Research Article

Extensive Metastatic Leiomyosarcoma to Multiple Abdominal Organs from a Prior Uterine High Grade Leiomyosarcoma. Report of a Case and Review of the Literature

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Abstract

Uterine leiomyosarcoma (uLMS) is a rare and aggressive form of sarcoma. uLMS accounts for 3-7% of all uterine malignancies with a propensity to metastasize in the abdomen, retroperitoneum, or perineum. Recurrence of uLMS is not uncommon and occurs within 6-18 months from initial diagnosis and surgical resection of the primary tumor. Current treatment for uLMS is early surgical resection of the primary tumor with addition of various chemotherapeutic treatments in cases of metastasis. We report a case of a patient previously diagnosed with high-grade uLMS with no evidence of metastasis for two years. Subsequently, abdominal imaging indicated extensive metastasis of uLMS to various organs. There is very limited literature on the recurrence of uLMS with massive metastasis. We hope that this report drives continued investigation and further development of efficacious diagnosis and safe treatments for improving patient outcomes.

ABBREVIATION

LMS: Leiomyosarcoma; **uLMS**: Uterine Leiomyosarcoma; **LM**: leiomyoma, **ESS**: Endometrial stromal sarcoma

INTRODUCTION

Leiomyosarcoma (LMS) is classified as a heterogenous group of malignant soft tissue sarcomas of smooth muscle mesenchymal origin. These sarcomas may originate from the uterus, abdomen, or epididymis in males, as well as any organ containing smooth muscles including blood vessels [1,2]. According to the College of American Pathologists' classification of sarcomas originating from the uterus, these malignant neoplasms present mainly as uterine LMS (uLMS), endometrial stromal sarcomas (ESS), and undifferentiated uterine sarcomas (UUS) [3]. While uterine sarcomas are relatively uncommon, they have a poor prognosis with a 5-year survival rate of approximately 40% due to their high frequency of metastasis [4]. Histological characteristics of uLMS involve pleomorphic spindle cells with blunt-ended nuclei with eosinophilic cytoplasm along with a variable mitotic index [5]. The current management protocol of uLMS involves

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surgical excision of the tumor, although recurrence rate of uLMS remains high. In cases of metastasis or unresectable tumors, Adriamycin-based chemotherapy is the gold standard treatment [4]. Recurrence of uLMS typically occurs within 6-18 months from the initial diagnosis, where surgical resection of the tumor proved to be the only effective protocol in increasing the survival rate of these patients [6]. We present an unusual case of a patient with a history of high-grade uLMS and no evidence of recurrence or metastasis after two years presenting with recurrent LMS with widespread metastases involving several abdominal organs while sparing the spleen.

CASE PRESENTATION

57-year-old woman presented with abdominal pain and swelling of her lower abdomen. She also complained of weakness, epigastric distress, weight loss, nausea, vomiting, and occasional upper gastrointestinal tract bleeding. CT scan studies revealed multiple abdominal masses suspicious for spreading malignant neoplasm with recommendation of tissue sampling for definitive diagnosis. MRI studies manifested large infiltrating soft tissue masses of heterogeneous hypointensity on T1-weighted images, with irregular and ill-defined margins involving the diaphragm, the liver, the peri-splenic tissue, the mesentery and the small bowel wall. Spleen and pancreas appeared free of tumor infiltration.

Patient reported history of high grade localized uterine leiomyosarcoma two years prior to current presentation, which was treated by surgical removal alone and no post-operative additional therapy. A CT guided fine needle aspiration with core biopsy of one of the current abdominal masses confirmed the diagnosis of wide-spread metastatic leiomyosarcoma. A multidisciplinary tumor board meeting recommended extensive debulking surgical removal of all abdominal tumor masses to be followed by Adriamycin-based chemotherapy.

The debulking surgery showed metastatic infiltrating soft tissue masses involving all organs identified by the MRI studies. The cut surface of the metastatic masses showed white tan necrotic hemorrhagic surface, largest mass measured 5 cm in greatest diameter (**Figure 1A**). Histomorphologic microscopic examination showed bundles of intersected fascicular growth pattern composed of palisading of pleomorphic spindle cells with eosinophilic fibrillary cytoplasm, and focal granularity (**Figure 1B**). Individual cell nuclei were cigar-shaped, blunt-ended with anaplastic severe nuclear atypia and multiple abnormal mitosis exceeding 20/10 HPF (High power field) (**Figure 1C**). Immunohistochemistry studies were utilized for definitive confirmation of the diagnosis. Tumor cells were positive for HHF35 (Anti-muscle Actin antibody), alpha-smooth muscle actin, desmin and H-caldesmon. Scattered tumor cells were positive for cytokeratin, S-100 and ER (Estrogen receptors approximately 7%). The tumor cells were negative for CD30, CD45, HMB-45, synaptophysin, PAX-8, myogenin and CD117 (**Figure 1D-E-F**). The histomorphology, together with the immunohistochemistry profile were consist with the diagnosis of recurrent uterine leiomyosarcoma in form of wide metastasis to various abdominal organs. Patient received Adriamycin-based chemotherapy as a post-operative treatment and was free of recurrence or metastasis for 18 months after which she expired due to extensive metastasis to the bone, liver, and lung.

DISCUSSION

Sarcomas are a group of malignancies that originate from mesenchymal cells that have the potential to arise in any part of the body [7]. Leiomyosarcoma (LMS) is a rare malignant neoplasm that originates from the smooth muscles. LMS most often begins in the abdomen or uterus. A specific subtype of LMS, uterine leiomyosarcoma (uLMS), is the most common uterine sarcoma with an estimated incidence of 1 out of 100,000 women [8]. uLMS is a rare entity among malignant gynecologic tumors with the highest prevalence in pre-menopausal and perimenopausal patients[9]. Uterine sarcomas tend to occur in an older patient population compared to leiomyomas, and account for 3–7% of all uterine malignancies. uLMS carry a poor prognosis even when confined only to the uterus. They are responsible for roughly 25% of deaths from uterine malignancies, with a 5-year survival rate of 46–53%. Additionally, uLMS also have a recurrence rate of 50–70% in which they tend to recur in the lungs (40%) and the pelvis (13%) [8].

Leiomyosarcomas originating in places other than the abdomen or uterus also exist. Retroperitoneal leiomyosarcoma often arises from larger veins, most commonly inferior vena cava and sometimes from the renal or iliac veins [10]. There have also been reported cases of leiomyosarcoma of the tonsil, perineum, mediastinum and triceps muscle [11-14].

One notable characteristic of uLMS is its propensity to metastasize. In a 2014 study of 113 patients with uLMS done by Tirumani et al., 81.4% of patients experienced distant metastasis. Common sites of metastasis include the lung (74%), peritoneum (41%), bone (33%), and liver (27%). Of the 113 patients, 51% experienced local tumor recurrence and of those that experienced local tumor recurrence, 89% showed distant metastasis of the tumor. The group reported a statistically significant correlation between local recurrence and peritoneal metastasis (p<0.001).
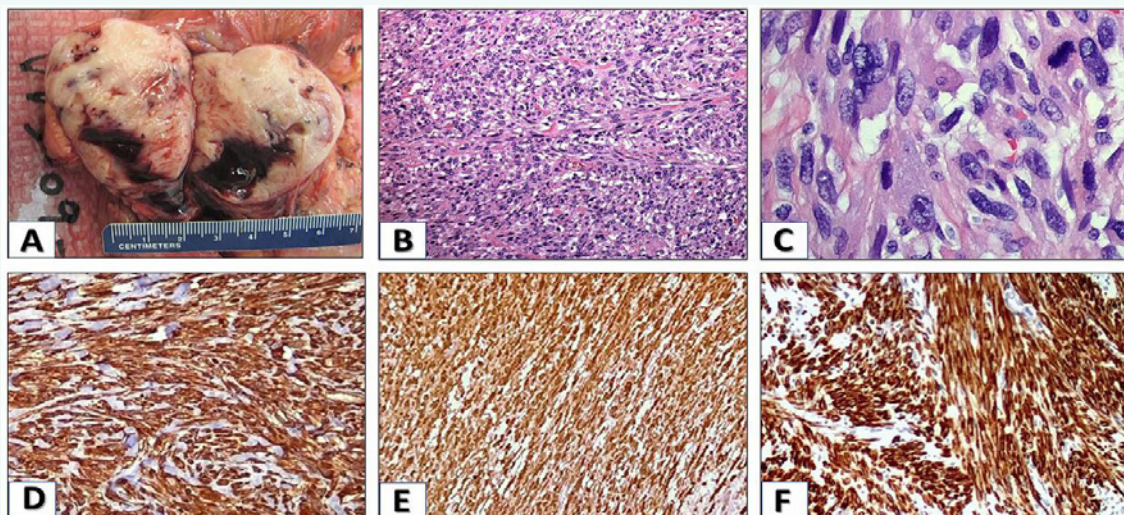

Figure 1 Histomorphology and immunohistochemistry profile of the excised abdominal masses of leiomyosarcoma
1A: Largest metastatic tumor mass showing white tan necrotic hemorrhagic surface.
1B: Low power view of the tumor showing bundles of intersected fascicular growth pattern composed of palisading of spindle cells with eosinophilic fibrillary cytoplasm (H&E stain X20 magnification)
1C: High power view of the tumor showing pleomorphic nuclei with cigar-shaped, blunt-ended displaying anaplastic severe nuclear atypia and multiple abnormal mitosis (H&E stain X60)
1D: Tumor cells positive for Actin
1E: Tumor cells positive for H-Caldesmon
1F: Tumor cells positive for Desmin

They also reported that age, serosal involvement, local recurrence and the International Federation of Gynecology and Obstetrics (FIGO) stage were all predictive factors for metastasis [15].

In general, correct diagnosis of uterine mesenchymal tumors continues to be a challenge due to their non-specific clinical presentation, grossly non-distinct appearance, varied and many times overlapping morphologic appearance. Specifically, LMS is often difficult to differentiate from benign leiomyomas (LM) which are far more common in women. Patients with both conditions often present with clinical symptoms including; profuse menstrual bleeding, pelvic discomfort, infertility, increased urinary frequency, incontinence, constipation, and dyspareunia [16]. However, the mean age of presentation for LMS is above 45 years of age whereas the mean age of those with LM is less than 45 years. Diagnostic imaging techniques including CT, MRI, and ultrasound have shown limited usefulness to differentiate LMS from LM [17]. On ultrasound, LM typically appears as a well-defined hypoechoic mass, with possible calcifications resulting in acoustic shadowing. However, these characteristics are often shared with LMS, limiting ultrasound's utility as a differentiation tool [18]. Some evidence shows increased vascularity on color doppler ultrasound in LMS with degenerative cystic changes, which can indicate malignancy [19]. CT scans show calcification; however, this is often found in both LM and LMS [20]. An algorithm to differentiate LM and LMS using MRI techniques exists but has yet to be studied in large groups [8].

Tumor markers have shown limited usefulness in differentiating LMS from LM. While not specific for uterine LM, cancer antigen 125 (CA125) is elevated in the presence of large or degenerated subserosal LM [21]. However, there is no general consensus on the usefulness of CA125 as a differentiation diagnostic tool. Juang et al. found significantly higher preoperative serum CA125 values in patients with uLMS than in those with uterine LM; while Menczer et al. was unable to detect CA125 expression in any of their LMS pathologic specimens [22, 23]. These conflicting studies propose CA125 may increase due to nonspecific irritation of epithelial surfaces caused by tumor cells [23]. In addition to the challenging clinical distinction, misdiagnosis of uLMS as a uterine LM can lead to other treatment complications. Benign LM is often managed with minimally invasive treatment such as laparoscopic morcellation, which may lead to iatrogenic dissemination if it is actually LMS. As well, a delay in uLMS diagnosis may occur if a conservative management approach is utilized, such as uterine artery embolization. The misdiagnosis of a uLMS for benign uterine LM may result in greater mortality, given the poor prognosis of uLMS and its high propensity to locally recur and metastasize [8].

Due to the challenging clinical presentation of uLMS, the diagnosis is often made at time of surgical resection [9]. uLMS is diagnosed based on hypercellularity, areas of necrosis, severe nuclear atypia, and high mitotic rate; however, this is not always clear-cut [24]. Another diagnostic challenge is due to the existence of myxoid and epithelial variants of LMS. These rare, but often aggressive variants show mild atypia, low mitotic rate, and

frequent absence of necrosis. Afzal et al. reported a challenging case of metastatic myxoid uterine leiomyosarcoma and described the usefulness of the use of immunohistochemistry studies to assist in diagnosis confirmation [25,42]. Uterine sarcoma can also present with suspicious histologic features without meeting full histologic diagnostic criteria of LMS. In these equivocal samples, they are classified as smooth muscle tumors of uncertain malignant potential (STUMP), which are generally thought to have a favorable prognosis [26]. The classical subtype of benign LM is characterized histologically by monotonous spindle cells with indistinct borders arranged in intersecting fascicles and low mitotic rate [27].

Another possible diagnosis of uterine sarcoma is endometrial stromal sarcoma (ESS). ESS and uLMS presents with nearly identical signs and symptoms of the condition including abnormal uterine bleeding, abdominal pain and/or distension, and frequent urination. Low grade ESS is the second most common pure mesenchymal malignancy of the uterus. ESS much more commonly involves the uterine corpus than the cervix, commonly containing multiple poorly defined, tan to yellow, soft nodules within the endometrium and myometrium. The majority of low grade ESSs show bland nuclear features with monotonous oval to spindle nuclei that resembles proliferative phase endometrial stroma; mitotic activity is generally low, and necrosis is usually absent. Surgical stage appears to be the most important prognostic factor. Patients with low-grade ESS have an excellent prognosis with a 90% 5-year disease-free survival if low stage and survival drops to 50% if high stage [28].

Another condition which needs to be distinguished from LMS is undifferentiated uterine carcinoma (UUS). UUS, which may occur in pure form or in combination with a low grade endometrioid adenocarcinoma ('de-differentiated endometrioid adenocarcinoma') is composed of a diffuse proliferation of epithelioid cells and may fall into the differential diagnosis of an ESS [28]. UUS is a diagnosis of exclusion and should only be made after extensive sampling at the time of hysterectomy.

A rare yet possible differential diagnosis of uLMS includes malignant mixed Mullerian tumor (MMMT) of the uterus. MMMT of the uterus only comprises 1-2% of uterine neoplasms and is considered to be a metaplastic form of uterine carcinoma [29, 30]. While MMMT of the uterus and uLMS are of unique origins, they both share similar clinical presentations [31].

Both LM and LMS express desmin, h-caldesmon, smooth muscle-actin and histone deacetylase (HDCA8). In contrast to LM, a certain amount of LMS show *p53* mutations and overexpression [9, 28]. LMS is often positive for CD10 and keratin. Positive reactions are found in 30-40% with estrogen receptor, progesterone receptor, and androgen receptor. CD117 may be positive, but c-KIT-mutations are not proven. Lack of KIT expression can be useful to separate LMS from gastrointestinal stromal tumors [10]. In a case report compared with LM, estrogen and progesterone receptor expression are significantly lower in LMS [32, 33]. LMS frequently contains TP53, RB1, α-thalassemia/mental retardation syndrome X-linked (ATRX), and mediator complex subunit 12 (MED12) alterations [8]. MED12 has proven

useful as an important biomarker to diagnose uLMS derived from LM [34]. Malignant cells of uLMS are most commonly positive for CD10, vimentin, actins, WT-1. Desmin and h-caldesmon are usually positive in areas of smooth muscle differentiation [28].

Current research into the molecular pathogenesis of uLMS recurrence is limited and the exact pathophysiology is not clearly understood. uLMS demonstrates a vast genomic profile with chromosomal losses involving tumor suppressor genes and/or hyperactivation cell proliferation pathways. One study characterized uLMS as two subtypes, type I and II. Subtype I, or low grade uLMS, involves overexpression of genes such LMOD1, SLMAP, MYLK, and MYH11 in smooth muscle cells. Subtype II, or high grade, is characterized as smooth muscle cells with overexpression of genes Epithelial–Mesenchymal Transition (EMT) and tumorigenesis, such as CDK6, MAPK13, and HOXA1. Bcl-2 is an inhibitor of apoptosis, leading to proliferative cell growth and tumour development. Expression of Bcl-2 has been described in 42–57% of LMS [35]. Other studies have shown hyperactivation of the PI3K/ AKT/ mTOR pathways which may contribute to the pathogenesis of LMS, with a large portion of the cells demonstrating phosphorylation of AKT and mTOR [36]. One study found that using mTOR pathway inhibitors with aurora kinase A inhibitors, MDM2 inhibitors and histone deacetylase inhibitors proved promising in preclinical responses acting on their respective pathways [37]. Other research suggests that other various genes such as OSTN, NLGN4X, NLGN1, SLITRK4, MASP1, XRN2, ASS1, RORB, HRASLS, and TSPAN7 were all found to be overexpressed in primary uLMS. And for metastatic uLMS the genes *TNNT1*, *FOLR3*, *TDO2*, *CRYM*, *GJA1*, *TSPAN10*, *THBS1*, *SGK1*, *SHMT1*, *EGR2*, and *AGT* were found to be overexpressed. The overexpression of unique genes may prove as an aid for effective targeted therapies in both primary and metastatic uLMS [38].

Current treatment for uLMS is early and complete surgical excision of the neoplasm. In cases of metastasis or unresectable tumors, Adriamycin-based regimens of chemotherapy are considered the gold standard treatment [4]. Gemcitabine/docetaxel and doxorubicin are the most active regimens in recurrent disease. However, these treatments have inadequate outcomes, with 5-year disease-specific survival of <30% . Pazopanib, trabectedin and Olaratumab are FDA-approved, targeted therapies with activity in LMS. Aromatase inhibitors and other targeted immunotherapies are currently under active investigation [39].

There is very limited literature on the recurrence of uLMS with massive metastasis. However, some cases of uLMS metastasis have been reported. Three cases of skull recurrence of uLMS have been reported in literature to date. Signs and symptoms of skull metastases appear as highly non-specific, depending on tumor extension [40]. There exists one case of multiple intracerebral metastases of a non-uterine LMS. A case of metastatic non-uterine LMS has been published, in which a single right frontal subcortical cerebral metastasis was detected in a patient with a right triceps muscle LMS [14]. Although LMS has well-known metastatic potential, cutaneous metastasis is an uncommon

occurrence. A review of the literature revealed 15 reported cases of LMS with metastases to the skin [41].

Medical literature reporting such widespread metastasis of recurrent leiomyosarcoma is limited, and standardized treatment for such tumors is not clearly established yet. We hope that this report drives continued investigation and further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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