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Review Article

Uterine sarcoma Part II—Uterine endometrial stromal sarcoma: The TAG systematic review

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ABSTRACT

Endometrial stromal tumors are rare uterine tumors (<1%). Four main categories include endometrial stromal nodule, low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and uterine undifferentiated sarcoma (UUS). This review is a series of articles discussing the uterine sarcomas. LG-ESS, a hormone-dependent tumor harboring chromosomal rearrangement, is an indolent tumor with a favorable prognosis, but characterized by late recurrences even in patients with Stage I disease, suggesting the requirement of a long-term follow-up. Patients with HG-ESS,

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undifferentiated sarcoma
uterine sarcoma
uterus

based on the identification of *YWHAE-NUTM2A/B* (*YWHAE-FAM22A/B*) gene fusion, typically present with advanced stage diseases and frequently have recurrences, usually within a few years after initial surgery. UUS is, a high-grade sarcoma, extremely rare, lacking a specific line of differentiation, which is a diagnosis of exclusion (the wastebasket category, which fails to fulfill the morphological and immunohistochemical criteria of translocation-positive ESS). Surgery is the main strategy in the management of uterine sarcoma. Due to rarity, complex biological characteristics, and unknown etiology and risk factors of uterine sarcomas, the role of adjuvant therapy is not clear. Only LG-ESS might respond to progestins or aromatase inhibitors.

Introduction

Endometrial stromal tumors (EST) account for less than 1% of all uterine tumors [1], which can be divided into four main categories, currently recognized by the World Health Organization, including endometrial stromal nodule (ESN); endometrial stromal sarcoma (ESS), low-grade (LG-ESS); endometrial stromal sarcoma, high-grade (HG-ESS); and uterine undifferentiated sarcoma (UUS) [2]. Endometrial stromal tumors, especially LG-ESS, represent the second most common category of mesenchymal uterine tumors (second to uterine leiomyosarcoma [uLMS]) [3]. A stage system, similar to the uLMS, has been introduced in the previous issue of the Taiwanese Journal of Obstetrics and Gynecology [3]. In brief, a tumor limited to the uterus is Federation International Gynecology and Obstetrics (FIGO) I [<5 cm in diameter (IA) and ≥5 cm (IB)]; a tumor limited to pelvic cavity but extended beyond the uterus is II [an adnexal involvement (IIA) and other pelvic cavity invasion (IIB)]; tumor outside the pelvic cavity is III [positive retroperitoneal lymph node metastases (IIIC)]; tumor invaded to bladder and rectum is IVA, and distant metastases is IVB [3].

To distinguish benign and malignant is based on the type of tumor margin, although it is sometimes not easy to define the category. The following key points may help to define the benign and malignant ESS (Table 1). In general, a well-circumscribed tumor is diagnosed as benign stromal nodules, whereas those exhibiting myometrial invasion and lymphovascular space (LVS) invasion are malignant [3]. Occasionally, benign ESN might have focal irregularity of the border and form finger-like or nodular projections. However, these unusual presentations should not extend >3 mm from the main tumor mass. As shown above, total absence of LVS invasion of these tumors (ESN) is considered a benign tumor [2].

Table 1
Useful key factors to distinguish benign and malignant endometrial stromal neoplasms.

Identify benign ESN
(1) Adequate sampling of the border/surrounding myometrium (tumor −myometrial interface)
(2) The projections into the adjacent myometrium <3 mm from the main tumor mass
(3) The projections into the adjacent myometrium <3 in number
(4) Absence of vascular invasion
Identify HG-ESS
(1) In a tumor with marked mitotic activity (>20−30 mitoses/10 high-power fields)
(2) Loss of hormone receptors
(3) Additional sampling to exclude the possibility of HG-ESS for fibrous or myxoid appearance
(4) Negative for smooth muscle markers
(5) Diffusely positive for c-kit but negative for DOG1
(6) Diffusely positive for cyclin D1 but negative for EMA and/or broad spectrum cytokeratin
Identify UUS
(1) Lacking smooth muscle or endometrial stromal differentiation
(2) Destructive myomatrial infiltration, a fascicular or patternless growth pattern, highly pleomorphic cells (nondescript cells)
(3) Positive CD10 immunoactivity
(4) Lacking the defining genetic rearrangement (complex karyotypes and genomic gains and losses without specific translocations)

CD10 = cluster of differentiation 10; DOG1 = Discovered On Gastrointestinal stromal tumors protein 1; EMA = Epithelial Membrane Antigen; ESN = endometrial stromal nodule; HG-ESS = high-grade endometrial stromal sarcoma; UUS = uterine undifferentiated sarcoma.

ESN

ESN is benign. The tumor is usually presented with abnormal vaginal bleeding or as an incidental finding in a hysterectomy specimen performed for other reasons [4]. Grossly, ESN is a well-circumscribed tumor with a fleshy and soft yellow to tan cut surface and can be found as an intramural mass or as a polypoid tumor protruding into the endometrial cavity [4]. Microscopically, ESN is expansible in nature without myometrial invasion and absence of LVS invasion. An immunohistochemical profile did not help to distinguish ESN and LG-ESS, suggesting that conventional morphological and histological features are important for the diagnosis of ESN [4].

LG-ESS

Overview

LG-ESS affects women primarily in the perimenopausal age group and more than half of patients were diagnosed premenopausally [1,2]. The most commonly presented symptoms or signs were abnormal uterine bleeding, pelvic pain, and dysmenorrhea [1,2]. Nearly one-third of patients present with symptoms or signs related to extrauterine spread and one-fourth of patients are asymptomatic [1,2]. The most frequent site of extrauterine pelvic extension is the ovary [1]. Extrauterine pelvic extension of LG-ESS is also frequently associated with endometriosis [4]. LG-ESS might manifest as an endometrial polyp, such that endometrial biopsy is more likely to be diagnostic [5]. Obesity, diabetes, younger age at menarche, and tamoxifen intake are associated with increased risk of LG-ESS [5].

Pathology

Grossly, LG-ESS may be submucosal or intramural, usually with ill-defined borders and wormlike permeation within the myometrium and parametrial tissue [6]. LG-ESS can form multiple poorly defined, frequently coalescent, fleshly tan to yellow, soft nodules within the endometrium and myometrium. LG-ESS appears paler, firmer and gray if the tumor underwent smooth muscle differentiation. Microscopically, LG-ESS shows extensive permeation of the myometrium as irregular islands with frequent LVS invasion [5], and the “tongue-like” patterns of myometrial and LVS invasion are