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Uterine Retiform Sertoli-Leydig Cell Tumor Report of a Case Providing Additional Evidence That Uterine Tumors Resembling Ovarian Sex Cord Tumors Have a Histologic and Immunohistochemical Phenotype of Genuine Sex Cord Tumors

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Summary: We report a case of a retiform Sertoli-Leydig cell tumor of intermediate differentiation presenting as a uterine intracavity polypoid mass in a 63-year-old woman. In contrast to sertoliform endometrioid carcinoma and to hitherto reported uterine tumors resembling ovarian sex cord tumors (UTROSCTs), which are primarily characterized by tubular glands and solid tubules, this tumor, which most likely represents a UTROSCT, showed a large spectrum of histologic features typical of a genuine retiform Sertoli-Leydig cell tumor. The diagnosis was confirmed by a battery of immunohistochemical stains, which also served as a tool for differential diagnosis with other neoplasms. The tumor cells were positive for broad spectrum keratin (CK) CK18, vimentin, calretinin, and progesterone receptor. Only a few isolated cells stained for inhibin. The tumor cells were negative for CK7, CK5/6, epithelial membrance antigen (EMA), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), thrombomodulin, 013 (CD99), melan A, alpha-fetoprotein (AFP), placental alkaline phosphatase (PLAP), α-1-antitrypsin, estrogen receptor, S100, neusone specific enolase (NSE), chromogranin, synaptophysin, desmin, caldesmon, and CD10. Divergent differentiation of uterine cells seems to be the most likely pathogenetic mechanism. To the best of our knowledge, no UTROSCT showing such a variety of histologic features indicative of a true sex cord tumor has been reported before. **Key Words:** Uterine tumors resembling ovarian sex cord tumor—Uterine retiform Sertoli-Leydig cell tumor—Differential diagnosis—Immunohistochemistry.

Endometrioid carcinomas resembling Sertoli cell tumors or so-called sertoliform carcinomas have been well documented in the ovary (1–4), and subsequently also in the endometrium (5–7). These tumors resemble well-differentiated Sertoli cell tumors and are associated with typical endometrioid carcinoma, which usually merges with the sertoliform areas (1–7). The immunophenotype of these neoplasms shows no evidence of genuine sex cord differentiation (3,4,6–8). Thus these tumors are considered to merely represent a morphologic variant of endometrioid carcinoma.

Sex cord–like elements have also been described in endometrial stromal tumors and in uterine intramural masses (9). The latter have been designated as a uterine tumor resembling ovarian sex cord tumor (UTROSCT). Histologically the sex cord–like structures in both of these lesions are similar to the sertoliform components in endometrioid carcinoma. However, in some cases of UTROSCTs, ultrastructural (10) and immunohistochemical

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features (11–14) have been found to be consistent with true sex cord differentiation.

In this paper, we report a case of a retiform Sertoli-Leydig cell tumor presenting as a large uterine intracavitary polypoid mass, which most likely represents a UTROSCT. However, in contrast to UTROSCTs reported thus far, this case showed a large variety of histologic features, including a widespread retiform pattern and an immunophenotype, which support our hypothesis that this neoplasm represents a genuine uterine sex cord stromal tumor that most likely developed as a result of divergent differentiation of uterine cellular elements.

CASE REPORT

A 63-year-old woman was admitted to the hospital because of massive vaginal bleeding. She had been suffering from hypertension for the last 7 years and had been treated with methyldopa. Her menopause was at the age of 50. She received no hormone replacement therapy. Ten months preceding her hospitalization, the patient developed episodes of vaginal bleeding, but refused medical workup. Gynecologic examination on admission, including abdominal ultrasound, showed an enlarged uterus of 10 weeks. The endometrium measured 28 mm in thickness, with cystic areas. A total abdominal hysterectomy with bilateral tubo-oophorectomy was performed. Postoperative computed tomography scan showed no residual tumor. The patient is alive and well with no evidence of disease 13 months after surgery.

Gross Findings

The uterus weighed 95 g and measured 7 × 6 × 4.5 cm. The uterine wall was 2 cm in thickness and showed what appeared to be a leiomyoma. A polypoid mass measuring 4.8 × 3 × 2.3 cm with a broad base arose from the uterine fundus and projected into the uterine cavity. The cut section of this polyp consisted of nodular soft gray tissue with scattered small cysts (Fig. 1). The remaining endometrium was unremarkable. Both tubes and ovaries showed no abnormalities.

The entire polypoid tumor was serially sectioned, and 25 microscopic slides were prepared. In addition, 10 microscopic slides were taken from the uterine wall, which was also serially sectioned.

Histologic and Immunohistochemical Findings

The entire intracavitary polypoid mass was composed of a neoplasm showing a predominant retiform pattern

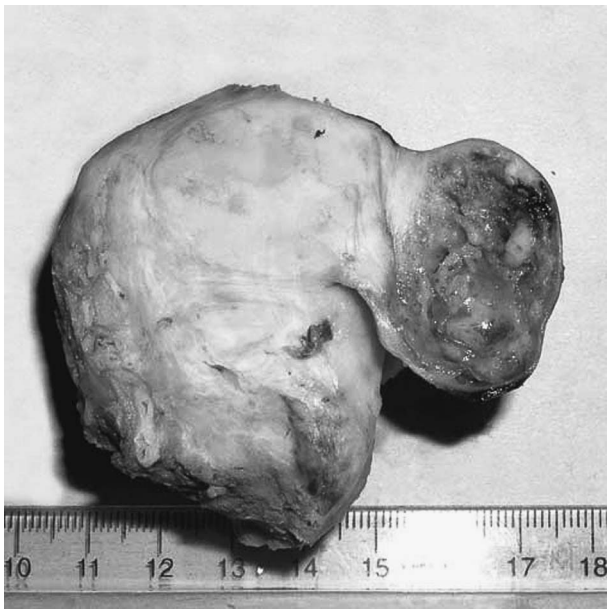

FIG. 1. Longitudinal section through the uterus showing mural leiomyoma and a broad-based intracavity polypoid mass with a nodular cut surface containing small cysts.

characterized by a diffuse irregular network of slit-like spaces into which projected rounded, bulbous, or blunt hyalinized papillae, which were lined by cuboidal or low columnar cells with hyperchromatic nuclei. Within the retiform areas were scattered numerous rounded glomeruloid-like structures composed of tight small tubular coils. In addition, the tumor showed hollow and solid tubules and cysts lined by epithelial type cells. Also seen were cords of cells arranged in a trabecular fashion. Finally, there were areas of solid tumor composed of crowded nest, cords, and small tubules lined by round cells with hyperchromatic nuclei. Mitotic figures were present in the latter areas. Some isolated stromal cells were suggestive of Leydig cells but could not be definitely identified as such (Fig. 2). In some areas, the endometrial mucosa partially covered the surface of the polypoid tumor mass. In one focus, the tumor was present within the endometrial mucosa. At the base of the tumor, no endometrial tissue was identified, and the tumor abutted directly against the underlying myometrium, which extended by strands into the tumor mass.

The endometrium was proliferative with focally distended glands and in areas showed a polypoid configuration. There was adenomyosis and a leiomyoma. The uterine cervix, ovaries, and fallopian tubes were unremarkable.

Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue using the standard avidin-biotin-complex peroxidase technique (Table 1). The

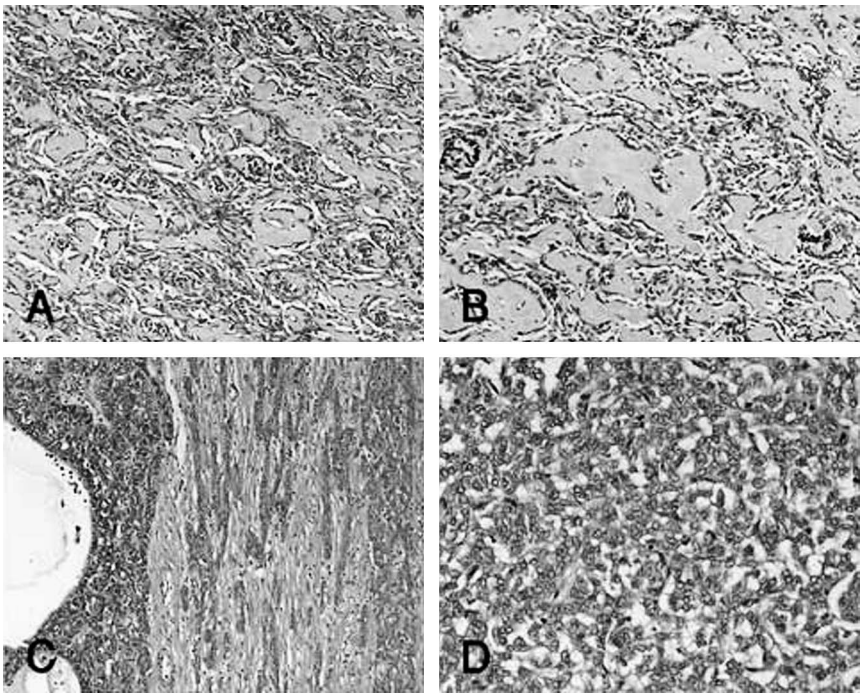

FIG. 2. Histologic features of the uterine Sertoli-Leydig cell tumor. (A) Retiform pattern showing hyalinized papillae and a network of slit-like spaces. (B) Higher magnification of retiform pattern showing epithelial-lined, bulbous papillae with hyalinized cores almost filling the spaces in which they project. (C) Cystic structures with adjacent tightly packed hollow and solid tubules. The surrounding stroma shows elongated columns of cells. (D) Solid area of tumor composed of short solid cords as well as of small solid and open tubules.

various components of the Sertoli-Leydig tumor stained strongly but not uniformly with antibodies to broad spectrum keratin (CK), CK18, vimentin, calretinin, and progesterone receptor (Fig. 3). Only a few isolated cells stained for inhibin. The tumor cells were negative for CK7, CK5/6, epithelial membrance antigen (EMA), carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), thrombomodulin, O13 (CD 99) melan A, alpha-fetoprotein (AFP), placental alkaline phosphatase (PLAP), α-1-antitrypsin, estrogen receptor, S100,

TABLE 1. *Antibodies used in this study*

Antibodies	Source	Dilution	Type	Pretreatment
Keratin (AE_1/AE_2)	Zymed, San-Francisco, CA, USA	1:100	Monoclonal	Pronase
CK18 (Cy90)	Sigma, Jerusalem, Israel	1:1000	Monoclonal	Pronase
CK7	BioGenex, San Ramon, CA, USA	1:100	Monoclonal	Microwave, Citrate buffer
C/K 5/6	DAKO, Glostrup Denmark	1:50	Monoclonal	Pressure Cooker, EDTA
EMA	DAKO	1:100	Monoclonal	Microwave, Citrate buffer
CEA	Zymed	1:200	Monoclonal	—
OC 125	Novocastra, Newcastle-Upon-Tyne, UK	Ready to use	Monoclonal	—
Vimentin	DAKO	1:1000	Monoclonal	Microwave Citrate buffer
Inhibin	DAKO	1:50	Monoclonal	Pressure Cooker, EDTA
Calretinin	Zymed	1:50	Monoclonal	Pressure Cooker, EDTA
Thrombomodulin	DAKO	1:50	Monoclonal	Pronase
013 (CD99)	Zymed	Ready to use	Monoclonal	Pressure Cooker, EDTA
MelanA	Neo Markers, Fremont, CA, USA	1:100	Monoclonal	Pressure Cooker, EDTA
AFP	Zymed	Ready to use	Monoclonal	—
PLAP	Zymed	Ready to use	Monoclonal	Pressure Cooker, EDTA
Alpha-1-antitrypsin	DBC, Los Angeles, CA, USA	Ready to use	Polyclonal	Pronase
Estrogen Receptor	Novocastra	1:100	Monoclonal	Pressure Cooker, EDTA
Progesterone Receptor	Zymed	1:200	Monoclonal	Pressure Cooker, EDTA
S100	DAKO	1:500	Polyclonal	Pronase
NSE	DAKO	1:200	Monoclonal	Microwave, Citrate buffer
Chromogranin	DAKO	1:100	Monoclonal	Microwave, Citrate buffer
Synystophysin	Neomarkers	1:100	Monoclonal	Microwave, Citrate buffer
Desmin	Zymed	1:40	Monoclonal	Microwave, Citrate buffer
Caldesmon	Neomarkers	1:50	Monoclonal	Pressure Cooker, EDTA
CD10	Novocastra	1:30	Monoclonal	Pressure Cooker, EDTA

CK, keratin; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; PLAP, placental alkaline phosphatase; NSE, neurone specific enolase; EDTA, ethylene diamine tetraacetic acid.

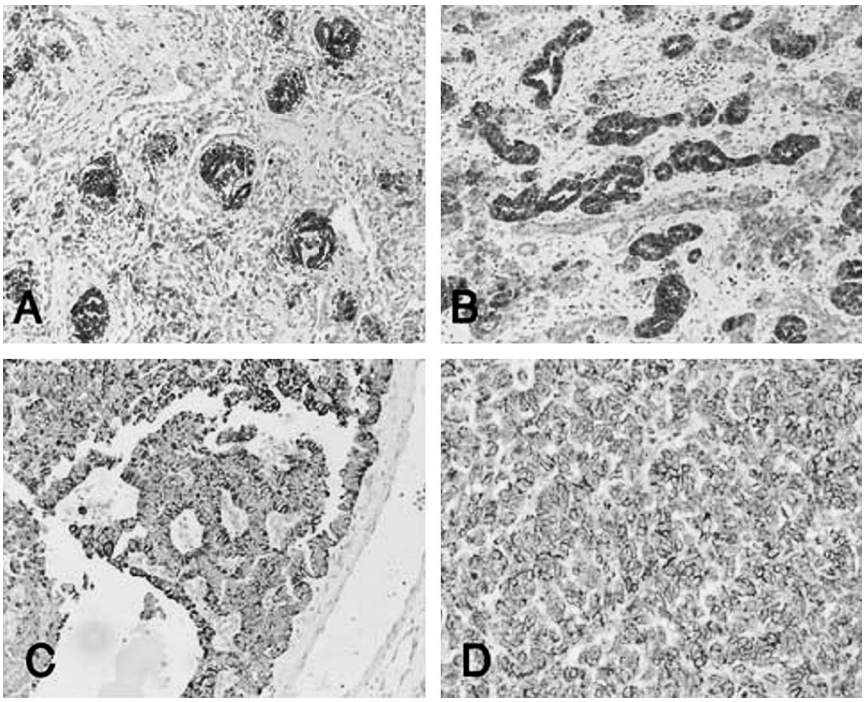

FIG. 3. Immunohistochemical staining of various histologic patterns of the uterine Sertoli-Leydig cell tumor. (A) Calretinin in retiform pattern staining especially nests composed of tight small tubular coils (glomeruloid structures). (B) Open tubules stained by calretinin. (C) Cyst and glandular area diffusely stained by cytokeratin 18. (D) Cells in solid area of tumor showing positive diffuse staining for vimentin.

neusone specific enolase (NSE), chromogranin, synaptophysin, desmin, caldesmon, and CD10 (Table 2).

DISCUSSION

Sertoliform endometrioid carcinoma of the endometrium (5–7) and UTROSCTs (9–14) consist mainly of tubularly glands and solid tubules. Recently a variant of uterine endometrioid carcinoma with prominent corded and hyalinized features has also been described (15). On morphologic grounds, it seems that these latter tumors may also belong to the category of endometrioid-sertoliform carcinomas.

In contrast to the above neoplasms, the case reported here showed a plethora of histologic features, such as hollow and solid tubules, cords of cells, cystic structures, and prominent retiform pattern consistent with a retiform Sertoli-Leydig cell tumor of intermediate differentiation (16,17). Because of the inability to definitely identify Leydig cells in this tumor, a Sertoli cell tumor also had to be considered. However, the presence of a widespread retiform pattern strongly favors a Sertoli-Leydig tumor rather than a Sertoli cell tumor (16). Furthermore, typical Leydig cells are not seen in all cases of Sertoli-Leydig cell tumors (16), and according to Talerman (17), are not evident in tumors with a prominent retiform pattern.

The differential diagnosis of this uterine tumor includes endometrioid, clear cell, and serous papillary

TABLE 2. *Results of immunohistochemical staining*

Antibody	Tumor cells
Keratin (AE_1/AE_3)	+
CK18 (Cy90)	+
CK7	–
CK5/6	–
EMA	–
CEA	–
OC 125	–
Vimentin	+
Inhibin	+, only very few cells
Calretinin	+
Thrombomodulin	–
013 (CD99)	–
Melan A	–
AFP	–
PLAP	–
Alpha-1-antitrypsin	–
Estrogen Receptor	–
Progesterone Receptor	+
S100	–
NSE	–
Chromogranin	–
Synaptophysin	–
Desmin	–
Caldesmon	–
CD10	–

CK, keratin; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; PLAP, placental alkaline phosphate; NSE, neurone specific enolase; Staining intensity: –, no staining; +, strong staining.

carcinoma, as well as the following neoplasms that only rarely occur as primary uterine tumors: yolk sac tumor (18), Wilm tumor (19), a large intracavitary adenomatoid tumor (20), and a neuroendocrine tumor (21).

Based on the immunohistochemical results, a diagnosis of carcinoma is very unlikely because of the lack of positive staining for CK7, EMA, and CA125. In contrast, the expression of calretinin and vimentin does not exclude carcinomas because coexpression of CK and vimentin is well known in mullerian tumors, and calretinin has also recently been described in mullerian epithelial tumors (22).

Yolk sac tumors are especially prone to be misdiagnosed as Sertoli-Leydig cell tumors because both neoplasms may present a wide range of similar histologic features (16,17). However, the complete absence of AFP and α-1-antitrypsin in the tumor reported here, which are characteristic for yolk sac tumors (23), and the lack of PLAP, which occurs in about 50% of yolk sac tumors (24), make a diagnosis of the latter most unlikely.

The rare primary uterine Wilm tissue can also be dismissed because this neoplasm is usually positive for EMA, muscle markers, and in the presence of neural elements, also positive for S100 and NSE. All these stains were negative in our tumor.

A uterine adenomatoid tumor also has to be considered in the differential diagnosis because of some morphologic features together with a positive calretinin stain. However, in the absence of CK5/6, thrombomodulin, and EMA expression, such a diagnosis cannot be reached.

Last, a diagnosis of a neuroectodermal uterine tumor can also be excluded because the tumor was negative for NSE, chromogranin, and synaptophysin.

Thus, on the basis of the histologic and immunohistochemical features of the uterine tumor reported here and after exclusion of other neoplasms, the diagnosis of a uterine Sertoli-Leydig cell tumor, most likely of the UTROSCT type, can be established in this case. Clinical features were not contributory because they consisted only of vaginal bleeding. There was no evidence of virilization. It is of interest, however, that, whereas the average age of patients with ovarian retiform Sertoli-Leydig cell tumors is 15 years (17), our patient was 63 years old.

The almost complete absence of inhibin, the classic marker for sex cord stromal tumors (25), in this uterine neoplasm, is not contrary to the diagnosis of a Sertoli-Leydig cell tumor, because the value of calretinin as a marker for sex cord–stromal tumors has been well documented (22,25–29). Although somewhat less specific than inhibin, in the series by Movahedi-Lankarani and Kurman (22), calretinin was positive in 100% of ovarian sex cord–stromal tumors including those that were inhibin negative. It was in this latter group in which calretinin was most useful as a diagnostic tool.

Concerning the histogenesis of this uterine Sertoli-Leydig cell tumor, it can be surmised, as previously for UTROSCTs (11), that the present neoplasm derived most likely from the capacity for divergent differentiation of uterine cells. What is unique in this case is the fact that the divergent differentiation resulted in a genuine retiform Sertoli-Leydig cell tumor composed of a variety of complex histologic elements far exceeding the tubular glands and solid tubules that characterize UTROSCTs reported thus far.

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