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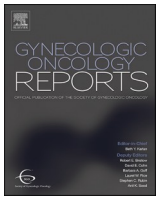

Case report

A case of pembrolizumab and lenvatinib as an alterntive therapy for leiomyosarcoma

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1. Introduction

Uterine sarcomas are rare gynecologic malignancies, representing 1 % of all female gynecologic cancers and 3–7 % of all uterine malignancies (Roberts et al., 2018). Leiomyosarcoma is the most common uterine sarcoma, with an incidence of 0.8 per 100,000 (Roberts et al., 2018). Symptoms of leiomyosarcoma include abnormal uterine bleeding and an enlarged uterus or pelvic pressure. Leiomyosarcomas can often be challenging to distinguish from benign gynecologic conditions such as leiomyomas or adenomyosis because of similar presentations. About 30–35 % of women present with leiomyosarcoma at an advanced stage (Roberts et al., 2018). The five-year survival rate for leiomyosarcoma ranges from 55.4 % for stage I disease to 13.1 % for stage IV disease (Seagle et al., 2017; Matsuzaki et al., 2021).

Surgical management via hysterectomy is the mainstay of treatment for leiomyosarcoma (Roberts et al., 2018). Evidence suggests that overall survival among women with leiomyosarcoma does not improve with bilateral salpingo-oophorectomy (Trojnarska and Zygmunt, 2019). Similarly, lymphadenectomy has been shown to bear little prognostic or therapeutic benefit (Si et al., 2017). Radiation has not been shown to be effective for leiomyosarcomas. Chemotherapy has been shown to have limited efficacy with no proven benefit in the early stages or in the recurrent setting (Roberts et al., 2018).

Pembrolizumab, a monoclonal PD-1 antibody, and lenvatinib, a tyrosine kinase inhibitor, have been reported to have activity for endometrial cancer (Fujiwara et al., 2022). Previous case reports have suggested Mullerian adenocarcinomas show clinical benefit in response to pembrolizumab and lenvatinib (Alcindor et al., 2021). Pembrolizumab treatment has also demonstrated encouraging activity in soft tissue sarcomas (Tawbi et al., 2017). This case report explores the utility of pembrolizumab and lenvatinib as an alternative therapy for advanced stage leiomyosarcoma.

2.

A 45 year old gravida 1 para 1 presented for heavy menses and symptoms of anemia. Past medical history included asthma, bronchitis, left bundle branch block, and laparoscopic cholecystectomy. Patient's heavy menses was found to be related to the presence of intramural and submucosal fibroids, and patient was prescribed oral iron for symptoms of anemia. Endometrial biopsy sample was also taken on initial evaluation, but resulted as suboptimal. She subsequently underwent a robotic-assisted hysterectomy with bilateral salpingectomy given her symptomatic fibroid uterus. The uterus was removed by manual morcellation through the vagina.

Pathology from the surgery returned as at least stage IB leiomyosarcoma. Immunohistochemistry demonstrated severe nuclear atypia, tumor cell necrosis, and lesional cells that were positive for desmin, caldesmon, ATRX, PR, and focally positive for CD10 and ER. Ki67 index was increased. Immunohistochemical stain for P53 was wild type. Mitotic figure count was 11 mitosis per 10 high power field.

Patient underwent 6 cycles of adjuvant gemcitabine and docetaxel. She underwent surveillance every-three to six months following completion of this regimen. Interval imaging during surveillance

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demonstrated no increase in disease initially. However, sixteen months after completion of her adjuvant chemotherapy, the patient presented with constipation. Imaging revealed recurrence throughout the abdomen and pelvis. There was interval development of multiple heterogenous soft-tissue masses, with the largest mass abutting the head and uncinate process of the pancreas (8.3 × 10 cm). Multiple pelvic masses were noted, the largest measuring 4.6 × 6.1 cm. An umbilical hernia was found to now contain tumor implants (6.0 × 6.0 cm). In addition, she was found to have an enlarged lytic lesion in the left aspect of the T12 vertebra measuring 1.4 × 0.9 cm, and other possible lumbar spine lytic metastases, which were not present at the time of diagnosis. The patient then underwent three cycles of single agent doxorubicin. Repeat imaging after three cycles demonstrated progression of disease, with increased size of a hepatic lesion in the caudate lobe of the liver to 2.3 × 2.3 cm from 1.5 × 1.4 cm.

Patient was counseled extensively on the poor prognosis of her disease given her lack of response to doxorubicin. She was counseled that given her limited options, she could attempt an off-label use of pembrolizumab and lenvatinib, though there is limited evidence for this regimen in sarcomas. The patient opted for palliative treatment with pembrolizumab and lenvatinib. Her course was complicated by grade 3 nausea and an emergent exploratory laparotomy after cycle 4 of pembrolizumab and lenvatinib for concern for a preoperative diagnosis of strangulated umbilical hernia, which was instead found to be tumor and confirmed on pathology. During this surgery, tumor at the anterior abdominal wall (largest nodule measuring approximately 8.0 × 6.0 cm) was exteriorized and resected. Given the emergent nature of the patient's presentation, no preoperative imaging was obtained and all disease was not fully debulked. At the time of the procedure, it was thought that the tumor may have herniated as it had decreased in size with pembrolizumab and lenvatinib. Magnetic resonance imaging (MRI) during this admission showed no evidence of metastatic disease within the spine that was previously visualized on CT abdomen pelvis (CTAP) prior to initiation of pembrolizumab and lenvatinib.

After patient had undergone 5 cycles of pembrolizumab and lenvatinib, CTAP demonstrated regression of disease (Figs. 1, 2). The abdominopelvic masses appeared 75 % smaller than on studies prior to initiation of pembrolizumab and lenvatinib as follows. Specifically, there was a regression in size of the mass in the mid-abdomen, abutting pancreatic head and mid to distal duodenum, measuring 5.5 × 4.0 cm, previously 9.2 × 9.5 cm on (Fig. 1). A left mid abdominal mass abutting the left psoas muscle measured 3.6 × 3.4 cm, though was previously 4.0 × 3.6 cm (Fig. 2), a 15 % decrease. The patient is currently undergoing treatment with pembrolizumab; lenvatinib was discontinued due to side effects (Fig. 3).

3. Discussion

This case reports demonstrates disease regression after use of pembrolizumab and lenvatinib in a patient with recurrent leiomyosarcoma. Though the five-year survival rate for leiomyosarcoma ranges from 55.4 % for stage I disease to 13.1 % for stage IV disease, this case report suggests that perhaps there is a role of immunotherapy in prolonging progression free intervals among patients with recurrent leiomyosarcoma (Kho et al., 2021).

Literature on treatment for recurrent leiomyosarcoma remains sparse. A phase III randomized control trial of patients with locally advanced or metastatic soft-tissue sarcoma showed no difference in overall survival between gemcitabine and docetaxel compared to single-agent doxorubicin (HR 1.28, 95 % CI 0.99–1.65). The study suggested that doxorubicin should be the first-line treatment for soft-tissue sarcomas, particularly given reduced toxicity and similar survival benefit to gemcitabine and docetaxel (Seddon et al., 2017). For patients with recurrent disease, combination therapy of doxorubicin and ifosfamide showed an increase in progression-free survival compared to doxorubicin alone, but there was no increase in overall survival (HR 0.83, 95 % CI 0.67–1.03) (Judson et al., 2014). Trabectedin, an alkylating agent that inhibits transcription by binding the guanine residues in the minor groove of DNA, is another agent with documented activity in leiomyosarcoma (Malley et al., 2018). Its use was supported by a phase III study demonstrating increased efficacy and safety of trabectedin versus dacarbazine in patients with recurrent disease (Demetri et al., 2016). In this study, progression free survival was four months for trabectedin. In a prospective phase II study of trabectedin in patients with advanced, persistent or recurrent leiomyosarcoma, progression-free survival (PFS) was 5.8 months. More than half of patients remained progression-free and without any evidence of treatment-ending toxicity for greater than six months (greater than ten cycles). The most common severe (grade 3 or 4) toxicity was neutropenia among 9.6 % of patients (De et al., 2015). Finally, the phase III PALETTE trial demonstrated that pazopanib, a multikinase inhibitor, delayed progression of leiomyosarcoma with a 6 % response rate (Wilky et al., 2013). It included leiomyosarcoma patients who had received at least two lines of prior chemotherapy, and found that the leiomyosarcoma cohort had a PFS of 4.6 months (Pautier et al., July 2019). However, this was limited by the dosing schedule of pazopanib starting at 200 mg twice daily for four days and then to a dose of 800 mg daily for the duration of participation as tolerated (Hirbe et al., 2020). Overall, there is limited evidence around optimal treatment options for leiomyosarcoma, and current therapies demonstrate poor response rate.

A recent trial by Makker et al. supports the use of pembrolizumab and lenvatinib as a potential standard of care treatment for advanced endometrial cancer (Malley et al., 2018). The trial demonstrated significantly longer progression-free survival and overall survival among those with advanced endometrial cancer who received pembrolizumab and lenvatinib compared to chemotherapy (HR 0.62, CI 0.51–0.75) (Malley et al., 2018). However, leiomyosarcoma was not included in this trial and these agents are currently not FDA-approved.

Our case report suggests that this combination immunotherapy may have activity in patients with recurrent leiomyosarcoma. However, leiomyosarcoma is often excluded in endometrial cancer trials. Few trials exist specifically for leiomyosarcoma, as leiomyosarcoma is included in larger trials as a subtype of soft tissue sarcoma (Kasper et al., 2022). SARC028, a phase II single-arm study, compared pembrolizumab efficacy in a soft tissue sarcoma cohort, including those with leiomyosarcoma, and a bone sarcoma cohort. All patients received 200 mg

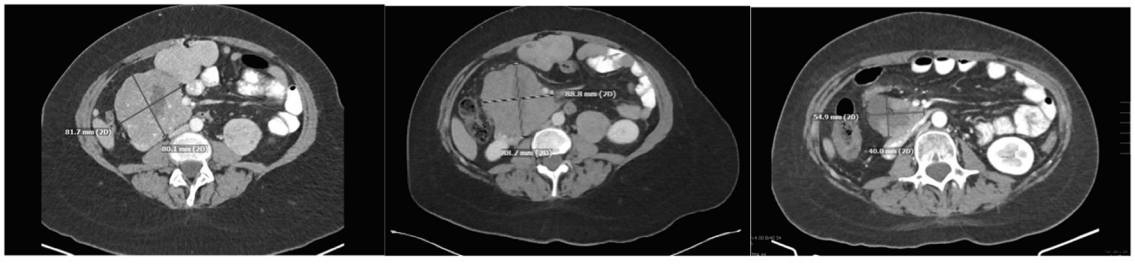

Fig. 1.

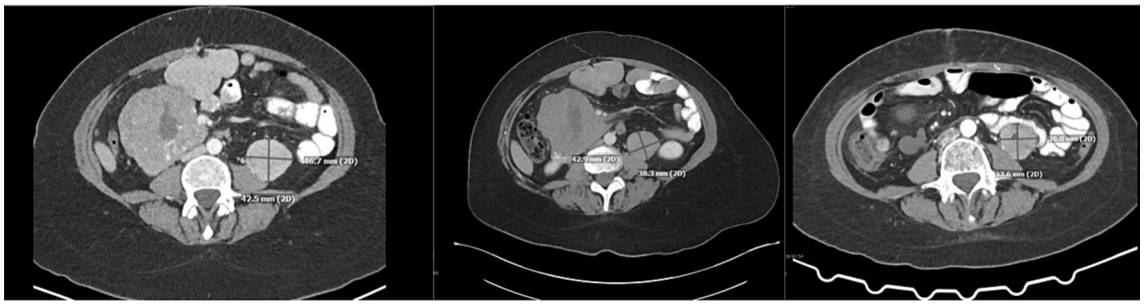

Fig. 2.

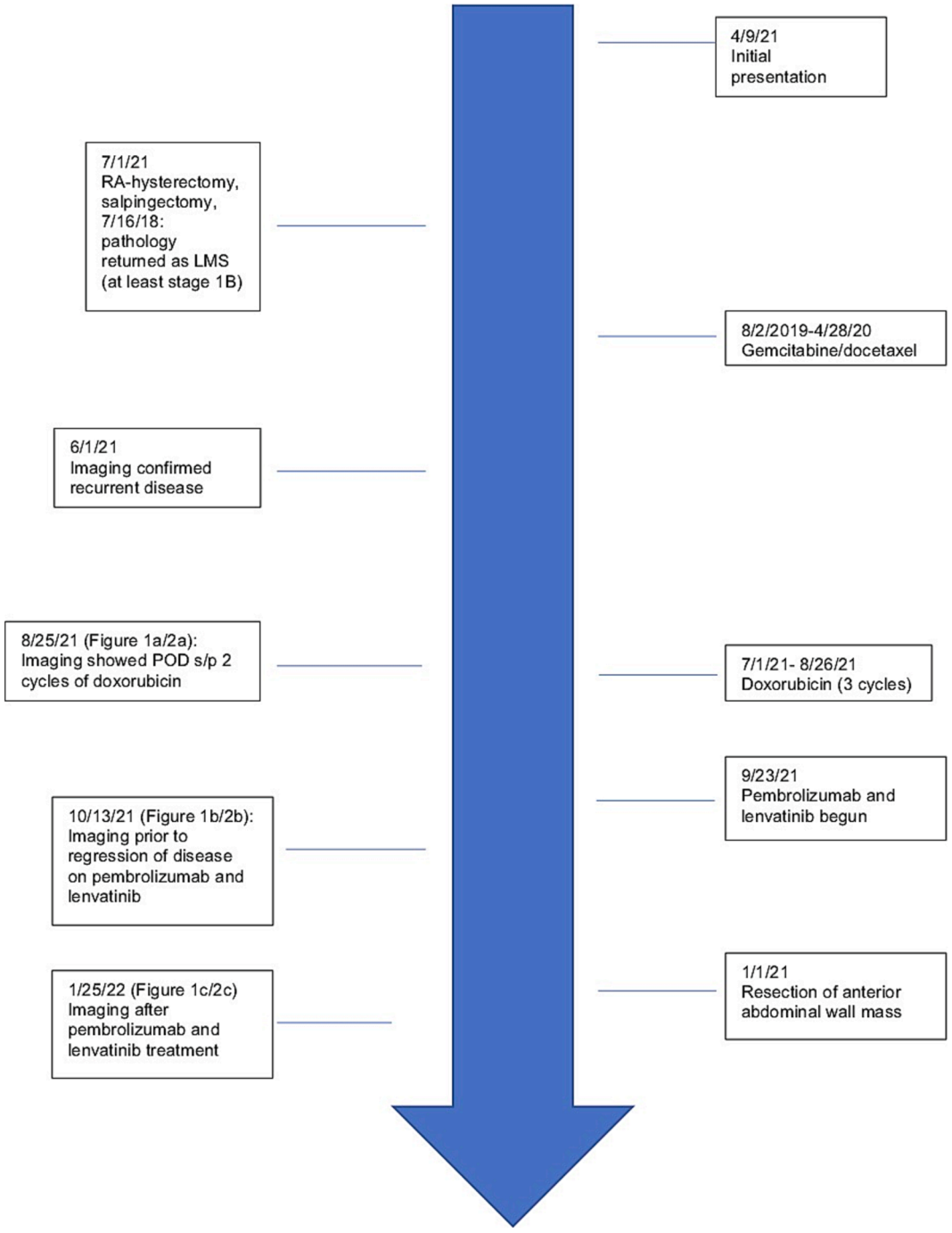
4/9/21
Initial presentation
7/1/21
RA-hysterectomy, salpingectomy, 7/16/18: pathology returned as LMS (at least stage 1B)
8/2/2019-4/28/20
Gemcitabine/docetaxel
6/1/21
Imaging confirmed recurrent disease
8/25/21 (Figure 1a/2a): Imaging showed POD s/p 2 cycles of doxorubicin
7/1/21- 8/26/21
Doxorubicin (3 cycles)
9/23/21
Pembrolizumab and lenvatinib begun
10/13/21 (Figure 1b/2b): Imaging prior to regression of disease on pembrolizumab and lenvatinib
1/25/22 (Figure 1c/2c) Imaging after pembrolizumab and lenvatinib treatment
1/1/21
Resection of anterior abdominal wall mass

Fig. 3.

intravenous pembrolizumab every 21 days. Of the soft tissue sarcoma arm, no objective responses were observed for leiomyosarcoma, which was a subset of 9 of 38 patients enrolled in that arm. Progression-free survival for leiomyosarcoma patients at eight weeks was 50 % (Tawbi et al., 2017). Though this is evidence that pembrolizumab has demonstrated encouraging activity in soft tissue sarcomas, convincing evidence regarding immunological treatments for leiomyosarcoma is rare (Malley et al., 2018).

New immunotherapies such as nivolumab have been explored as potential treatments for advanced leiomyosarcoma. For instance, in a phase II study, twelve patients with previously treated uterine leiomyosarcoma underwent treatment with nivolumab with a median of five two-week cycles of nivolumab. Of the twelve patients, no patients responded to treatment, with the overall median progression-free survival of 1.8 months. Trials for leiomyosarcoma represent a high unmet need for this patient population with minimal treatment options in the recurrent setting.

A limitation of this study is that no molecular sequencing was done, as it is not routinely performed for leiomyosarcoma patients. Therefore, we do not know if the patient would have met criteria for pembrolizumab or both pembrolizumab and lenvatinib by mismatch repair deficiency (dMMR). A large multiomic analysis detected a dMMR or microsatellite instability-high (MSI-H) mutation in only 1.5 % of leiomyosarcoma samples, suggesting that perhaps pembrolizumab and lenvatinib would be the preferred option compared to pembrolizumab alone in this patient, particularly given that MMR/MSI status was unknown in this patient (Lagos Galina et al., 2021). A case report supported use of pembrolizumab in a patient with MSI-H leiomyosarcoma, further suggesting that molecular sequencing could have provided additional evidence of pembrolizumab's efficacy among this specific cohort (Wang et al., 2021). An additional limitation to this study is the role of the emergent surgery in decreasing the patient's mass size versus the effect of pembrolizumab and lenvatinib. As noted above, the tumor may have herniated because of a decrease in size after pembrolizumab and lenvatinib treatment. Given the emergent nature of the surgery, tumor resection was limited to the umbilicus and the abdominal wall mass that herniated through. Despite this, there was a response to pembrolizumab and lenvatinib in other measurable nodules. Overall, this case reports suggests that perhaps there may be a beneficial role for pembrolizumab and lenvatinib among a subset of patients with leiomyosarcoma.

Clinical trials exploring treatment options for leiomyosarcoma are an unmet need. This report highlights a potential benefit of the use of pembrolizumab and lenvatinib among patients with leiomyosarcoma, supporting a need for further research.

4. Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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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