Uterine Tumors Resembling Ovarian Sex Cord Tumors

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Uterine tumors resembling ovarian sex cord tumors (UTROSCT) are rare neoplasms of unknown etiology. Only 67 cases have been reported in the literature, to our knowledge, so far. The neoplasm usually occurs in middle-aged women. Most patients present with abnormal uterine bleeding and/or abdominal pain, along with an enlarged uterus or a palpable uterine mass. There is no specific imaging finding, and the diagnosis is made exclusively on histopathologic examination. A multitude of architectural patterns are described, which include plexiform cords, anastomosing trabeculae, watered-silk, microfollicle, macrofollicle, tubules, retiform, solid cellular islands, and diffuse pattern of growth. The neoplastic cells are usually small with round to ovoid nuclei, nuclear monotony, mild nuclear hyperchromasia, and inconspicuous nucleoli with scant eosinophilic cytoplasm. Nuclear grooves are rare. Mitotic figures are infrequent, and necrosis is mostly absent. This tumor depicts a diverse immunohistochemical profile with expression of sex cord, epithelial, and smooth muscle lineages markers. Sex cord markers, such as inhibin, calretinin, CD99, WT1, and MART-1; epithelial markers, such as pancytokeratin and epithelial membrane antigen; smooth muscle markers, such as smooth muscle actin, desmin, and histone deacetylase 8; and miscellaneous markers, such as CD10, estrogen receptor, progesterone receptor, S100, and CD117, are often coexpressed. Immunoexpression for calretinin and at least for one of the other sex cord markers is required to establish a diagnosis of UTROSCT. Hysterectomy with or without bilateral salpingo-oophorectomy is usually the treatment for UTROSCT. Although most UTROSCTs behave benignly, some do recur, and thus, this entity should be considered as a tumor of low malignant potential. In this review, we discuss the current knowledge on UTROSCT and its clinical relevance.

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CLINICAL FEATURES

The UTROSCT is classically considered a disease of perimenopausal and postmenopausal women. The main clinical manifestations are abnormal uterine bleeding and/or abdominal pain. Most patients have an enlarged uterus or a palpable mass. Imaging studies are not diagnostic, and occasional series of UTROSCTs have been described in the literature. In this review, we discuss the clinical profile, pathologic features, pathogenesis, differential diagnosis, treatment, and prognosis for patients with UTROSCT.

PATHOLOGIC FEATURES

Macroscopic Features

The UTROSCTs generally present as intramural, submucosal, and subserosal masses, usually in the uterine fundus. They are usually well circumscribed and nonencapsulated, with pushing or infiltrative borders. Polypoid masses projecting into the uterine cavity are common. The overlying endometrium may also be involved. The maximum dimension of the tumor ranges from 2 to 15 cm (mean, 6 cm). The cut surfaces are fleshy, grey-yellow to white (Figure 1). Necrosis and hemorrhage are unusual.
Microscopic Features

Microscopically, a UTROSCT displays a variety of architectural patterns, including anastomosing cords of 1 to 2 cells wide, broad trabeculae, small nests, and sertoli-form or retiform tubular structures, Call-Exner-like bodies and diffuse sheets of uniform granulosa cell tumorlike areas (Figures 2 and 3, A and B). The neoplastic cells are usually small with round to ovoid nuclei, little nuclear pleomorphism, inconspicuous nucleoli, and scant, indistinct eosinophilic cytoplasm. In rare instances, nuclear grooves may be seen (Figure 3, B, inset). Sometimes, the neoplastic cells are spindle shaped, suggesting a biphenotypic (mixture of epithelial and mesenchymal elements) derivation for the tumor. The intervening stroma shows hyalinization with a sparse lymphocytic infiltrate accompanied by foamy histiocytes, a few multinucleated giant cells, hemosiderin deposition, and/or cholesterol crystals. Mitotic figures are usually not observed, and necrosis is generally absent. The presence of Charcot-Böttcher crystals in the cells of a UTROSCT suggests that some of these lesions have a true Sertoli differentiation.

Immunophenotypic Features

After analyzing the plethora of IHC data on UTROSCT, Irving et al concluded that the most common and reliable IHC markers for UTROSCT are calretinin, inhibin, CD99, and Melan-A and that immunoreactivity for calretinin and for at least one of the other 3 sex cord markers in that immunopanel is highly suggestive of UTROSCT. Leval et al found that UTROSCT has a diverse IHC profile with shared expression of sex cord, epithelial, and smooth muscle markers. Sex cord markers, such as calretinin (Figure 4, a) (positive in up to 95.8% of cases), inhibin (Figure 4, d) (positive in up to 48% of cases), CD99, WT1 (positive in up to 83.3% of cases), and Melan-A (positive in up to 85% of cases).
cases); epithelial markers, such as pancytokeratin (positive in up to 50% of cases) and epithelial membrane antigen (positive in up to 34.4% of cases); and smooth muscle markers, such as smooth muscle actin (positive in up to 40.8% of cases), desmin (positive in up to 25.3% of cases), and histone deacetylase 8 (positive in up to 66.6% of cases), are expressed along with few miscellaneous markers, such as CD10 (positive in up to 60% of cases), estrogen receptor (Figure 4, c), progesterone receptor (Figure 4, b), S100 (positive in up to 18.2% of cases), and CD117 (positive in up to 33.3% of cases). The IHC profile of these tumors appears to be intermediate between that of ESTS克莱 (which typically show less sex cord marker expression) and ovarian sex cord stromal tumors of the ovary (which show marked expression of sex cord markers).

Ultrastructural Features

The UTROSCTs have diverse findings under the electron microscope, including both epithelial (desmosome–like junctions, tonofilaments, lumina formation, and microvilli) and sex-cordlike features (nuclear indentation, abundant intracellular filaments, sparse to moderate rough endoplasmic reticulum [granulosa cells], and abundant intracytoplasmic lipid [Sertoli]), along with aggregates of perinuclear filaments with concordant IHC positivity for markers of epithelial and sex cord differentiation. These findings indicate that UTROSCTs are polyphenotypic neoplasms at the ultrastructural level and show evidence of variable sex-cordlike differentiation.

CYTOGENETICS

Endometrial stromal tumors and their variants, including ESTS克莱, show t(7;17)(p15;q21) translocation, resulting in the fusion of 2 novel genes, JAZF1 and JJAZ1; however, no specific or significant genetic alteration, including t(7;17), is observed in UTROSCT. Therefore, UTROSCT most likely represents a distinct neoplasm unrelated to ESTS克莱 and endometrial stromal tumors.17,18 Interestingly, Wang et al19 described a case of UTROSCT with t(X;6)(p22.3;q23.1) and t(4;18)(q21.1;q21.3). Various known tumor-associated genes (bcl2, MALT1 and DCC at 18q21; and RAP1 at 4q21) and a gene related to the embryogenesis of gonads such as H-Y regulator gene at Xp22.3 are located at or near the translocation breakpoints. The tumor cells of sex-cordlike elements in this case showed strong and diffuse immuno-reactivity for BCL2. These cytogenetic and IHC data may suggest potential molecular mechanisms of tumorigenesis for UTROSCT.19

Figure 4. Immunohistochemical profile of uterine tumors resembling ovarian sex cord tumors. a, Calretinin positive. b, Progesterone receptor positive. c, Estrogen receptor positive. d, Inhibin positive (original magnifications ×200 [a through d]).
PATHOGENESIS

In the 1976 article by Clement and Scully, an origin from the endometrial stromal cells, adenomyosis, stromal myosis, endometriosis, or multipotential myometrial cells was postulated for these stromal tumors. Various studies postulated stromal, epithelial, smooth muscle, sex-cord differentiation, or pluripotent mesenchymal cell origin. The histogenesis of UTROSCT is uncertain, but endometrial stroma has been suggested. A more recent ultrastructural study on 13 cases of UTROSCT has shown that these tumors display epithelial and sex-cordlike differentiation but no smooth muscle differentiation, which supports a polyphenotypic histogenesis.

DIFFERENTIAL DIAGNOSIS

Although UTROSCT is a distinct histopathologic entity, several benign and malignant neoplasms can cause a diagnostic dilemma. Some of these distinctions are of morphologic importance, and others are important from a prognostic standpoint. These include epithelioid leiomyoma, low-grade endometrial stromal sarcoma with sex-cord elements, endometrioid carcinoma with sex-cordlike features, plexiform tumorlet, vascular plexiform leiomyoma, and metastatic ovarian sex-cord stromal tumors.

Other conditions that may enter into the differential diagnostic consideration less frequently are adenosarcoma, carcinosarcoma, perivascular epithelioid cell tumor, and adenomatoid tumor.

Epithelioid leiomyoma is a form of uterine leiomyoma with more than 50% round to polygonal cells. Epithelioid leiomyomas and UTROSCT show striking macroscopic resemblance. Both conditions present as a well-circumscribed, intramural mass with soft consistency, and yellow to tan cut surfaces. Immunohistochemically, these tumors are positive for epithelial and smooth muscle markers; however, epithelioid leiomyoma lacks the typical sex-cord phenotype of UTROSCT.

Low-grade endometrial stromal sarcoma with sex cord elements is a rare, malignant tumor of the uterine corpus. Histologically, low-grade endometrial stromal sarcoma has an infiltrative margin and diffuse growth pattern with very few scattered glands or tubules. Low-grade endometrial stromal sarcoma is typically positive for CD10 and negative for sex cord markers.

The UTROSCTs are generally discovered only after hysterectomy, and most of the patients reported so far were managed with hysterectomy with or without bilateral salpingo-oophorectomy. The UTROSCTs are generally considered tumors of low malignant potential, although most of them behave in a benign fashion. These tumors recur in very few cases; however, no deaths have been reported, to our knowledge. Infiltrative border, vascular invasion, frequent mitotic figures, serosal rupture, stromal predominance, and cytologic atypia are associated with recurrence.

ENDOMETRIOID CARCINOMA WITH SEX-CORDLIKE FEATURES

Endometrioid carcinoma with sex-cordlike features is an unusual tumor of the endometrium. Microscopically, the tumor consists of small, hollow tubules, anastomosing cords and trabeculae and tightly packed nests. The retiform spaces show mitosis and nuclear atypia. Endometrioid carcinomas are diffusely immunoreactive for epithelial membrane antigen and estrogen receptor, whereas calretinin and WT1 are usually negative. These tumors, however, usually display areas with architecture and morphology typical of endometrioid carcinoma and behave like the parent tumor in a malignant fashion.

Vascular plexiform leiomyoma is a vascular, uterine, smooth muscle tumor with a plexiform growth pattern. On microscopy, vascular plexiform leiomyoma shows a well-circumscribed, intramural nodule with anastomosing cords and trabeculae of 2 to 3 cell layers predominant in a perivascular location. The cord lumens often contain red blood cells. The neoplastic cells are invariably positive for smooth muscle actin, caldesmon, and CD99 in a more diffuse fashion, which may be observed in UTROSCT but to a lesser extent. Moreover, unlike UTROSCT, vascular plexiform leiomyoma is negative for sex-cord markers.

However, that distinction is less important because both these entities behave in a benign fashion.

Plexiform tumorlet are rare tumors affecting patients with an average age of 48 to 60 years. They are solitary or multiple (in about one-quarter of the cases), minute, well-circumscribed nodular collections. The lesions are usually seen in association with leiomyomas. On histologic examination, the individual cells are arranged in cords or rows in a branching pattern separated by hyalinized stroma. The cells may merge with foam cells similar to luteinized ovarian stromal cells. Mitotic activity is sparse. The neoplastic cells coexpress myoid, epithelial, and sex-cord markers. However, calretinin, inhibin, cytokeratin 7, and epithelial membrane antigen are negative, in contrast to UTROSCT. This tumor also has a benign behavior.

Metastatic ovarian sex-cord stromal tumor may pose difficulty in differentiation. However, the complete clinical picture and imaging studies reveal the primary ovarian tumor to solve the dilemma.

TREATMENT AND PROGNOSIS

A UTROSCT is generally discovered only after hysterectomy, and most of the patients reported so far were managed with hysterectomy with or without bilateral salpingo-oophorectomy. The UTROSCTs are generally considered tumors of low malignant potential, although most of them behave in a benign fashion. These tumors recur in very few cases; however, no deaths have been reported, to our knowledge.

Infiltrative border, vascular invasion, frequent mitotic figures, serosal rupture, stromal predominance, and cytologic atypia are associated with recurrence. Patients treated with hysterectomy for well-circumscribed tumors with bland features typically have a benign course.

CONCLUSION

The UTROSCTs are a unique group of uterine neoplasms that exhibit diverse morphologic and immunophenotypic characteristics, often coexpressing sex cord, epithelial, and smooth muscle markers. Also, because UTROSCT has no specific imaging findings, preoperative differential diagnosis from other tumors can be difficult. Similarly, intraoperative frozen sections have limited value in making a correct diagnosis of UTROSCT because many benign and malignant lesions show similar histopathologic patterns. Therefore, it is important for the surgical pathologist to recognize this rare entity and differentiate it from other lesions, particularly tumors of intermediate malignant potential, such as low-grade endometrial stromal sarcoma or endometrioid carcinoma with sex-cordlike features and the highly aggressive adenosarcoma, carcinosarcoma, and metastatic ovarian sex-cord stromal tumor by thorough sampling, use of a proper IHC panel, and awareness of the patient’s complete clinical picture. In the future, in tumors with atypical histomorphology, novel molecular markers of sex-cord differentiation, such as forkhead box L2 (FOXL2),
splicing factor 1 (SF1), and dicer 1, ribonuclease type III (Dicer1) may be used to arrive at a definitive diagnosis and further subclassify the tumor.23,34

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