



## Case report

## High grade sarcoma with chondrosarcomatous differentiation in primary uterine leiomyosarcoma; A rare case and review of literature

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## ABSTRACT

Primary uterine leiomyosarcoma (LMS) with chondrosarcomatous differentiation is extremely rare. We report a case of a 68-year-old, African American woman who presented with postmenopausal bleeding. Ultrasonography (USG) revealed multiple uterine fibroids. Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) was performed. Microscopic examination of the largest intramural nodule showed high-grade sarcoma, comprising of LMS with a focal transformation to undifferentiated sarcoma with chondrosarcomatous differentiation. Endometrium was benign excluding carcinosarcoma. Heterologous differentiation has rarely been described in metastatic or recurrent uterine LMS; however, a primary uterine LMS with chondrosarcomatous differentiation has not been reported previously.

## 1. Introduction

LMS, a malignant mesenchymal tumor of smooth muscle origin represents 1–2% of all uterine malignancies accounting for ~ 40% of all uterine sarcomas. The peak age of incidence is 50 years (Roberts et al., 2018 Dec; Angelo and Prat, 2010 Jan). LMS exhibits a variety of morphologic variants including spindle cell (most common), epithelioid, myxoid, LMS with osteoclast-like giant cells, and very rarely skeletal muscle differentiation (Cui et al., 2017 Jun). The presence of heterologous elements in LMS poses diagnostic confusion with carcinosarcoma/malignant mixed Mullerian tumor (MMMT) which characteristically exhibits homologous or heterologous sarcomatous elements. Extensive sampling and detailed histological examination of endometrium in such cases are critical for correct diagnosis and appropriate patient management.

## 2. Case presentation

A 68-year-old postmenopausal, African American, female presented with complaints of vaginal bleeding. Her past medical history was unremarkable. She had a negative pap smear. On pelvic USG, several uterine fibroids were noted, with the largest measuring 2.5 cm in diameter. There was no evidence of adnexal mass or free fluid. An endometrial biopsy was performed which showed scant tissue and she

was scheduled to follow up at 3 months period. Repeat endometrial biopsy showed benign atrophic endometrium. No malignancy was identified. Clinician discussed with patient all options and cautioned her that no test is 100% accurate and she elected to proceed with the surgical intervention and underwent TAH/BSO.

Grossly, the endometrial cavity was distorted by multiple submucosal, intramural and subserosal gray-white, whorled nodules with rubbery cut surface. The largest tan-yellow intramural nodule measured 4 cm. The endometrium was smooth, glistening, and averages 1 mm in thickness. A 1.0 cm endocervical polyp was also identified. Bilateral adnexa was unremarkable. Previously ligated left fallopian tube measured 3.0 × 0.7 cm and right fallopian tube measured 3.2 × 0.7 cm with unremarkable fimbriae. The left ovary measured 1.5 × 1.0 × 0.5 cm and right ovary measured 1.5 × 1.2 × 0.5 cm. Cut sectioning revealed pale tan solid ovarian stroma.

On microscopic examination, the largest intramural nodule showed malignant spindle cell tumor with smooth muscle differentiation displaying marked cytologic atypia and brisk mitotic activity (18/10hpf), consistent with LMS (Fig. 1). No tumor cell necrosis was identified. The nodule was submitted entirely for histopathologic examination. Additional sections showed transformation to undifferentiated sarcoma with chondrosarcomatous differentiation (Fig. 2). No lymphovascular space invasion (LVI) was identified. Background endometrium was weakly proliferative with a benign endometrial polyp. The remaining

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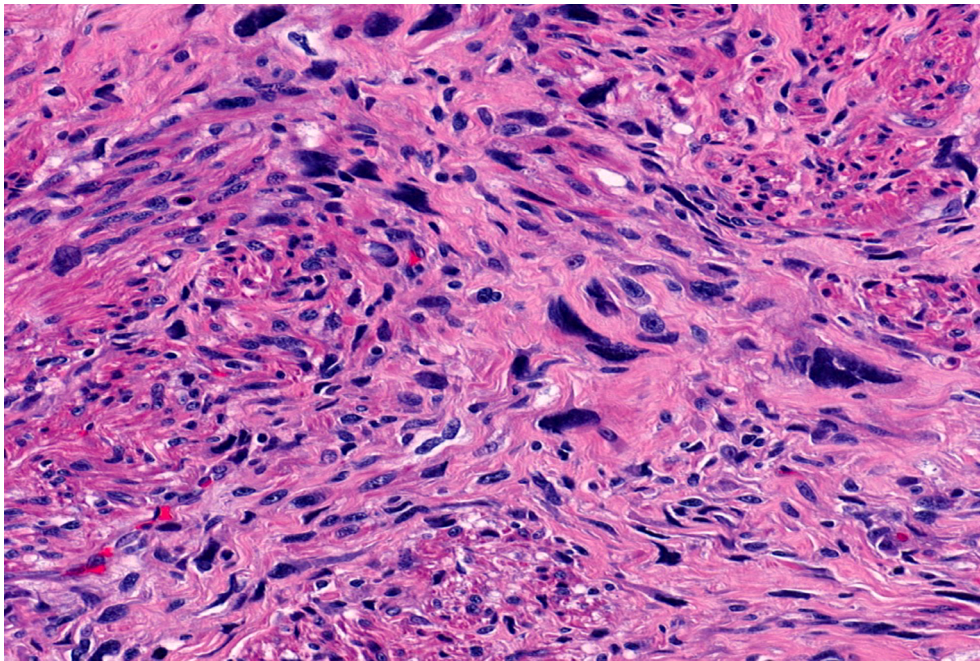


Fig. 1. Malignant spindle cell tumor with smooth muscle differentiation displaying marked cytologic atypia.

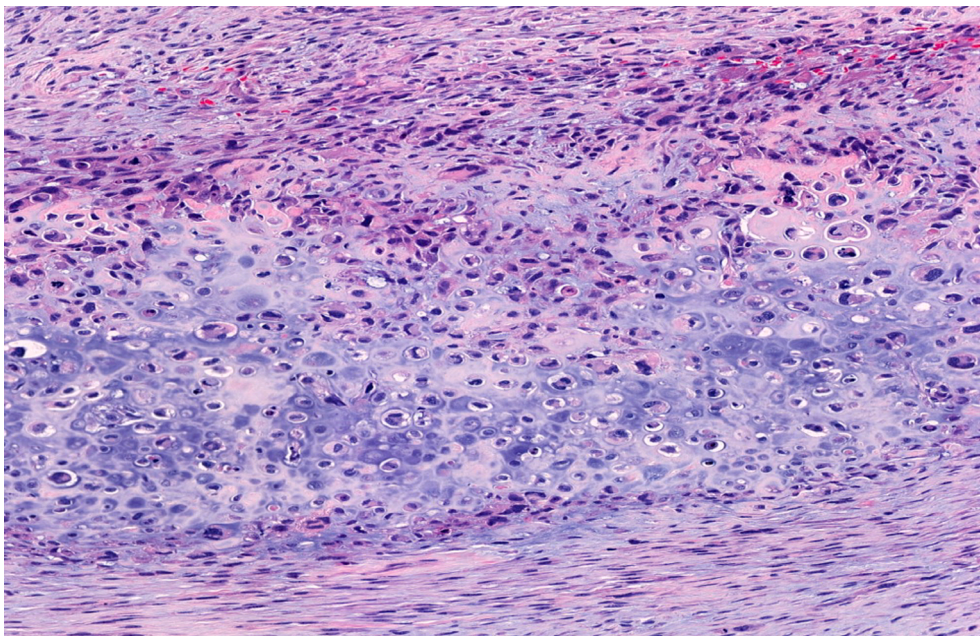


Fig. 2. Chondrosarcomatous differentiation.

identifiable endometrium was submitted entirely to rule out carcinosarcoma. Tumor cells were focally reactive to Desmin (Fig. 3), CD10, and ER immunostains. CD34, S100, CD117, and CK Oscar immunostains were non-reactive in neoplastic cells. The morphologic and immunophenotypic findings were suggestive of high-grade sarcoma with a component of smooth muscle differentiation, consistent with LMS with the transformation to an undifferentiated sarcoma showing chondrosarcomatous differentiation.

### 3. Discussion

LMS represents the most common malignant mesenchymal neoplasm of the uterus accounting for ~ 40% of all uterine sarcomas. It is typically

seen in women > 40 years of age presenting with postmenopausal bleeding. LMS is an aggressive tumor with early metastases and a poor overall prognosis. The outcome is mainly determined by the pathological stage of the disease at the time of diagnosis (Roberts et al., 2018 Dec). The underlying pathogenetic mechanism is unclear, and multiple molecular alterations, including p53 and p16 overexpression, have been reported in association with LMS, but none have any diagnostic significance (Roberts et al., 2018 Dec; Angelo and Prat, 2010 Jan; Cui et al., 2017 Jun; Gockley et al., 2014 Nov).

LMS is characterized by variable morphology and degree of differentiation. Spindle cell is the most common subtype, followed by epithelioid and myxoid variants. The tumor is characteristically hypercellular with variable cytological atypia, increased mitotic count (>10



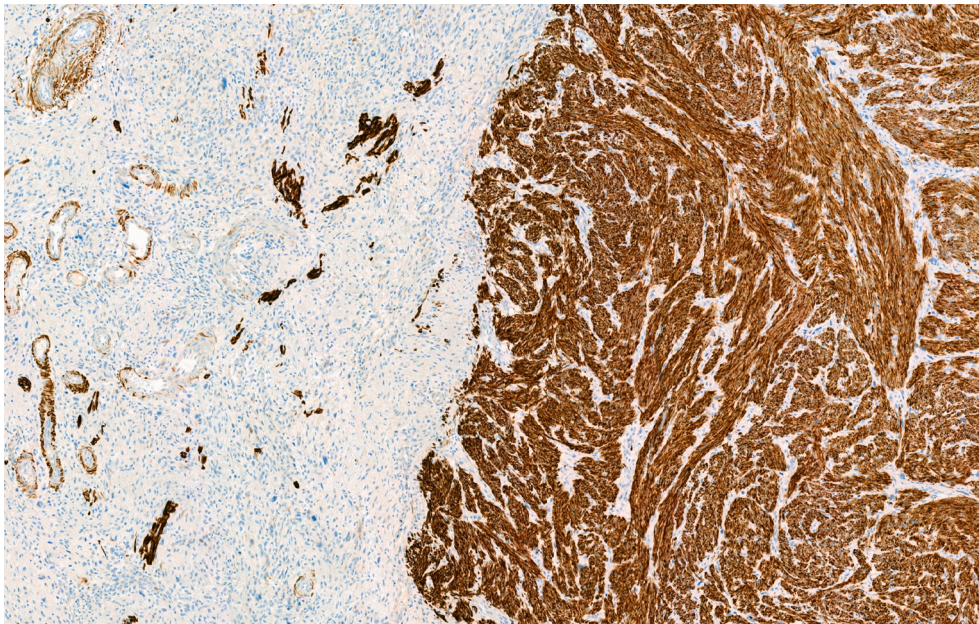


Fig. 3. Desmin immunostain.

per 10 high power fields), and tumor necrosis (Roberts et al., 2018 Dec; Angelo and Prat, 2010 Jan; Cui et al., 2017 Jun; Gockley et al., 2014 Nov). The presence of any two of three criteria is diagnostic of LMS although coagulative necrosis may sometimes be difficult to distinguish from tumor cell necrosis (Lim et al., 2013 May). Rarely, LMS may undergo de-differentiation. De-differentiation into poorly differentiated sarcoma with heterologous elements is seen in a variety of soft tissue tumors including extrauterine LMS and generally portends a poor prognosis (Chen et al., 2011 Dec). Osteosarcomatous differentiation had been reported in a recurrent right groin LMS in a 35-year-old woman by Grabellus et al in 2006 (Grabellus et al., 2006). This phenomenon is extremely rare in primary uterine smooth muscle neoplasms. Damjanov et al (2006) described a case of metastatic LMS in the right anterior rectus muscle with multiple foci of chondroblastic differentiation which was not evident in the primary uterine tumor. Osteoid differentiation has also been reported in a case of local recurrence of malignant smooth muscle tumor of the uterus. The primary tumor showed morphology consistent with high-grade LMS. The patient presented with the recurrent disease six months later and histomorphological examination revealed undifferentiated sarcoma with osteoid formation (Rawish and Fadare, 2012). Chen et al (2011) investigated 18 cases of de-differentiated LMS from various sites including two uterine cases. Heterologous elements were identified in two cases of retroperitoneal LMS but not observed in any of the uterine tumors. The study defined the criteria for de-differentiation as abrupt transitioning from low-grade areas of smooth muscle differentiation to high-grade, poorly differentiated morphology that lacks the usual immunophenotypic expression of smooth muscle markers. This is consistent with the present case. Clear demarcation was seen between well-differentiated and poorly differentiated high-grade areas with malignant cartilaginous elements. Desmin showed diffuse immunoreactivity in well-differentiated, low-grade areas while complete loss is observed in the adjacent poorly differentiated sarcomatous tumor.

Heterologous osteoid or chondroid differentiation in primary uterine LMS presents a potential diagnostic pitfall. This is a more typical feature of carcinosarcoma characterized by juxtaposed malignant epithelial and mesenchymal components. Sarcomatous component of carcinosarcoma may be homologous resembling fibrosarcoma, LMS, or undifferentiated sarcoma. Rhabdomyosarcoma is the most common heterologous element, however, liposarcoma, chondrosarcoma, osteosarcoma, and

liposarcoma have also been reported (Murali et al., 2019). The entire endometrium was evaluated and no malignant epithelial component was identified in our case, ruling out the possibility of the uterine biphasic tumor with heterologous elements.

This case study highlights the significance of considering the possibility of chondrosarcomatous differentiation in primary uterine LMS. Extensive microscopic evaluation is required to exclude the possibility of carcinosarcoma for appropriate patient management. Adjuvant treatment (radiation/chemotherapy) can be considered in patients with leiomyosarcoma with transformation to high grade chondrosarcoma including those presenting with early stage. However, more cases are required to determine the clinical behavior and role of adjuvant treatment with certainty.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Authors contribution

QS was involved in review of literature and made significant contribution to drafting the manuscript. FK helped in revising the paper in keeping with the intellectual contents including final approval of the draft before publication.

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**Consent statement**

The manuscript is carefully reviewed to avoid patient identification details and/or figures.

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