MOLECULAR GENETICS OF MESENCHYMAL TUMORS OF THE FEMALE GENITAL TRACT

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KEYWORDS

• Leiomyoma • Leiomyosarcoma • HMGA2 • Low-grade endometrial stromal sarcoma
• Undifferentiated endometrial sarcoma

ABSTRACT

Mesenchymal tumors of the female genital tract are a heterogeneous group of neoplasms that can be classified based on cellular differentiation into 3 main groups: smooth-muscle tumors, endometrial stromal tumors, and other differentiated and undifferentiated tumors. Although ovarian sex cord-stromal tumors could be considered mesenchymal tumors, their unique clinical and pathologic aspects place them in a separate category, and they are thus not covered in this article. Genomic analysis techniques have revealed important genetic aberrations such as the t(7;17) translocation, resulting in JAZF1-JJAZ1 gene fusion, characteristic of endometrial stromal tumors. These analyses have demonstrated genetic complexity and heterogeneity in many mesenchymal tumor types. This article focuses on current understanding of the molecular genetics of mesenchymal tumors of the female genital tract, with emphasis on diagnostic and prognostic molecular features.

OVERVIEW

Benign mesenchymal tumors of the female genital tract are the most common group of neoplasms in the gynecologic tract. Uterine leiomyomas (LM) account for most of this group of tumors and it is estimated that up to 80% of women by age 50 years have 1 or more uterine LMs. Other benign mesenchymal tumors of the female genital tract are uncommon, including endometrial stromal nodule (ESN), aggressive angiomyxoma (AAM), and other tumor types that are not exclusive to the gynecologic tract, arising from neural, adipose, vascular, and other soft-tissue tumors. In contrast, malignant mesenchymal tumors are less common, particularly if carcinosarcoma/malignant müllerian

Key Features
MESENCHYMAL TUMORS OF THE FEMALE GENITAL TRACT

1. Characteristic genetic rearrangements seen in leiomyoma, endometrial stromal nodule, endometrial stromal sarcoma, aggressive angiomyxoma, and alveolar rhabdomyosarcoma
2. Leiomyosarcomas typically have numerous genetic abnormalities, reflecting underlying genetic instability
3. Undifferentiated endometrial sarcomas represent a heterogeneous group of highly malignant tumors
4. Molecular diagnostic testing not usually required for diagnosis but can be a helpful confirmatory tool
5. Genetic rearrangements do not serve as targets for therapy at this time

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mixed tumor (MMMT) and low-grade müllerian adenosarcoma are excluded. Pure malignant mesenchymal tumors account for approximately 2% of all uterine malignancies, and a smaller proportion of malignant tumors of the ovary, vagina, and vulva. Leiomyosarcoma (LMS), low-grade endometrial stromal sarcoma (ESS), and the heterogeneous ill-defined group of undifferentiated endometrial sarcomas (UES) form the bulk of this group of malignancies in adults, whereas rhabdomyosarcoma (RMS) is more common in children. Other types of sarcomas have been documented to arise in the female genital tract but they are extremely rare.

Mesenchymal tumors of the female genital tract can be classified into 3 major groups based on the line of cellular differentiation:

1. Smooth-muscle tumors
2. Endometrial stromal tumors
3. Miscellaneous category of mesenchymal tumors

The smooth-muscle tumors are the most common group and are composed of tumor cells showing morphologic or immunophenotypic evidence of smooth-muscle differentiation. They differ from benign and malignant smooth-muscle tumors arising outside the female genital tract in that most gynecologic smooth-muscle tumors express estrogen and progesterone receptors (ER and PR), which can be used as a diagnostic tool in patients in whom there is doubt about whether a smooth-muscle tumor in the pelvis is of gynecologic or nongynecologic origin.[1] Uterine smooth-muscle tumors account for most smooth-muscle tumors of the female genital tract and are believed to originate from myometrial smooth muscle, although a subset of these tumors may originate from vascular smooth muscle in the rich blood-vessel networks of the uterine wall. They encompass a morphologically and biologically diverse group of neoplasms that range from LM to LMS. The endometrial stromal tumors include ESN and low-grade ESS. They are a group of neoplasms that morphologically and immunophenotypically recapitulate endometrial stromal cell differentiation. They usually arise in the uterus but can occur at other sites in the female genital tract. The recent identification of genetic translocations common to ESN and low-grade ESS further supports the notion that they are related tumors derived from the same progenitor cell. The miscellaneous group of mesenchymal tumors includes UES, a uterine tumor lacking demonstrable evidence of specific cellular differentiation despite careful morphologic and immunohistochemical evaluation. Although the nature and the cell of origin for UES remain elusive, it is likely that they are a heterogeneous group of tumors that include sarcomatous overgrowth of a carcinosarcoma or low-grade müllerian adenosarcoma and poorly differentiated/dedifferentiated LMS or ESS. This article provides a brief overview and update on the molecular genetics of these and other rarer mesenchymal tumors of the female genital tract for which molecular genetic data are available. **Table 1** provides a summarization of genetic alterations in mesenchymal tumors.

LEIOMYOMAS

As LMs most commonly occur in the uterus, molecular data almost exclusively reflect studies of these tumors at this site. These tumors can also occur in the ovary, vagina, and vulva and they are morphologically indistinguishable from their uterine counterparts. Although this discussion pertains specifically to uterine LM, it is likely that the molecular genetic data are similar to those from LM arising elsewhere in the female genital tract. Uterine LMs are common among premenopausal and perimenopausal women.[2,3] They can cause significant symptoms in up to one-quarter of patients and are the leading cause for hysterectomy in the United States.[4] Risk factors include obesity, early menarche, late menopause, late reproductive age, and nulliparity,[5] all of which reflect increased exposure to cyclical hormonal stimulation. In women of African American descent, LMs are more likely to be multiple, and symptomatic.[3,6] Most tumors occur sporadically; however, there seems to be a component of genetic susceptibility to the development of LM in some patients, as familial aggregation has been noted.[7] The syndrome of cutaneous and uterine leiomyomatosis/hereditary leiomyomatosis and renal cell carcinoma is associated with the development of LMs.[7–10] Patients with this syndrome have germline inactivating mutations in a single copy of the fumarate hydratase (FH) gene and are susceptible to develop multiple cutaneous LMs (at young age), symptomatic uterine LMs,[11] and renal cell carcinomas.[12] Loss of FH through a somatic mutation has also been reported in occasional non-syndromic (sporadic) uterine LMs.[13] Patients with Cowden syndrome, characterized by phosphatase and tensin homolog (PTEN) mutation also tend to develop multiple uterine LMs, typically with a younger age of onset.[14]

Most LMs display normal karyotypes by cytogenetic and fluorescence in situ hybridization (FISH) analysis.[15] Approximately 40% of LM have