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Cytological features of uterine tumors resembling ovarian sex cord tumors (UTROSCTs) in liquid-based cervical cytology: a potential pitfall. Report of a unique and rare case.

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Abstract:

Uterine tumors resembling ovarian sex cord tumors (UTROSCTs) are rare uterine neoplasms of uncertain etiology that resemble the well-known sex cord tumors of the ovary and display a combined sex cord, epithelial, and smooth muscle immunophenotype. Most tumors are associated with a benign clinical course. Here, we report the first cytological description of uterine UTROSCTs in liquid-based cervical cytology. A 56-year-old menopausal woman who complained of vaginal bleeding was admitted to the emergency room and was discovered to have a uterine intraluminal polypoid mass protruding through the vagina. A Papanicolaou (Pap) test was performed, and the liquid-based cytology (LBC) (ThinPrep) preparation showed isolated tumor cells with scant cytoplasm and slightly irregular, ovoid nuclei with fine chromatin and small nucleoli. Mitotic figures were not observed. The background was hemorrhagic without necrosis. These features raised the differential diagnosis of cervical adenocarcinoma, endometrioid adenocarcinoma and, less likely, an epithelial component of a malignant mixed Müllerian tumor (MMMT) (as clinically suspected). Polypectomy and subsequent hysterectomy were performed, and the final histological evaluation identified a UTROSCT. This is the first case describing the cytological features of a UTROSCT consisting of malignant-appearing adenocarcinomatous cells in LBC Pap smears. This diagnostic possibility, albeit rare, should be included in the differential diagnosis when isolated atypical cells are seen in women in the above scenario. As these features are not specific, they may result in misinterpretation with tumors that are more common and aggressive.

Key words: liquid-based cytology, Pap smears, uterine tumor resembling ovarian sex-cord tumor, UTROSCT, differential diagnosis.

Introduction

Uterine tumors resembling ovarian sex-cord tumors (UTROSCTs) are rare uterine neoplasms that were first reported by Clement and Scully in 1976.[1] Since then, this tumor entity has been delineated into two distinct subtypes. Type I tumors, known as endometrial stromal tumors with sex cord-like elements (ESTSCLEs), have been recognized to have malignant potential, as they have a conventional component of endometrial stromal neoplasia that, if invasive, determines the prognosis of the patient. Type II tumors comprise tumors composed exclusively of sex cord-like elements, and most are considered to behave in a benign fashion, with some showing metastasis and recurrence.[2] The last World Health Organization (WHO) Classification of Tumors of the Female Reproductive Organs placed UTROSCTs in the category of 'endometrial stromal and related neoplasms'.[3] Approximately 43 cases have been reported histologically in the literature.[4,5] However, only two reports have described the cytological features with touch imprint,[6,7] and none have been described with conventional or liquid-based cytology (LBC). Current cervical screening programs using LBC increase the possibility of encountering UTROSCTs in such specimens, thus leading to potential diagnostic pitfalls.

Here, we report a unique case of a UTROSCT with preoperative LBC, in which the diagnosis was not expected. The cytological features and the differential cytological diagnosis are discussed.

Case report

A 56-year-old menopausal woman with no particular medical history presented to her family gynecologist with vaginal bleeding. During the gynecological examination, a hemorrhagic and necrotic mass protruding through the vagina was noted, and the cervix was difficult to reach behind the mass. The patient was transferred to our gynecological emergency department for further examination, and a Papanicolaou (Pap) test was initially performed. As the patient presented with severe menorrhagia, an excision of the vaginal mass was first performed. During surgery, a necrotic mass (7 cm) was observed inside the vagina, with a pedicle coming from the endocervix. Excision of the mass and hemostasis were performed via a vaginal approach. The protruded mass was sent for pathology. The surgery was followed by a pelvic MRI. This approach demonstrated a residual solid mass of 2.6 cm originating from the right uterine wall and protruding inside the lumen (Figure 1A and 1B). The lesion appeared to be isosignal to the myometrium on T1- and T2-weighted imaging with homogeneous enhancement after a gadolinium injection. On diffusion-weighted planes, we observed a restricted diffusion limited to the pediculated component (Supplemental Figure 1). The uterine wall was thus not suspected to be invaded. Apart from an obstructive hematometra and some physiological free pelvic fluid, no other abnormalities were seen. A secondary hysterectomy and bilateral salpingo-oophorectomy were performed following the final pathological report.

Cytological Findings

The cytological specimen was processed using the ThinPrep technique (Hologic Inc., Marlborough, Mass., USA). The Pap test showed a hemorrhagic background with atypical cells. The cells were often isolated (Figure 1C) or arranged in small clusters (Figure 1D), with scant cytoplasm. The nuclei were slightly irregular and ovoid, with fine granular chromatin and conspicuous nucleoli. Mitotic figures or necrosis were not observed. These cells were more consistent with cells of glandular origin; thus, the preliminary diagnosis was that of "atypical glandular cells consistent with adenocarcinoma, NOS".

Histological findings:

Macroscopically, the mass was fragmented and hemorrhagic. Microscopic examination showed a tumor organized in papillary structures as well as slit-likes spaces, trabeculae and solid areas (Figure 1E). The tumor cells were small and regular with eosinophilic cytoplasm, although some had clear cytoplasm. Frequent dense eosinophilic intracytoplasmic (rhabdoid) inclusions were noted (Figure 1F). The nuclei were oval, with finely distributed chromatin and one clearly visible nucleolus, and the overall appearance was bland and monotonous (Figure 1E, inset). Rare mitoses were found. The intervening stroma was scant and fibroblastic, with associated scattered foamy histiocytes.

The tumor cells showed diffuse positivity for CKAE1/AE (Figure 1F, upper right inset) and estrogen receptors, patchy staining for smooth muscle markers (AML and desmin), and focal expression of sex cord markers (calretinin, inhibin (Figure 1F, lower right inset), MelanA, CD99, CD56, and WT1). No staining was observed for neuroendocrine markers (synaptophysin and chromogranin), PAX8, S100, HMB-45, EMA, CK7, CK20, CD117, CD30, CEA, or glypican3. The final diagnosis was a UTROSCT. A hysterectomy showed that the tumor originated from the right uterine wall and protruded into the cavity. The greatest dimension of the tumor was 2.6 cm. The cut surface was yellowish with hemorrhagic areas. Microscopically, the tumor showed similar histological features. There was neither myometrial invasion nor cervical involvement, and the peritoneal lavage did not exhibit tumor cells. The patient remained under radiological surveillance with a short follow up (4 months).

Discussion:

A UTROSCT is an uncommon uterine neoplasm that accounts for less than 0.5% of all uterine malignancies and 10-15% of mesenchymal uterine malignancies. Most UTROSCTs exhibit benign behavior but occasionally recur or metastasize; hence, these tumors are considered neoplasms of uncertain malignant potential that rarely behave in an aggressive manner.[5,8] Histogenesis remains uncertain, and postulated theories include derivation from ovarian sex cord cells that have been displaced during embryogenesis, derivation from uncommitted mesenchymal stem cells, and overgrowth of sex cord elements within an endometrial stromal neoplasm or an adenosarcoma.[9] The last hypothesis appears unlikely because UTROSCTs lack *JAZF1-JJAZ1* gene fusion or *PFH1*

rearrangement, in contrast to endometrial stromal tumors with or without sex cord elements, suggesting an independent origin.[10] The tumors are often polypoid and submucosal but can be intramyometrial, subserosal, or cervical.[11] Given the rarity of this tumor, the diagnosis of UTROSCT is usually made postoperatively via histopathological analysis. Morphologically, these tumors closely resemble the morphological spectrum of ovarian sex cord-stromal tumors, with organization in sheets, cords, nests, trabeculae or tubules. Neoplastic cells are epithelioid with scant eosinophilic, clear cytoplasm or, rarely, with a rhabdoid appearance.[12] The nuclei are bland with minimal atypia and rare mitoses. These tumors characteristically exhibit polyphenotypic immunophenotypes with coexpression of cytokeratins, smooth muscle markers, hormone receptors, and markers, which are commonly positive in ovarian sex cord-stromal neoplasms.[12,13]

We could find only 2 cases in the literature that described cytological features obtained by touch imprint. Nishikimi et al. reported the intraoperative touch imprint of ESTSCLEs.[6] Cytological examination revealed abundant hyaline-like substances and tumor cells aligned in a cord or glandular form, with scant cytoplasm and ovoid-to-spindle-shaped nuclei with little atypia. More recently, Kondo et al. described stump smears from resected lung metastases of a UTROSCT.[7] In their case, imprint cytology of the tumor showed round to short spindle-shaped cells with bare nuclei and no atypia. These cells were organized in diverse patterns: isolated, scattered or in sheets with poor cohesion; cords or glandular forms were not seen.

In the present case, however, cytological examination demonstrated neoplastic small epithelial cells that were isolated or in clustered formation. At first glance, these cells appeared slightly atypical: scant cytoplasm, ovoid nuclei with nuclear membrane irregularities, fine chromatin and conspicuous nucleoli (Figure 1C). No mitoses or necrosis were seen, and the background was clean. The abundance of cells present and the clinical presentation of a protruding mass into the uterine cavity were all together suspicious for us in the sense of a neoplasm. Therefore, the diagnosis of atypical glandular cells consistent with well-differentiated adenocarcinoma was first suspected. In the differential diagnosis, we suggested the possibility of cervical adenocarcinoma or an epithelial component of an MMMT. However, retrospectively, large sheets of glandular cells or crowded groups of tumor cells with feathery edges were not present. Clinical presentation with a necrotic mass protruding in the vaginal cavity raises the possibility of a diagnosis of MMMT.[14] In fact, the sarcomatous component does not easily shed, and Pap tests may only show the malignant epithelial component.[15] In the present case, neoplastic cells could represent an epithelial component. However, the morphological characteristics of endometrial adenocarcinoma were missing. There were no chromatin abnormalities; additionally, macronucleoli are uncommon in this entity, and watery diathesis is frequently seen (Table 1). Moreover, tumor diathesis, which is a characteristic cytological finding of MMMT, was not present.

In conclusion, we describe the first case of a UTROSCT on preoperative LBC. Pap tests usually cannot detect mesenchymal tumors of the female genital tract since characteristic cells rarely exfoliate. When

exfoliation occurs due to several factors, such as necrosis, ulceration, and tumor location, as in the present case, tumor cells can be recognized but are difficult to classify by cytology alone. UTROSCTs in a Pap test could give rise to important diagnostic pitfalls. Cytopathologists should include this entity in the differential diagnosis in cases that contain isolated, mildly atypical cells without other cytological findings oriented to more common malignant diagnosis and in the presence of characteristic cytological findings. Indeed, the distinction among other malignant tumors is important because the postoperative management of a UTROSCT is different, as this tumor has a benign course with limited potential for recurrence.[5,16]

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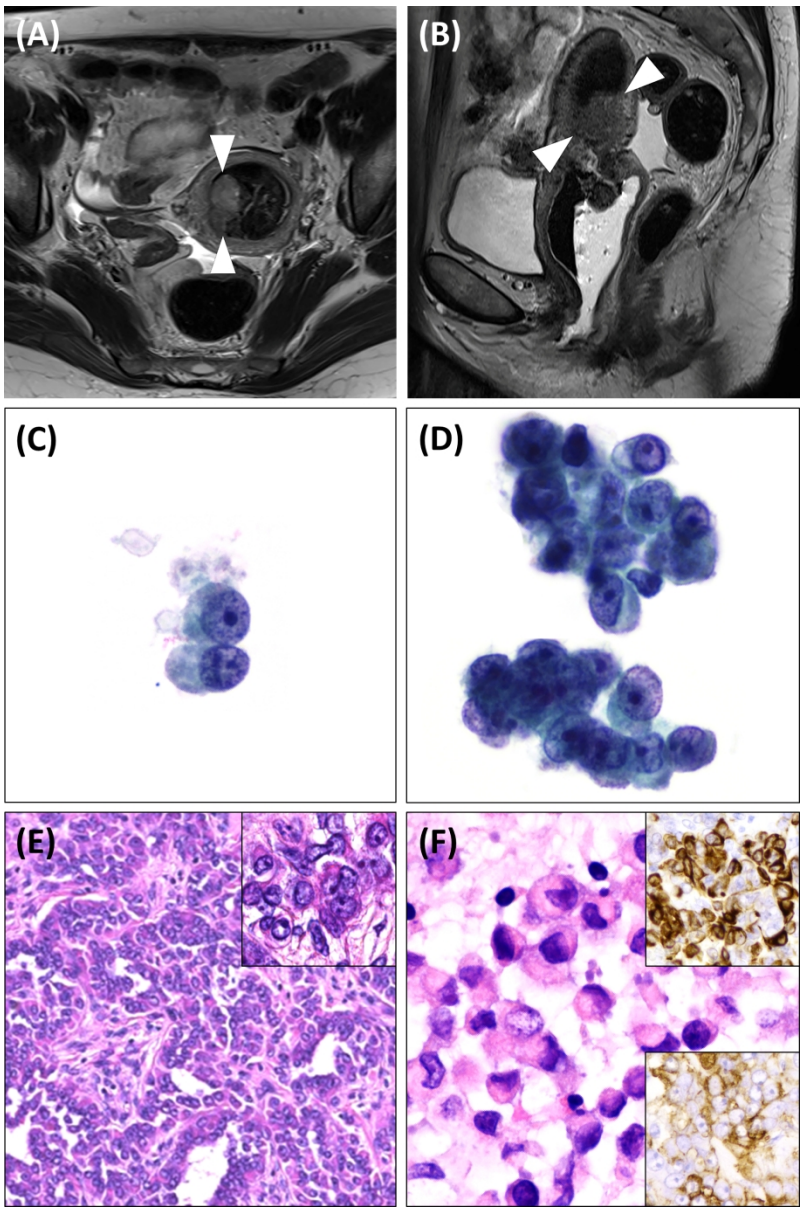
Table 1. Cytomorphological features of uterine tumors resembling ovarian sex cord tumors (UTROSCTs) and differential diagnosis.

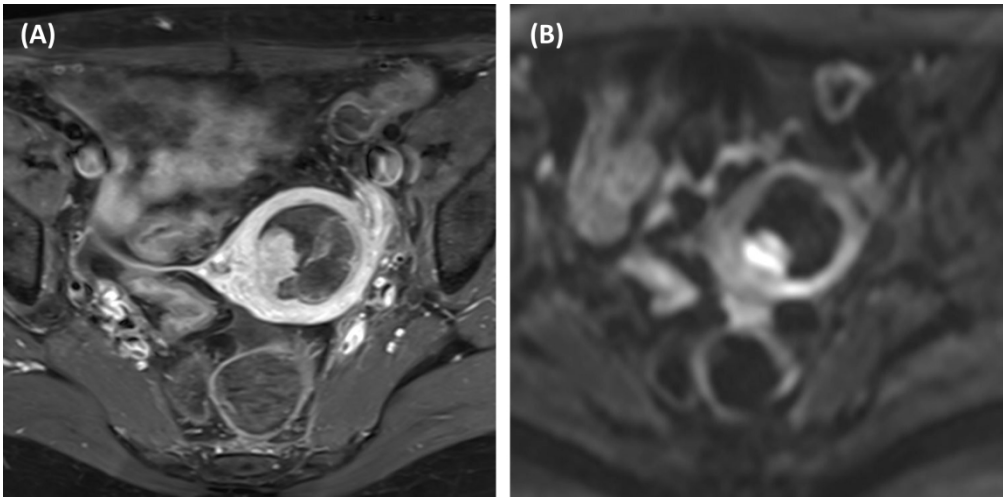
	Uterine tumors resembling ovarian sex cord tumors (UTROSCTs)	**Endocervical adenocarcinoma**	**Endometrial adenocarcinoma (serous and endometrioid)**
Architecture	Isolated or poor cohesion. Rosette-like or trabecular arrangement (touch imprint)	Sheets, feathering, marked cellular crowding	Small cluster, spheres
Cells	Medium sized, round	Abundant endocervical cells, columnar	Sparse, round
Cytoplasm	Scanty	Abundant, foamy or granular	Scant or abundant, vacuolated and cytoplasmic neutrophils
Nuclei	Finely granular chromatin, no mitosis	Large, pale or hyperchromatic	hyperchromatic
Nucleoli	Sometimes one, prominent	Multiple, large	Single, prominent
N/C ratio	High	High	High
Background	Clear	Coarse tumor diathesis	Histiocytes, watery tumor diathesis
IHC, positive	CK, hormone receptors, smooth muscle and sex cord-like markers (inhibin, calretinine)	CEA, p16	Vimentin, hormone receptors.
IHC, negative		hormone receptors, sex cord-like and smooth muscle markers	sex cord-like and smooth muscle markers
Molecular findings	Lacks *FOXL2* and *DICER1* mutations. No *JAZF1-SUZ12* fusion No *PHF1* gene rearrangements		*POLE* (ultramutated), MSI (hypermutated), copy-number low (endometrioid), copy-number high (serous-like)

Legend: UTROSCTs: uterine tumors resembling ovarian sex cord tumors; CK: cytokeratin; N/C: nuclear/cytoplasmic; IHC: immunohistochemistry.



Radiological, cytological, histological and immunohistochemical aspects of UTROSCT. A: Pelvic MRI with vaginal ultrasound gel filling in T2-weighted transverse and (B) sagittal planes. A residual broad-based solid mass of 2.6 cm is seen (white arrowheads) originating from the right uterine wall and protruding inside the uterine cavity. The cavity is dilated by an organized hematometra, which partially protrude through the cervix. Pelvic free fluid is also present. C: Pap test demonstrated isolated atypical cells or in some clusters (D) with scanty cytoplasm, oval nuclei with fine chromatin and conspicuous nucleoli (C and D, liquid-based cytology, Papanicolaou staining, x200). E: Histologically, a uniform population of tumor cells organized in trabeculae or solid areas with occasional round and slit-likes spaces was present (hematoxylin and eosin staining, x100). E, inset: Tumor cells were small with oval nuclei with one clearly visible nucleolus (hematoxylin and eosin staining, x400). F: A different area of the tumor showed cells with rhabdoid features (hematoxylin and eosin staining, x400). F, upper right inset: immunohistochemical expression of cytokeratin AE1/AE3 and (F, lower right inset) of Alpha-inhibin by tumor cells (x100).

182x274mm (300 x 300 DPI)



T1-weighted post-gadolinium transverse (A) and diffusion-weighted transverse (B, b = 800) images. After injection (A), there is a homogeneous enhancement of the lesion, equal to that of the adjacent uterine wall, but well circumscribed restricted diffusion (B) limited to the pediculated component.

338x166mm (300 x 300 DPI)