Its diagnostic utility for Sertoli cell tumor is comparable with that of other good immunohistochemical sex cord-stromal markers, such as inhibin and WT1. As the majority of the experience with sex cord-stromal tumor immunohistochemical markers in the literature is based on inhibin and calretinin, those 2 markers should continue to be routinely used as part of a panel for this differential diagnosis; however, in cases in which the obtained immunohistochemical results for inhibin and calretinin are unsatisfactory or noncontributory, the addition of SF-1 to the panel may be helpful.

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