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Original contribution

Vascular invasion in uterine sarcomas and its significance. A multi-institutional study☆,☆☆

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Summary Although metastases and high-mortality are frequent in high-grade endometrial sarcomas (HGSs), these findings are less commonly seen in low-grade endometrial stromal sarcomas (LGESSs), even in cases with lymphovascular invasion (LVI). We hypothesized that the "bulging plugs" of tumor characteristic of LVI in LGESS are fundamentally different from LVI seen in HGS. We reviewed 70 uterine sarcomas: 42 HGSs (high-grade endometrial stromal sarcomas, undifferentiated uterine sarcoma, and leiomyosarcoma) and 28 LGESSs. All cases had LVI documented on the histologic slides. Immunostains for CD31, ERG, and D2-40 were performed. LGESS harbored cohesive intravascular tumor foci with direct communication from the main tumor and attached to the vessel wall. The intravascular foci included tumor cells and small arteriole-type vessels and were surrounded by a thin fibrous band. Vascular markers confirmed the LVI and highlighted positively stained endothelial cells separating intravascular tumor foci from the blood itself. In contrast, intravascular tumor foci in HGS were composed of discohesive cells clusters, lacking the features described in LGESS. Only 8 (30.8%) patients with LGESS had recurrence/metastases (6 with lung metastasis); only 1 patient died of disease. Thirty (77%) patients with HGS had recurrence/metastases, 27 (69%) patients had lung metastases, and 22 (56.4%) patients died of disease. We propose that in most LGESSs, LVI represents vascular intrusion; manipulation or trauma is potentially responsible for tumor cell detachment into the circulation increasing the chances of recurrence/metastases. Classic LVI features were identified in HGS. This important distinction may allow for better management of patients and avoid unnecessary treatment in LGESS, reducing morbidity.

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1. Introduction

Uterine sarcomas are rare and account for less than 5% of all uterine malignancies [1–5]. The new 2014 *World Health Organization Classification of Tumours of the Female Reproductive Organs* classifies uterine sarcomas as low-grade endometrial stromal sarcoma (LGESS), high-grade endometrial stromal sarcoma (HGESS), undifferentiated uterine sarcoma (UUS), leiomyosarcoma (LMS), and adenosarcomas [6]. Carcinosarcomas are biphasic tumors, now regarded as metaplastic carcinomas.

Uterine sarcomas have a worse prognosis than do carcinomas, with a 5-year overall survival rate between 25% and 55%—although better survival is noted for LGESS, from 80% to 100% in stage I tumors [4,7,8]. Survival studies have determined that stage, age, and tumor size independently influence overall survival [4,7].

Lymphovascular invasion (LVI) is common in both low- and high-grade uterine sarcomas and ranges from 34% in LMS, 55% in UUS, to 67% in LGESS [4]. Although metastases are frequent in high-grade sarcomas, they are less commonly seen in low-grade sarcomas, even in cases with LVI [8].

We evaluated morphologically and immunohistochemically 70 uterine sarcomas with documented LVI in the histologic slides in the most common sarcoma types to determine the significance of LVI in sarcomas and compare with outcome.

2. Materials and methods

Briefly, after institutional review board approval at each institution, cases diagnosed as uterine sarcoma (from January 1997 to July 2014) from 7 national and international institutions from the above-mentioned authors were retrieved and studied. Selection criteria included the following: (1) diagnosis of uterine sarcoma, including LGESS, LMS, HGESS, or UUS, and (2) LVI present on histologic slides. In every case, all histologic slides were initially reviewed by the pathologist at each institution, who selected 1 slide from each case fulfilling these selection criteria; the respective block was obtained to perform immunostains for vascular markers CD31 (all cases) and ERG (22 cases, 10 LGESSs, 12 high-grade endometrial sarcoma [HGSs]) and lymphatic marker D2-40 (all cases). Two cases were excluded because LVI foci were not present on immunostain slides.

Members of the participating institutions then convened in one consensus meeting at Cedars Sinai Medical Center in Los Angeles, California. All selected slides and immunostains were subsequently reviewed by the entire group using a multiheaded microscope to confirm LVI foci and review immunostains. The following information was then gathered and recorded from patients' pathology reports and/or clinical histories: patients' age, tumor size as determined clinically and/or grossly, International Federation of Gynecology and Obstetrics (FIGO) stage [9], lymph node (LN) status, recurrence/metastasis and site of occurrence, treatment, and status at last follow-up.

LVI foci were evaluated and classified as "true" LVI or vascular intrusion (pseudoinvasion) as outlined below (Table 1). All vessels expressing CD31 were also positive for ERG, and vice versa. Vessels expressing D2-40 were interpreted as lymphatics. Morphologic features that represented vascular intrusion as opposed to true LVI included tumor foci involving vascular spaces with direct communication from the main tumor suggesting a polypoid intrusion into the vascular lumen, cohesive intravascular tumor attached to the vessel wall with predominantly smooth edges, and features similar to the main tumor, some including small arteriole-type vessels, and surrounded by a thin fibrous band that separated it from the blood at the most invasive leading intravascular front. Immunohistochemical features of vascular intrusion highlighted positive stained endothelial cells surrounding intravascular tumor foci and separating it from the blood (Fig. 1).

Morphologic features that suggested true LVI included intravascular discohesive clusters of tumor cells, predominantly with irregular/ragged edges, surrounded, at least in

Table 1 Morphologic features of vascular intrusion/pseudoinvasion *vs* true LVI

Type of vascular invasion	Morphologic features
Vascular intrusion/pseudoinvasion	Intravascular tumor foci with direct communication from the main tumor suggesting polypoid intrusion Intravascular tumor foci attached to the vessel wall Cohesive intravascular tumor foci with predominantly smooth edges Intravascular tumor resembles main mass, including small arteriole-type vessels Intravascular tumor surrounded by thin fibrous band at the most invasive intravascular front Immunohistochemically stained endothelial cells surrounding intravascular tumor foci and separating it from the blood either with CD31, ERG, and/or D2-40
True LVI	Discohesive clusters of cells with irregular/ragged edges Intravascular tumor foci surrounded, at least in part, by a fibrinous reaction Lack of vasculature within the intravascular tumor foci Lack of immunohistochemically proven endothelial cells surrounding intravascular tumor foci

Abbreviation: LVI, lymphovascular invasion.