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Case series

Low mitotic count may affect the prognosis of uterine leiomyosarcoma: A report of two cases

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ABSTRACT

Introduction: Uterine leiomyosarcoma (uLMS) is characterized by its aggressive nature, early metastatic potential, and poor clinical outcomes. Diagnosis of uLMS requires two out of the following three diagnostic criteria: marked cytologic atypia, 10 mitoses per 10 high power fields, tumor cell necrosis. This case series presents two cases of uLMS with a low mitotic rate and an indolent disease course, with excellent response to hormone therapies.
Case 1: A 44-year-old female was diagnosed with uLMS following a supracervical hysterectomy in 2006. The primary tumor demonstrated tumor cell necrosis, cytologic atypic, and 6 mitoses per 10 HPF. Her 18-year disease course is notable for four debulking surgeries and multiple courses of hormonal therapy resulting in durable responses.
Case 2: A 75-year-old female was diagnosed with smooth muscle tumor of uncertain malignant potential (STUMP) status post debulking surgery which was revised to leiomyosarcoma following lung biopsy confirmation of metastasis. The primary tumor and lung biopsy demonstrated tumor cell necrosis, cytologic atypia and 2 mitosis per 10 HPF. She demonstrated stable disease on letrozole for 11 months.
Discussion: These cases demonstrate that uLMS with low mitotic activity may exhibit less aggressive behavior than typical high-grade sarcomas. Recognizing this distinction can guide prognostication and treatment selection.

1. Introduction

Uterine leiomyosarcoma (uLMS), representing 1–2 % of uterine malignancies, is characterized by aggressive behavior, high recurrence rates, and poor prognosis with 5-year survival rates of 10–15 % for those with metastatic disease (D'Angelo and Prat, 2010, Reichert et al., 2023). Pathologic diagnosis requires two of three Stanford Criteria: diffuse moderate-to-severe nuclear atypia, coagulative necrosis, and high mitotic index (≥10 mitoses/10 HPF) (Bell et al., 1994, Sanfilippo et al., 2023). uLMS exhibits three distinct pathological subtypes: spindled/conventional, myxoid, and epithelioid (Ip and Cheung, 2011). Myxoid and epithelioid subtypes are rare and usually show mild nuclear atypia and low mitotic indexes (Mbatani et al., 2018).

According to the World Health Organization (WHO) classification, uterine smooth muscle tumors of uncertain malignant potential (STUMP) are an intermediate group of uterine smooth muscle tumors that present a diagnostic challenge. STUMP tumors do not satisfy criteria for benign leiomyoma and do not meet Stanford Criteria for uLMS (Tavassoli and Devilee, 2003). Pathologic differentiation between STUMP and uLMS can be difficult, specifically in cases where mitotic index is low, and are sometimes classified as "low-grade uLMS" (Sanfilippo et al., 2023).

There is no universally accepted grading system for uLMS. uLMS are considered to be high-grade tumors, which can result in a failure to recognize a subset of uLMS with low mitotic index (Devereaux and Schoolmeester, 2019). However, tumors that demonstrate cytologic atypia and necrosis with a low mitotic index meet Stanford criteria for uLMS and should not be misclassified as STUMP. These low mitotic index uLMS tumors, though reported in small numbers in the literature, demonstrate favorable outcomes compared to conventional uLMS (Sanfilippo et al., 2023). Current treatment guidelines for uLMS do not take mitotic index into consideration (Hensley et al., 2015).

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We present two cases of low-mitotic index (<10 mitoses/10 HPF) uLMS that demonstrate an indolent disease course, favorable survival outcomes, and excellent response to hormonal therapy. These cases highlight the value of mitotic index in prognostication and treatment decision-making for patients with uLMS.

2. Case #1

In March 2006, a 43-year-old female patient underwent a supracervical hysterectomy for an enlarging fibroid and was subsequently diagnosed with epithelioid leiomyosarcoma. The mass demonstrated cytologic atypia, extensive tumor necrosis, and 6 mitoses per 10 HPF. Immunohistochemistry (IHC) was positive for ER, PR and smooth muscle actin (SMA). In June 2008, a computed tomography (CT) scan identified a large 22 cm lobulated pelvic mass and peritoneal deposits consistent with recurrent leiomyosarcoma. She received 3 cycles of gemcitabine and docetaxel. Disease progression was noted on CT scan performed in September 2008 and she was transitioned to doxorubicin. The patient progressed after 3 cycles of doxorubicin. Ifosfamide was added to her chemotherapy regimen for an additional 3 cycles. She was transitioned to temozolomide and maintained on this therapy until December 2009.

Due to mass effect symptoms, the patient elected to undergo extensive tumor debulking in December 2009. Pathology confirmed recurrent leiomyosarcoma. The patient was without evidence of disease until she was lost to follow up in 2014.

She presented in May 2020 with lower back and buttock pain. CT scan described a large pelvic mass with central areas of hypoenhancement suspicious for necrosis and no pelvic lymphadenopathy. July 2020 patient underwent exploratory laparotomy, lysis of adhesions, tumor debulking. Pathology confirmed recurrent epithelioid leiomyosarcoma. IHC staining was positive for SMA, caldesmon and ER. The patient was initiated on letrozole therapy in August 2020 and remained disease-free for 11 months while on this treatment.

She had magnetic resonance imaging performed in May 2021 to evaluate back pain and an 8 cm pelvic mass suspicious for recurrence was noted. Exploratory laparotomy, tumor debulking was performed on July 2021. Pathology confirmed recurrent leiomyosarcoma. Postoperatively, the patient was maintained on Tamoxifen and Megace and remained disease free for 26 months on this treatment.

A CT in September 2023 showed a lobulated pelvic mass concerning for progression. CT guided biopsy confirmed progression. She was initiated on gemcitabine and docetaxel but experienced progression after 3 cycles. She underwent a transcatheter aortic valve replacement for aortic stenosis. Then in July 2024, the patient underwent an exploratory laparotomy and tumor debulking with no residual disease. The tumor demonstrated necrosis, cytologic atypia, and 7 mitoses per 10 HPF, consistent with recurrent uLMS (Fig. 1). Exemestane was initiated

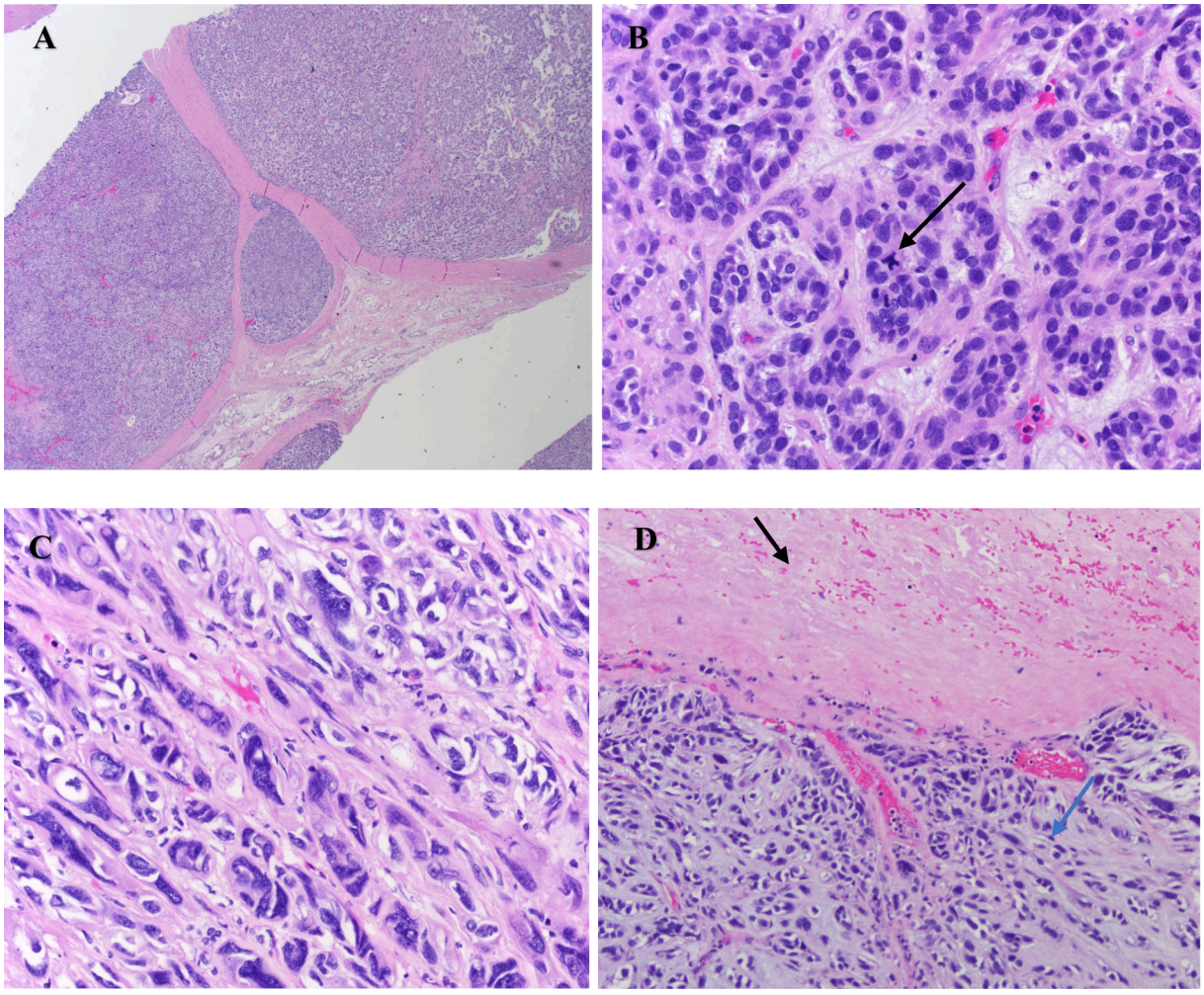

Fig. 1. Case #1 A. Malignant mesenchymal neoplasm composed of multiple nodules of atypical spindled cells within a fibrous tissue background. B. The neoplasm is composed of nests of pleomorphic spindled to round cells with dark chromatin and occassional atypical mitotic figures (arrow). The mitotic index is measured at 7/10 high power fields. C. Area of extreme nuclear atypia. D. Areas of myxoid stromal changes (blue arrow) and large foci of tumor cell necrosis (black arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in August 2024 due to continued ER expression. As of last follow up, she has multiple small peritoneal nodules (6 mm, 10 mm, 20 mm) in the left pericolic region. She is maintained on exemestane.

The patient's 18-year disease course underscores the importance of mitotic index on prognosis and treatment in uLMS. She experienced disease-free intervals ranging from 11 to 26 months on hormonal therapy following surgical debulking, which is atypical for classic uLMS.

3. Case #2

A 75-year-old female presented to her primary care provider with upper respiratory infection symptoms in August 2023. A routine chest radiograph incidentally revealed pulmonary nodules, prompting further evaluation with a CT scan of the chest. CT scan performed August 2023 demonstrated bilateral pulmonary nodules. A subsequent positron emission tomography (PET) scan identified fluorodeoxyglucose (FDG) avid bilateral pulmonary nodules and a heterogeneously dense 15 cm pelvic mass with scattered areas of calcification and marked peripheral FDG uptake. MRI confirmed that a 15.8 cm mass involved the majority of the uterus sparing the lower uterine segment. This mass was previously identified on a CT scan in 2019 and measured 10.5 cm at that time. A referral was placed to Gynecologic Oncology. An endometrial biopsy was attempted at her initial visit but was unsuccessful.

In October 2023, the patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy. Pathologic findings were significant for a smooth muscle tumor with areas of marked cytologic atypia, tumor necrosis, and a maximum mitotic index of 2 mitoses per 10 HPF (Fig. 2). IHC stains were positive for desmin, SMA, ER (95 %, strong), and PR (70 %, moderate). The tumor cells also showed retained expression of fumarate hydratase (FH) and were negative for 2-SC expression, excluding a FH deficient smooth muscle neoplasm. Comprehensive molecular testing (CARIS) was negative for TP53 mutation, but identified two mutations in mutations in *MEN1* (1 pathogenic variant, 1 likely pathogenic variant) and one mutation in *PPM1D* (pathogenic variant).

A CT-guided biopsy of the lung nodules confirmed a metastatic smooth muscle tumor of uterine origin. The patient was diagnosed with the International Federation of Gynecology and Obstetrics (FIGO) stage IVB uLMS.

Multidisciplinary consultation with cardiothoracic surgery and

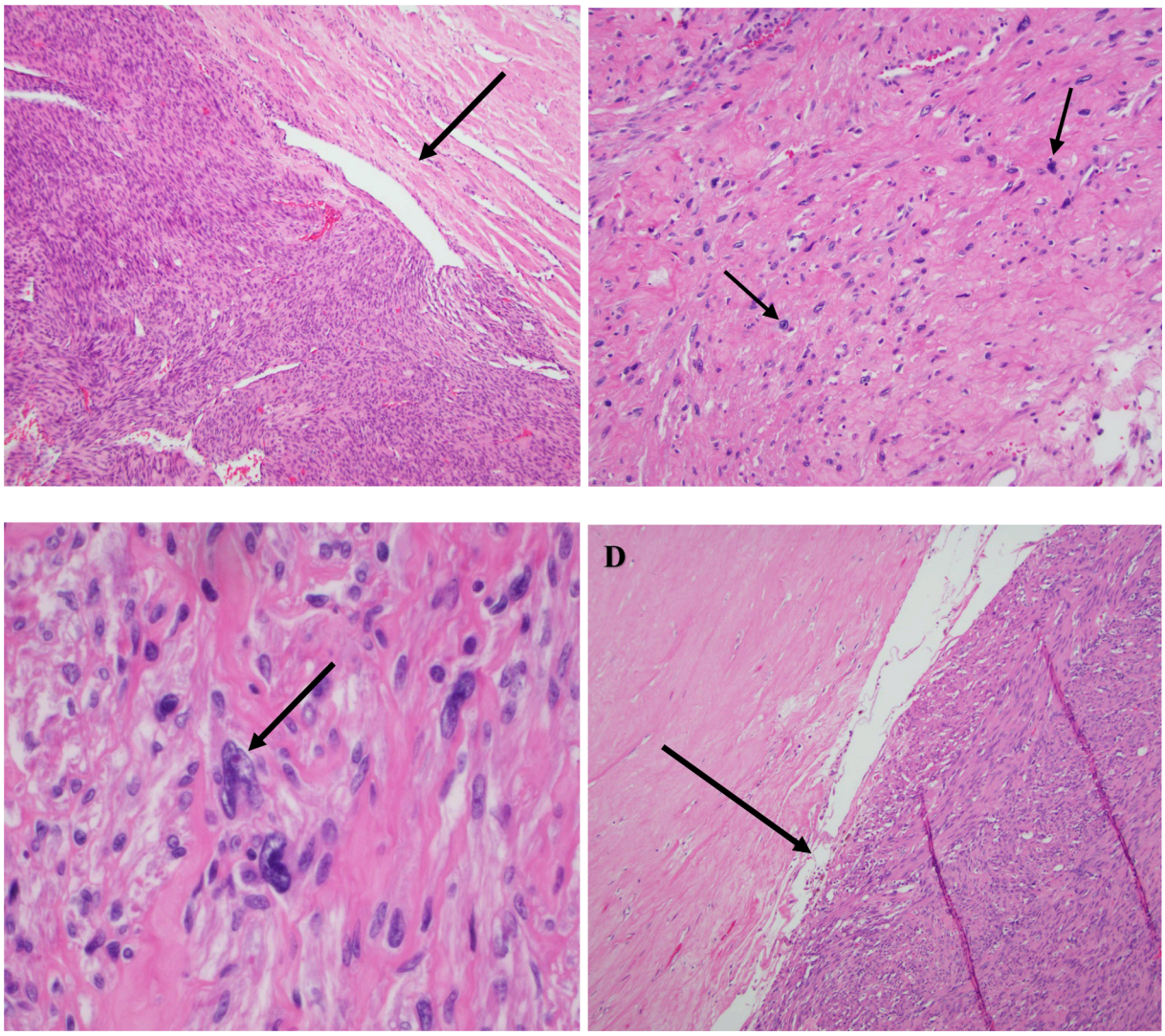

Fig. 2. Case #2 A. Well circumscribed neoplasm composed of intersecting fascicles of spindle cells and scattered, thin walled "staghorn" vessels (arrow). B. Patchy areas of marked cytologic atypia characterized by large pleomorphic nuclei, irregular nuclear membranes, and course chromatin (arrows). The maximum mitotic index is measured at 2/10 high power fields. C. Occasional atypical multinucleated cells are seen with prominent cherry-red nucleoli (arrow). D. Focal areas of tumor-cell (geographic) necrosis are identified, characterized by an abrupt transition (arrow) between viable tumor cells and necrosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

radiation oncology was pursued to consider local ablative therapies, including surgical resection and possible radiation therapy for lung metastasis. However, due to the multifocality of the lung nodules, local ablative approaches were deemed unsuitable. Given the low mitotic index of the tumor and its ER-positive status, the patient was started on letrozole in November 2023. The patient's disease remained stable on letrozole therapy for 11 months. CT imaging on October 2024, revealed increase in size of pulmonary nodules consistent with progression of disease. The patient declined additional treatment and elects to remain on hormonal therapy as she tolerates this treatment well.

4. Discussion

These cases represent examples of uLMS with low mitotic index and an indolent clinical course. Case 1 highlights an individual with a prolonged disease course who remains alive with disease 18 years after her initial diagnosis. Additionally, she had excellent response to hormone therapy with 11 months disease free on letrozole and 26 months disease free on tamoxifen. Case 2 demonstrated disease stability on letrozole therapy for 11 months. Duration of progression-free survival in each case exceeds the median of 23.3 weeks observed in individuals with metastatic soft-tissue sarcoma being treated with chemotherapy (Seddon et al., 2017). Furthermore, these patients far surpassed the reported median overall survival for patients with locally advanced or metastatic soft-tissue sarcoma of 12.8 to 14.3 months (Judson et al., 2014, Karavasilis et al., 2008). Both patients tolerated hormone therapy well with minimal side effects and excellent quality of life.

Though mitotic index $\geq$ 10 mitoses per HPF is one of three diagnostic criteria for uLMS, it is not necessary for the diagnosis of uLMS when the other two pathologic criteria are met. While all uLMS are currently classified as high-grade, this broad categorization may not adequately reflect the biological heterogeneity of these tumors (Serrano et al., 2014). Furthermore, it is important to avoid misclassification of low mitotic index uLMS as STUMP tumors. Multiple predictive nomograms have been proposed which demonstrate more accurate prognostication and take into consideration many factors including age, tumor size, mitotic index, locoregional involvement, metastatic disease, and lymphovascular space invasion (Chapel et al., 2022). However, these models have not yet been adopted by the FIGO and the American Joint Cancer Committee (AJCC) staging systems, nor by the National Comprehensive Cancer Network (NCCN).

The Memorial Sloan-Kettering Cancer Center (MSKCC) developed a predictive nomogram that estimates 5-year survival rates for uLMS based on individual patient factors including age at diagnosis, tumor size, tumor grade, cervical involvement, metastasis and mitotic index. When applying this nomogram, the two cases presented had a 5-year survival prediction of 69 % and 75 %, respectively. The MSKCC nomogram model was internally validated and shown in one study to be a better tool for prognostic factor predictability over traditional staging systems (Zivanovic et al., 2012).

These cases demonstrate that uLMS with low mitotic activity may exhibit less aggressive behavior than typical high-grade sarcomas. Recognizing this distinction can guide prognostication and treatment selection. The incorporation of established nomograms into clinical practice may allow for a more individualized approach to these patients.

Consent Statement

Written informed consent was obtained from the patients for publication of this case series and accompanying images.

CRediT authorship contribution statement

Christine Cho: Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Ciara Marshall:** Writing – review & editing, Data curation, Conceptualization. **Erik Washburn:** Writing – review & editing, Visualization. **Edward Podczaski:** Writing – review & editing. **Joel Sorosky:** Writing – review & editing. **Shaina Bruce:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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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