



Case report

Uterine sarcoma with ambiguous histomorphology: A case report

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ABSTRACT

Background: Leiomyosarcomas (LMS) and endometrial stromal sarcomas (ESS) may display overlapping histomorphology, which may challenge diagnostic accuracy. Since LMS and ESS have vastly different clinical behavior and adjuvant therapy recommendations, accurate diagnosis is critical.

Case: We present the case of an 83-year-old female with postmenopausal bleeding who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy for clinically atypical appearing leiomyomata. Histologically, dual populations of cells with morphologic features of low-grade ESS and high-grade spindle cell sarcoma were seen. Immunohistochemistry and molecular studies revealed the cells to be of smooth muscle derivation, rendering a diagnosis of high-grade LMS with heterogeneous morphology (stage IB). The patient received adjuvant gemcitabine plus docetaxel. She recurred 8 months after completion of chemotherapy and was transferred to hospice care.

Conclusion: Ancillary studies, such as immunohistochemistry and molecular testing, aid in accurate subcategorization of uterine sarcomas with ambiguous histomorphology.

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1. Introduction

Uterine sarcomas are a rare class of mesenchymal tumors that account for 3–7% of uterine malignancies (D'Angelo and Prat, 2010). Revised in 2014, the WHO defines diagnostic criteria, by which they are categorized as low-grade or high-grade endometrial stromal sarcomas (ESS), leiomyosarcomas (LMS), or undifferentiated sarcomas (UUS). Most sarcomas demonstrate characteristic features, allowing for straightforward diagnosis based on histology alone. However, some LMS and ESS variants display overlapping histologic features, complicating accurate characterization (Oliva, 2016; Nucci, 2016; Lee and Nucci, 2015). In those cases, immunohistochemical and molecular studies may help determine the true immunohistophenotype of the tumor and guide appropriate treatment. We present an unusual case of a uterine sarcoma with histomorphologic features of a low-grade ESS with an associated high-grade spindle cell sarcoma component, in which immunophenotyping and molecular testing were the defining steps for diagnosis of LMS.

2. Case presentation

An 83-year-old female presented with postmenopausal bleeding and symptomatic anemia. Pelvic examination was remarkable for an enlarged uterus. Transvaginal ultrasonography demonstrated a myomatous uterus with a 7-mm endometrial lining. She underwent hysterectomy with dilation and curettage. Pathologic evaluation revealed a benign endometrial polyp. Magnetic resonance imaging revealed a 21 × 12 × 18 cm anteverted uterus, containing innumerable typical appearing leiomyomata and a dominant heterogeneous 14 cm mass with internal nodular enhancement, subserosal bulging, and thinning of the overlying myometrium. There was no lymphadenopathy or extra-uterine disease. The patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, and omental biopsy. The intraoperative frozen section revealed a spindle cell neoplasm with cytologic atypia, increased mitotic activity, and necrosis, favoring malignancy.

Gross examination revealed an 1850 g uterus distorted by multiple intramural and subserosal nodular masses with a dominant 14 cm intramural mass containing areas of hemorrhage and cystic degeneration. Microscopically, the tumor permeated through the myometrium, with areas of solid destructive growth and extensive necrosis. Lymphovascular space invasion was present (Fig. 1). Histomorphologically, the tumor exhibited dual populations of neoplastic cells, including solid areas comprised of monotonous small round cells with minimal nuclear atypia, scant cytoplasm, brisk mitotic activity, and delicate vasculature,

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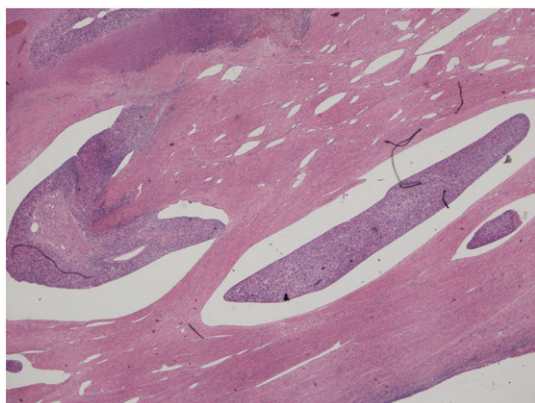


Fig. 1. (H&E, 100 \times): Lymphovascular invasion with the solid tumor nests.

juxtaposed with spindle cells with marked nuclear pleomorphism and cytologic atypia (Figs. 2 and 3). The latter histologic pattern, along with involvement of the endometrium, raised the possibility of a high-grade/dedifferentiated ESS component. Immunohistochemical studies demonstrated pure smooth muscle immunophenotype in both spindle and round cell components with strong and diffuse immunoreactivity for desmin, smooth muscle actin (SMA), muscle specific antigen (MSA), and h-caldesmon. The CD10 and cyclin D1 immunostains were diffusely negative in both components (Fig. 4).

Molecular studies did not reveal aberrant rearrangements involving *JAZF1*, thus arguing against low-grade ESS. Next generation sequencing of the tumor revealed several genetic alterations, including *ATRX* (S2094), *DNMT3A* (R167fs*58), *MED12* (G44V), and *TP53* (R181P). Overall, the morphologic and immunophenotypic findings, as well as molecular studies, supported the diagnosis of high-grade uterine leiomyosarcoma with heterogeneous histomorphology.

The patient received adjuvant gemcitabine plus docetaxel, which was discontinued after 3 cycles due to grade 3 infectious and vascular toxicities. She recurred 8 months after completion of chemotherapy and was discharged to hospice care.

3. Discussion

LMS and ESS have vastly different clinical behavior. Though 62–79% of patients with LMS present with stage I disease, recurrences are frequent, ranging 53–71% for those with stage I–II disease (D'Angelo and Prat, 2010; Amant et al., 2014; Abeler et al., 2009; Giuntoli et al., 2003). In one study, the 5-year overall survival was 51% and 25% for patients with stage I and stage II LMS, respectively (Amant et al., 2014).

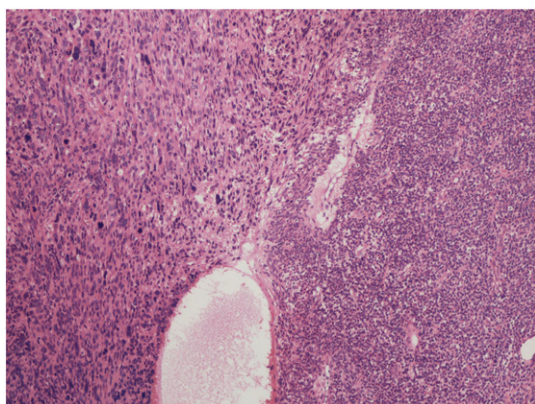


Fig. 2. (H&E, 100 \times): Dual populations of tumor cells, including spindle cell component with marked nuclear pleomorphism (left), juxtaposed with solid areas of small round monotonous cells with minimal nuclear atypia (right).

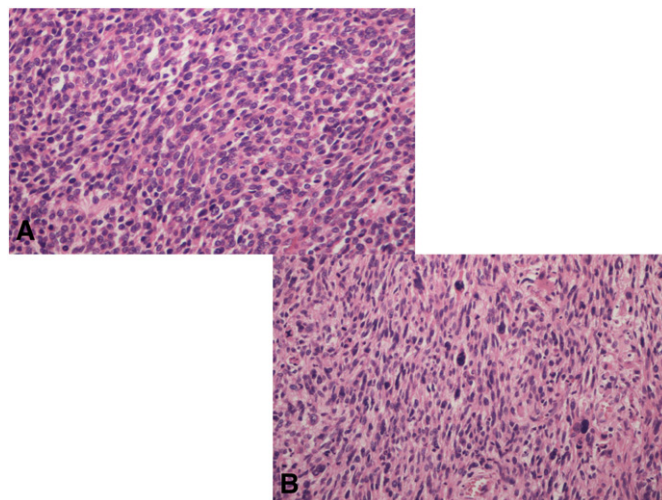


Fig. 3. (H&E, 400 \times): Monotonous round cells (A) and spindle cell population with marked nuclear pleomorphism, occasional multinucleated tumor giant cells, and high mitotic activity (B) (higher magnification).

Conversely, low-grade ESS is an indolent tumor and 60–76% of cases are confined to the uterus at diagnosis (Amant et al., 2014; Major et al., 1993). Recurrences are less frequent, occurring in 1/3 of patients and may occur many years after primary diagnosis. High-grade ESS is believed to behave more like LMS than low-grade ESS. In two small studies, 80% of cases were diagnosed with extra-uterine spread and recurrence rates ranged 70–90% following surgical resection (Sciallis et al., 2014).

Defined histologic criteria aid in the classification of uterine sarcomas. Arising from uterine smooth muscle, leiomyosarcoma displays severe nuclear atypia, tumor cell necrosis, and high mitotic activity (D'Angelo and Prat, 2010). Endometrial stromal sarcoma arises from the endometrial stroma, infiltrates the myometrium, and demonstrates tumor plugs within lymphovascular spaces. Reminiscent of proliferative-phase endometrial stroma, low-grade ESS characteristically displays bland nuclear features with minimal nuclear atypia, low to variable mitotic rates, and rare necrosis (D'Angelo and Prat, 2010). High-grade ESS shows more confluent and destructive myoinfiltration, and demonstrates high-grade nuclear features, higher mitotic rates (>10 per 10 HPF), and necrosis. The absence of marked nuclear pleomorphism distinguishes high-grade ESS from UUS (Lee and Nucci, 2015). Despite well-defined diagnostic criteria, LMS and ESS are notably heterogeneous with varying degrees of cytologic atypia and cellular differentiation, resulting in overlapping histologic features and difficulty with pathologic pattern recognition (D'Angelo and Prat, 2010; Oliva, 2016; Nucci, 2016; Lee and Nucci, 2015). Furthermore, low-grade and high-grade components may arise simultaneously (Cheung et al., 1996). In these cases, immunohistochemical (IHC) and molecular testing may provide insight into histologic subcategorization (Table 1).

While some immunomarkers are expressed in both LMS and ESS, others are preferentially expressed in one or the other. LMS usually expresses smooth muscle markers, including desmin, h-caldesmon, MSA, and SMA. Focal to patchy immunoreactivity for CD10 may also be seen in LMS. They may also express estrogen and progesterone receptors (ER/PgR) in 30–40% of cases (D'Angelo and Prat, 2010). Additionally, epithelioid LMS may express epithelial markers, such as cytokeratin and EMA. Smooth muscle markers may be particularly helpful in distinguishing LMS from ESS. While SMA and MSA may be positive in both, desmin and h-caldesmon are infrequently expressed in ESS (D'Angelo and Prat, 2010; Oliva, 2016; Oliva et al., 2002). Additionally, CD10, ER, and PgR, which may be expressed in LMS and low-grade ESS, are typically negative in high-grade ESS, which frequently expresses cyclin D1 (Nucci, 2016; Lee and Nucci, 2015).

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