MIXED MÜLLERIAN TUMORS OF THE FEMALE GENITAL TRACT

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KEYWORDS

• Malignant mixed müllerian tumor • Malignant mixed mesodermal • Carcinosarcoma
• Low-grade müllerian/mesodermal adenosarcoma • Adenofibroma
• Atypical polypoid adenomyoma • Polypoid endometriosis • Female genital tract

ABSTRACT

Malignant mixed müllerian/mesodermal tumor (MMMT) and low-grade müllerian/mesodermal adenosarcoma are two of the most common mixed müllerian tumors of the female genital tract. MMMT is a biphasic neoplasm, composed of morphologically malignant epithelial and stromal elements. MMMT should be distinguished from endometrioid adenocarcinoma with spindled cell elements, ''dedifferentiated'' endometrioid carcinoma, and combined adenocarcinoma and neuroendocrine carcinoma. Low-grade müllerian adenosarcoma is also a biphasic tumor composed of morphologically benign or low-grade epithelial and malignant stromal elements. The differential diagnosis of adenosarcoma includes MMMT, endometrial stromal tumor containing endometrioid glands, benign endometrial or endocervical polyp, adenofibroma, adenomyoma, including atypical polypoid adenomyoma, botryoid embryonal rhabdomyosarcoma (sarcoma botryoides), and endometriosis, including polypoid endometriosis. Gross and microscopic features, including immunophenotype, should permit discrimination of the various entities.

OVERVIEW

Mixed müllerian tumors of the female genital tract constitute a group of interesting neoplasms that contain neoplastic epithelial and mesenchymal components. Malignant mixed müllerian tumor, also referred to as ''malignant müllerian mixed tumor,'' ''malignant mixed mesodermal tumor,'' carcinosarcoma, or simply ''MMMT,'' is the most common mixed epithelial and stromal tumor. Although they can arise in any genital organ, MMMTs are found most frequently in the endometrium where they represent less than 5% of malignant neoplasms; they can also arise in the cervix, ovary, fallopian tube and, rarely, the peritoneum. These tumors are increasingly thought of as carcinomas that demonstrate sarcomatoid differentiation,[1–4] although many gynecologists persist in classifying them as sarcomas. The imprecise nature of the entity's current definition is responsible for difficulties in accurate diagnosis. As is discussed herein, there is a group of unusual biphasic uterine neoplasms that have been historically considered MMMTs. With the advent of carcinoma-style staging surgeries for MMMT, treatment with effective chemotherapeutic agents for high-risk and high-grade uterine and ovarian malignancies, specific treatment protocols for MMMT, increased use of immunohistochemistry, and advances in the understanding of the interplay of genetics, tumor biology, and epidemiology, it has become clear that only a subset of tumors historically considered MMMT conforms to most of the commonly held assumptions about MMMT. As a group, MMMTs are highly aggressive tumors, more clinically aggressive than carcinomas, composed of malignant epithelial and mesenchymal elements. Like MMMTs, low-grade adenosarcomas and adenofibromas can occur in endometrium, cervix, fallopian tube, and ovary.

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Low-grade müllerian/mesodermal adenosarcoma, also commonly referred to as "adenosarcoma," most commonly arises in the uterus, whereas adenofibroma is more commonly found in the ovary or fallopian tube. Adenosarcomas can arise in association with endometriosis, which means that occasional cases are diagnosed in the gastrointestinal tract[5] and other sites where endometriosis can be situated.

GROSS FEATURES

MALIGNANT MIXED MÜLLERIAN/MESODERMAL TUMOR

MMMTs of the uterine corpus and cervix are usually described as large, bulky polypoid tumors. Uterine corpus tumors are occasionally so large that they fill the endometrial cavity and protrude through the cervical os, giving the impression of a cervical primary tumor (**Fig. 1**). On sectioning, they show a fleshy, heterogeneous cut surface with extensive areas of hemorrhage and necrosis. Deep and destructive infiltration of the myometrium or cervical stroma is easily identified in many cases, although on occasion the tumor appears limited to an endometrial or endocervical polyp. Ovarian tumors are typically large, solid and cystic, with foci of hemorrhage and necrosis.

Key Features
MALIGNANT MIXED MÜLLERIAN/MESODERMAL TUMOR

- Biphasic neoplasm composed of morphologically malignant epithelial and stromal elements
- The epithelial component is typically serous, International Federation of Gynecology and Obstetrics (FIGO) grade 3 endometrioid, or too poorly differentiated to subclassify
- The stromal component is histologically high grade, featuring obvious nuclear atypia, pleomorphism, and mitotic activity
- The stromal component may be homologous or heterologous
- Homologous stroma resembles pleomorphic, undifferentiated spindled cell sarcoma ("malignant fibrous histiocytoma"-like), high-grade fibrosarcoma, or pleomorphic round cell sarcoma
- Heterologous stroma is usually rhabdomyoblastic or cartilaginous (histologically malignant)

MÜLLERIAN/MESODERMAL ADENOSARCOMA

Endometrial and cervical adenosarcomas typically form large, polypoid tumors with a soft or rubbery consistency. Many neoplasms exhibit clefts between round and bulbous projections, some of which have blunted ends. On section, they are tan in color and frequently contain fluid-filled cysts. Most endometrial and cervical tumors fail to invade myometrium or cervical stroma. Ovarian and peritoneal adenosarcomas are generally similar in appearance. Gross findings suggestive of endometriosis are also frequently seen.

ADENOFIBROMA

Endometrial and cervical adenofibromas are so rare that a reliable description of their gross appearance would probably not be accurate. Such tumors would be assumed to resemble low-grade müllerian adenosarcomas. Ovarian adenofibromas, on the other hand, are common. Endometrioid adenofibroma, the subtype that is most similar in appearance to adenosarcoma, is usually a solid tumor containing small cysts on sectioning. Rare tumors are predominantly cystic.

Key Features
MÜLLERIAN/MESODERMAL ADENOSARCOMA

- Biphasic neoplasm composed of morphologically benign or low-grade appearing epithelial and malignant stromal elements
- Overall appearance reminiscent of fibroadenoma or phyllodes tumor of the breast
- Broad, polypoid fronds and cysts with intraglandular stromal papillae, leaf-like formations, and crescent-shaped and slit-like spaces lined by epithelium associated with subepithelial stromal condensation
- The eithelium is benign and endometrioid, or metaplastic or hyperplastic; rarely, it is a well-differentiated endometrioid adenocarcinoma
- The stroma resembles that of an endometrioid stromal tumor when low-grade and homologous. Sex cord–like features may also be present
- Stromal overgrowth (defined as stroma constituting >25% of the tumor), high-grade sarcoma, and heterologous elements (particularly rhabdomyoblasts) may be present alone or in combination. The former 2 features are more common in ovarian than endometrial tumors