Treatment of recurrent metastatic uterine leiomyosarcoma of the spine: a multimodality approach using resection, radiosurgery, and chemotherapy

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The authors describe the case of a patient who initially presented with uterine leiomyosarcoma (LMS) that later metastasized to the spine. The patient was treated at another institution for her primary uterine LMS, undergoing resection followed by adjuvant chemotherapy. After several years of disease remission, the patient presented in January 2011 to the authors' institution with recurrent uterine LMS metastatic to the spine, which has been treated with multiple therapeutic modalities in a combination of surgery, radiosurgery, and chemotherapy. As a result of this approach, the patient has been progression free for 35 months since her presentation (April 2011 to March 2014). We herein describe our experience treating this patient with recurrent uterine LMS of the spine and suggest that patients with recurrent uterine LMSs should be considered for treatment using a multimodality approach with emphasis on enrollment into clinical trials.

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UTERINE leiomyosarcoma (LMS) is a rare, aggressive smooth muscle malignancy of the uterus, comprising only 1% of all uterine malignancies.¹² Due to the infrequency of uterine LMSs and CNS/spinal involvement, as well as to the lack of agreement on the most optimal therapeutic approach to treating, 5-year survival rates vary from 0% to 75%. The 5-year survival rate for Stage I uterine LMS is approximately 50%–70%, but the rate becomes dismal, 0%–22%, in the setting of advanced disease.^{6,12,13,16,18,23,26} Although local control after hysterectomy is good, many patients die of disease at a distant site. The reported risk of recurrence is relatively high, with rates ranging from 45% to 73%.⁶ Distant metastatic lesions generally occur in the lungs, liver, kidney,

brain, and skin, and there is limited involvement with bony structures, such as the spine.⁴ In fact, there is very little information in the current literature about uterine LMS and spinal involvement, and there is no clear consensus about how to best proceed.

We report on a case of recurrence of a uterine LMS to the lumbosacral spine. In a review of the literature, we found only 5 other published reports of a spinal lesion as the first recurrence of metastatic uterine LMS, and none of the cases involved the sacral region.^{4,21,22,25} Spinal involvement can be highly morbid and fatal, requiring individualized multimodality treatments. The goal of this report is to present our experience with combined multimodality therapies to treat this rare recurrent malignancy.

ABBREVIATIONS DM-CHOC-PEN: 4-demethyl-4-cholesteryloxycarbonylpenclomedine; LMS = leiomyosarcoma; TAHBSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy; TMZ = temozolomide.

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Case Report

Clinical History

This 52-year-old woman was diagnosed in 2007 with a uterine LMS and underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) for complete tumor resection at an outside institution. Four years later she presented to our institution. Figure 1 depicts the clinical timeline for this patient. On gross examination, the primary tumor was relatively large (10 cm) with irregular borders. Histopathological examination revealed extensive coagulative necrosis with 20 mitotic figures per 10 hpf, suggesting a high proliferation index. Surface marker staining showed the presence of estrogen and progesterone receptors on roughly 40% of the tumor cells. The patient was subsequently enrolled into a Phase II trial of adjuvant letrozole at the outside institution and remained clinically stable during the course of the study until the disease progressed approximately 3.5 years after her initial surgery (December 2010).

Metastatic Spread to the Spine

In December 2010, the patient presented with progressive transient shooting pains in her left posterior thigh and leg. She also developed a deep throbbing pain in her left buttock, making it difficult to sit. Magnetic resonance imaging revealed an enhancing tumor in the lumbosacral epidural space, but additional imaging of the brain, cervical spine, and thoracic spine demonstrated no other disease at that time. The patient underwent spinal debulking surgery with an L-5 laminectomy at the same outside institution.

First Recurrence of Spinal Uterine LMS

Shortly after the patient underwent spinal tumor debulking, she presented to our institution and requested to be enrolled into our open Phase I drug trial (DTI-021) with 4-demethyl-4-cholesteryloxycarbonyl-penclomedine (DM-CHOC-PEN), a novel anticancer drug being studied as a treatment for metastatic cancer to the nervous system.^{15,29} As a prerequisite for enrolling into our study, MRI was performed, which showed evidence of tumor recurrence in the spine (Fig. 2A and B). The patient was offered additional surgery and radiation therapy but declined both at that time. Since she declined surgery and radiation ther-

apy, and since there is no established standard of care for patients with uterine LMS, she was enrolled in the Phase I study to receive DM-CHOC-PEN (course schedule: 39 mg/m² to be repeated every 21 days) in early January 2011.

Second Recurrence of Spinal Uterine LMS

Unfortunately, after the end of her first course of treatment, the patient presented with new-onset left lower-extremity pain and paresthesias, which progressed to weakness and numbness. She also experienced several days of urinary hesitancy. Lumbar MRI showed evidence of tumor growth, with an extramedullary enhancing mass that measured 5.2 × 5.1 cm, with effacement and right upward displacement of the thecal sac (Fig. 2C and D). As a result of the imaging evidence of further tumor progression, she was taken out of the Phase I study.

Salvage Treatment With Staged Complex Spine Surgery Followed by Radiosurgery and Chemotherapy

Our multidisciplinary team, consisting of a neurosurgeon, radiation oncologist, and medical oncologist, evaluated the patient after she was taken out of the Phase I study. After consultation with the patient and family, we devised a plan for maximal safe resection followed by chemotherapy and radiosurgery of the resection bed. The plan also included pharmacokinetic studies to assess the chemotherapeutic sensitivity of the tumor and intratumoral concentrations of DM-CHOC-PEN. The patient was taken to the operating room for tumor debulking and L5–S1 and S-2 laminectomies via a standard approach during continuous nerve root monitoring. The tumor appeared fibrous in nature, adherent to the dura mater and exiting nerve roots, and was of moderate vascularity. Based on these characteristics, we were limited to a subtotal resection. Tumor that was easily separated from the exiting nerve roots was safely removed. Samples of fresh viable tumor tissue were sent to our laboratory for pharmacokinetic studies, including assessment of the tumor's chemotherapeutic sensitivity and levels of DM-CHOC-PEN within the samples. Residual tumor was left in areas where the lesion adhered to the exiting nerve roots and in the S1–2 foramina. Postoperative MRI confirmed residual tumor with enhancement seen abutting the thecal sac and within the left L5–S1 and S1–2 neural foramina, as well as abnor-

FIG. 1. Clinical timeline of findings and treatments. Figure is available in color online only.

FIG. 2. MR images demonstrating the clinical course of spinal uterine LMS tumor progression. Sagittal (A) and axial (B) T1-weighted images of the patient prior to entrance into DM-CHOC-PEN study. Sagittal (C) and axial (D) T1-weighted images after the patient's first course of DM-CHOC-PEN resulting in the second tumor recurrence. Sagittal (E) and axial (F) T1-weighted images after the patient received multimodality treatment including 3 courses of DM-CHOC-PEN resulting in the third recurrence.

mal enhancement of the medial sacrum. Immediately after surgery her symptoms were worse, but these symptoms improved to baseline several weeks later.

Three weeks after partial surgical debulking, the patient was treated with a single course of adjuvant temozolomide (TMZ) prior to undergoing radiosurgery therapy. Although the patient's tumor was not chemosensitive to TMZ (Table 1), TMZ was chosen because of its synergistic relationship with radiation.^{8,27,28,30} Since sarcomas, including uterine LMSs, are typically radioresistant,^{5,9} our rationale was to make the metastasis more radiosensitive, as demonstrated with other tumors such as malignant gliomas.^{2,24} The tumor bed was then treated concomitantly with a single 20-Gy dose of conformational radiation (Fig. 3). The patient tolerated this procedure well, with transient urinary hesitancy that was gradually improving and weakness in dorsiflexion of the left foot that unfortunately was not improving to baseline.

Assessment of Tumor Chemotherapy Sensitivity and Levels of DM-CHOC-PEN

As part of the patient's care, pharmacokinetic studies

TABLE 1. Drug sensitivities for uterine LMS

Drug	IC ₅₀ (μg/ml)
DM-CHOC-PEN	0.5 ± 0.01
Actinomycin D	0.5 ± 0.02
BCNU	0.9 ± 0.1
Cis-platinum	1.5 ± 0.1
doxorubicin	0.7 ± 0.1
TMZ	>3.0
HOOI	0.8 ± 0.2
A-007	0.3 ± 0.2

A-007 = 4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazine (a control marker for drug sensitivity; < 1 μg/mL is considered a chemo-sensitive tumor); BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea; HOOI = 4-hydroperoxyifosamide.

were performed to assist with the patient's treatment plan. Tumor tissue obtained at the time of the second debulking was portioned to determine chemotherapeutic sensitivity and intratumoral concentrations of DM-CHOC-PEN. Briefly for the chemotherapeutic assay, primary explant cultures were established to perform an in vitro tumor colony-forming assay to measure the lesion's sensitivity to standard and experimental chemotherapeutic agents (Table 1). Each value in Table 1 represents the average of 5 doses (0.1–10 μg/ml) evaluated in triplicate. In addition, A-007 (4,4'-dihydroxybenzophenone-2,4-dinitrophenylhydrazine), which is an experimental cytotoxic agent, was used to identify drug sensitivity. A ratio of cytotoxicity for A-007 versus each drug was compared with the sensitivity of the individual drugs (Table 1). Tumors with an IC₅₀ for A-007 in concentrations < 1 μg/ml are considered chemotherapy sensitive.¹⁴ The tumor tissue from this patient showed sensitivity to a number of agents including DM-CHOC-PEN (Table 1). Finally, the measurement of intratumoral DM-CHOC-PEN drug concentration was determined by high-performance liquid chromatography.

We found that explanted tumor tissue was sensitive to DM-CHOC-PEN in our in vitro chemosensitivity assay, despite the fact that the patient received DM-CHOC-PEN at a relatively low dose (39 mg/m²) in vivo. Furthermore, the bioavailability of DM-CHOC-PEN demonstrated that

FIG. 3. Radiosurgical dose distribution map shown in sagittal (left) and axial (right) views. Figure is available in color online only.

there was adequate uptake of the drug with concentrations of 119–192 ng/1 g of tumor tissue from multiple sites 21 days after the last administration of DM-CHOC-PEN. Taken together, the results of our pharmacokinetic studies suggested the patient might respond at a higher dose of DM-CHOC-PEN.

Third Recurrence of Spinal Uterine LMS

Upon completion of surgery, chemotherapy, and radiosurgery, the patient again requested to reenter the Phase I DM-CHOC-PEN study. Based on our chemosensitivity and DM-CHOC-PEN bioavailability assays of the patient's tumor, we felt confident about reenrolling her into our Phase I clinical trial. She reentered the study and received a higher initial drug dose (50 mg/m² compared with 39 mg/m²) per treatment protocol. After her third course of treatment, MRI showed evidence of tumor progression, with increased enhancement in the sacrum but without the mass effect seen previously (Fig. 2E and F). The patient was subsequently removed from the drug trial.

Remission

After exiting the drug trial in April 2011, the patient was started on doxorubicin (70 mg/m² every 21 days for 6 courses) and then reevaluated for disease progression. She continues to be followed by her oncologist and is clinically stable without evidence of progression. Follow-up imaging showed reduction in tumor mass and enhancement (Fig. 4A and B). The patient's most recent PET CT scan (Fig. 4C) showed no evidence of disease, and her period of progression-free survival has exceeded 30 months.

Discussion

Uterine LMS is a rare, aggressive malignancy affecting the smooth muscle layer of the uterus, and it has a relatively high recurrence rate even when aggressive therapy is used. When uterine LMS recurs, its treatment has

often been palliative because of the disease's high mortality rate. Specifically, tumors showing the cluster of > 20 mitotic figures/10 hpf, positive Ki 67 staining, large tumor size (> 10 cm), and negative BCL2 staining have a markedly unfavorable prognosis.³ We present a case of recurrent metastatic uterine LMS to the spine, with evidence of remission since 2011 after a multimodality therapeutic approach.

In our case, a complete resection of the uterine LMS was not possible because of the tumor's location and its intimate involvement with the dura and exiting spinal nerve roots. Although negative margins are warranted to attain optimal outcomes in cases of metastatic spinal sarcomas, including LMSs, achieving a gross-total tumor resection is hindered by the tumor anatomy and the desire to preserve neurological function.¹ In cases involving a residual metastatic tumor of the spine, postoperative radiation therapy may be helpful in improving local control but not overall survival.^{11,20} Furthermore, in the European Organization for Research and Treatment of Cancer Gynecological Cancer Group Study (EORTC-GCC) 55874 trial,¹⁹ unlike sarcomas in general, uterine LMS-specific local control rates were not optimal, with similar local failure rates seen between the fractionated radiotherapy arm (20%) and observational arm (24%). Despite limited success using conventional fractionated radiotherapy to treat metastatic spinal sarcomas, radiosurgery has been shown to be effective in achieving good local control rates of 84%–88% in some studies.^{5,9} Therefore, radiosurgery was chosen over fractionated radiotherapy for this patient.

Efficacious chemotherapy for uterine LMS with spinal and CNS involvement is still lacking, as illustrated by the poor prognosis seen in cases of metastatic uterine LMS, even when detected early. To address this growing concern, recent efforts by several groups have increased uterine LMS patients' participation in clinical trials; however, patients with CNS involvement are often excluded.

There have been several novel chemotherapeutic agents tested in recent years in Phase I/II trials, but limited or no activity is frequently reported.¹⁷ Combination therapy has demonstrated improved response rates, with the two most active treatment regimens being gemcitabine plus docetaxel and doxorubicin with or without ifosfamide.¹⁷ Studies have demonstrated a 48% response rate in patients treated with doxorubicin and ifosfamide¹⁰ and a 53% overall response rate for patients treated with gemcitabine and docetaxel.⁷ With the high preponderance of hematological spread and the relatively low chemotherapeutic response rates for uterine LMSs, new chemotherapeutic agents are warranted. Although it is still in the early stages of drug trial, DM-CHOC-PEN shows promise as an effective adjuvant chemotherapeutic drug for recurrent uterine LMSs because of its ability to penetrate and concentrate in malignant tissue, as demonstrated by our DM-CHOC-PEN intratumoral bioavailability assessment.

In the present case, the exact reason for the long-term progression-free survival is unclear. Our patient's treatment plan was complex and included surgery followed by radiosurgery and three different modes of chemotherapy (TMZ, DM-CHOC-PEN, and doxorubicin). Any one of these treatment modalities could have contributed to our

FIG. 4. Posttreatment images. Lumbo-sacral sagittal (A) and axial (B) T1-weighted MR images reflecting more than 30 months of progression-free survival. Axial PET CT scan (C) also demonstrating no evidence of disease progression. Figure is available in color online only.

patient's improved outcome, but a combination of these agents is more likely to explain the successful result. It is noteworthy that despite our aggressive regimen with multiple modes of treatment, the patient was able to tolerate her treatments well.

Lastly, we realize that radiosurgery alone has been associated with good local control^{5,9} and that the enhancement seen on follow-up MRI may have been pseudo-progression and/or an adverse radiation effect from the radiosurgery. Our early experience with DM-CHOC-PEN, however, has shown a preponderance of pseudo-progression prior to longer-term progression-free survival (unpublished data). Therefore, on the basis of the presence of DM-CHOC-PEN at levels of 119–192 ng/1 g of tumor tissue after the initial single dose (39 mg/m²), we feel confident that there was probably drug present after the 3 courses of 50 mg/m², playing a possible contributory role in this patient's progression-free survival. In addition, doxorubicin was started 21 days after the third dose of DM-CHOC-PEN was administered, and the combination of these two drugs is unknown. Both drugs have the novel ability of inducing reduction-oxidation–cycling cytotoxic changes in tumors and may be synergistic. To understand the efficacy of DM-CHOC-PEN on uterine LMSs, additional studies in a clinical trial platform are needed.

Conclusions

Uterine LMS is a rare and aggressive malignancy that very rarely spreads to the spine. Treatment should aim to preserve function. In the present case, the patient responded well to a multimodal therapeutic approach involving subtotal resection followed by single-fraction radiosurgery and a combination chemotherapy regimen, which included chemotherapeutic sensitivity testing. Patients with recurrent uterine LMSs should be considered for treatment using a multimodality approach with emphasis on enrollment in clinical trials.

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