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CASE REPORT

Lung metastases regression with increased CD8+ T lymphocyte infiltration following preoperative spinal embolization and total en bloc spondylectomy using tumor-bearing frozen autograft in a patient with spinal metastatic leiomyosarcoma

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Abstract

Purpose To report systemic immunological enhancement following preoperative spinal embolization and total en bloc spondylectomy (TES) using tumor-bearing frozen autograft in a patient with spinal metastatic leiomyosarcoma.

Methods A 44-year-old woman with metastatic uterine leiomyosarcoma of the lung and L1 vertebra underwent TES following bilateral three-level preoperative segmental artery embolization. Resected tumor-bearing lamina was frozen using liquid nitrogen and used as tumor-bearing bone graft for spinal reconstruction.

Results Tumor necrosis and obstructing material used in preoperative embolization were detected in the resected specimen of L1. Five days after TES, chest computed tomography scan demonstrated decreased solitary lung mass size without adjuvant treatment. Lobectomy was performed for the lung metastasis 42 days after TES. Infiltration of CD8+ T lymphocyte into tumor tissue significantly increased in shrunk lung metastasis. On the other hand, slight infiltration in both the resected L1 and primary uterine lesion was observed. Six months after TES, activities of daily living were normal with no evidence of local recurrence or distant metastasis. One year after TES, however, lung CT revealed occurrence of another lung metastasis, and molecular-targeting therapy (pazopanib) was initiated.

Conclusions There were no reports demonstrating metastasis regression with CD8+ T lymphocyte infiltration after TES. This case demonstrated that preoperative tumor embolization combined with TES using tumor-bearing autograft provided both a local radical cure and systemic antitumor immunological enhancement, although the long-term effect can be limited.

Keywords Frozen autograft · Embolization · CD8 · Leiomyosarcoma · Spondylectomy

Introduction

Leiomyosarcoma is a malignant soft tissue sarcoma rarely arising in the uterus. Uterine leiomyosarcoma comprises only 1% of all uterus malignancies [1], but has high recurrence rates (45–73%) [2] even with aggressive management. Distant metastasis indicates late-stage disease and has limited treatment options with a 10–35.8% 5-year survival rate [3–5]. Skeletal metastasis occurs in 13.8% of cases [5]. The spine is one of the more common skeletal sites and can be highly morbid and deadly. The surgical options for spinal metastatic leiomyosarcoma range from spinal decompression to en bloc excision. Postoperative radiation and chemotherapy have been used, but no definitive guidelines exist due to their controversial efficacy. Herein, we present a case of metastatic uterine leiomyosarcoma of the lung and L1 vertebra that was successfully treated with total en bloc spondylectomy (TES) using tumor-bearing frozen autograft for reconstruction. After surgery, solitary lung metastasis regression was observed. CD8+ T lymphocyte infiltration into tumor tissue significantly increased in shrunk lung

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metastasis with slight infiltration in both L1 and the primary lesion, suggesting systemic immunological enhancement.

Case report

History and clinical evaluation

A 44-year-old woman was diagnosed with a malignant tumor of the uterus. Three months later, she underwent total hysterectomy at another institution. Histopathological evaluation revealed uterine leiomyosarcoma. She complained of low back pain 2 years later. Lumbar anteroposterior and lateral plain radiographs revealed cortical erosion of the superior and inferior endplates of L1 vertebral body, while the other lumbar vertebrae appeared normal (Fig. 1). Computed tomography (CT) scan and T2-weighted magnetic resonance imaging revealed extensive destruction of L1 vertebral body, causing pathological fracture and extracompartmental invasion of the tumor into the spinal canal and left side of the vertebral body (Figs. 2, 3). Chest CT scan revealed 20 × 21 mm solitary left lung mass suspected of lung metastasis (Fig. 4a).

Treatment

Preoperative embolization of bilateral segmental arteries at three levels was performed 3 days before TES (Fig. 5). Combined left anterolateral retroperitoneal and posterior approach TES was performed without preoperative chemotherapy or radiation. Left anterolateral retroperitoneal approach was initially performed to dissect the segmental arteries from the left lateral aspect of the vertebral body due to extra-compartmental invasion of the tumor on the left side of the vertebral body. The left psoas major muscle was cut to expose the adjacent disks, and the bilateral segmental vessels of L1 were cut (Fig. 6a, b). The posterior approach was subsequently performed. The lower half of T12 lamina was removed to expose the L1 superior articular facet. L1 posterior elements were removed using flexible multifilament thread wire (T-saw; Pro Medical, Kanazawa, Japan) [6], and bilateral L1 nerve roots were ligated and cut. Blunt dissection was performed around the affected vertebra and adjacent disk level. Bilateral pedicle screws were inserted and affixed with a rod on the right side. T12/L1 and L1/2 intervertebral disks were then cut using an L-shaped chisel. L1 vertebral body was then removed en bloc posteriorly (Fig. 6c). After removal of surrounding musculoligamentous tissues, the excised tumor-bearing lamina was frozen by immersing in liquid nitrogen for 20 min. For spinal reconstruction, the frozen lamina was crushed and packed into a titanium mesh cage that was inserted into the anterior defect. A large amount of excess frozen autograft was placed around the cage. The posterior instrumentation was adjusted to slightly compress the inserted cage.

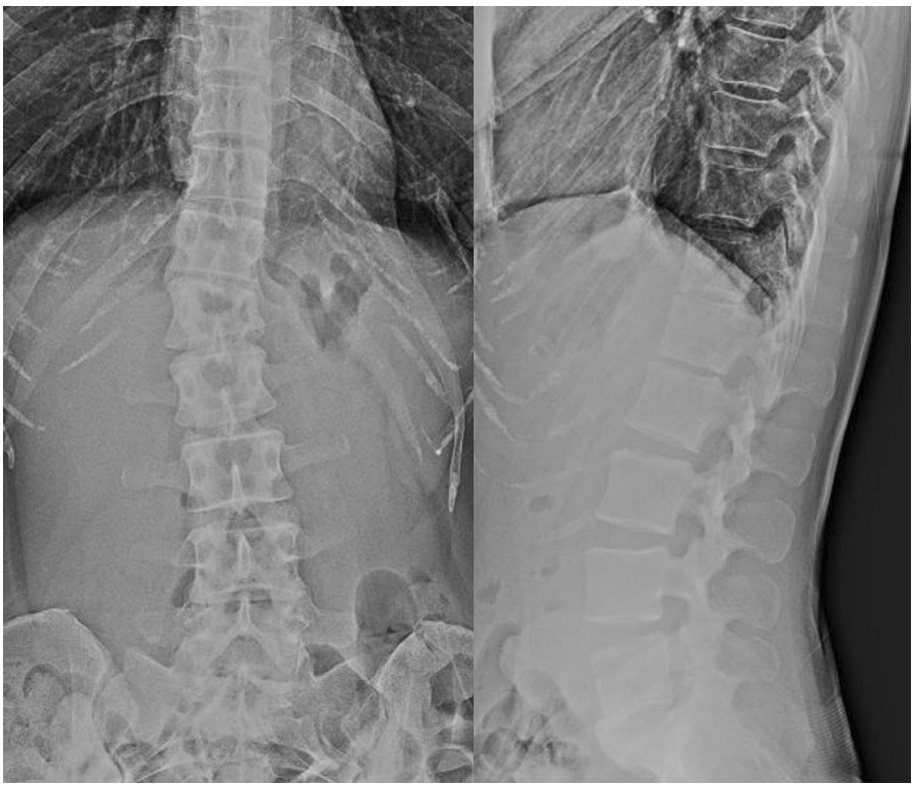

Fig. 1 Preoperative radiograph of the lumbar spine. A radiograph revealed cortical erosion at the superior and inferior endplates of L1 with pathological fracture

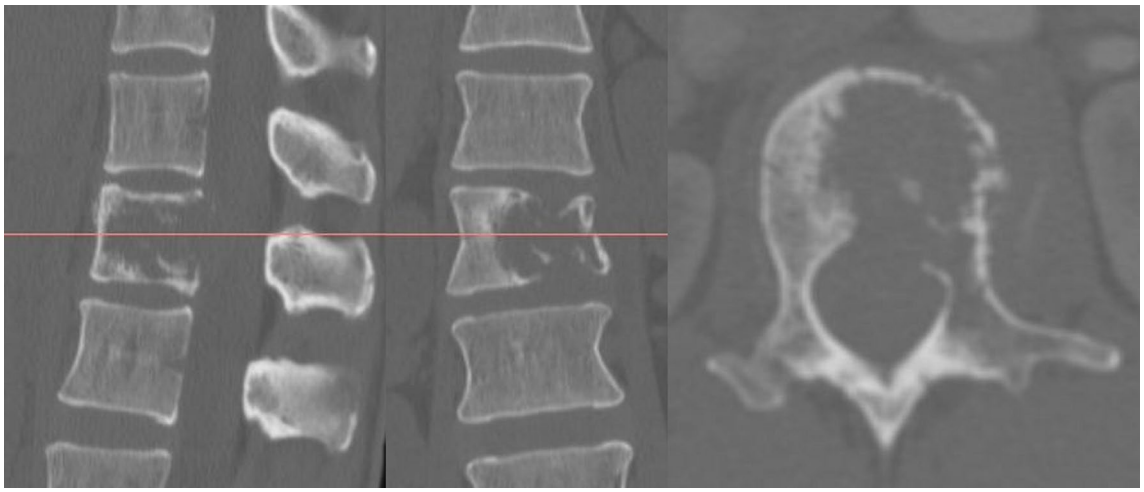

Fig. 2 Preoperative computed tomography images of the lumbar spine. Computed tomography image revealed osteolytic tumor involving the L1 vertebral body

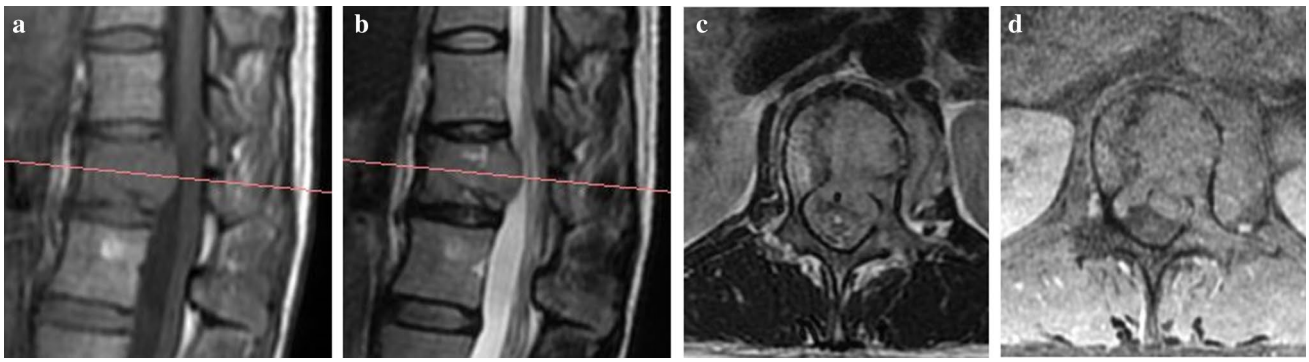

Fig. 3 Preoperative magnetic resonance imaging of the lumbar spine. T1- (**a**) and T2-weighted (**b** and **c**) images. Tumor enhancement was observed with gadolinium contrast (**d**)

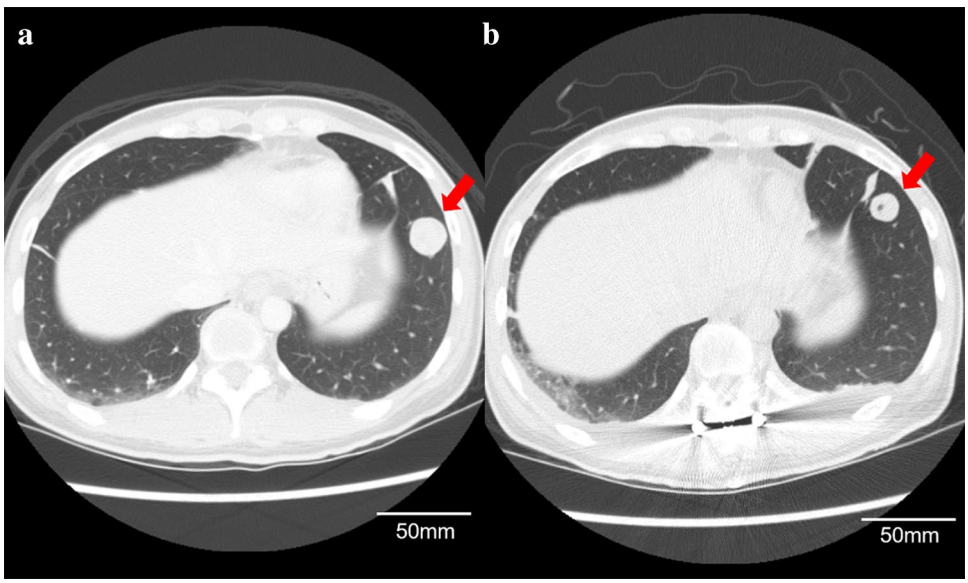

Fig. 4 Pre- and postoperative chest computed tomography images. Before surgery (**a**) and 5 days after total en bloc spondylectomy (**b**). Chest computed tomography scan demonstrated decreased solitary lung mass size to 16×18 mm without receiving any adjuvant treatment

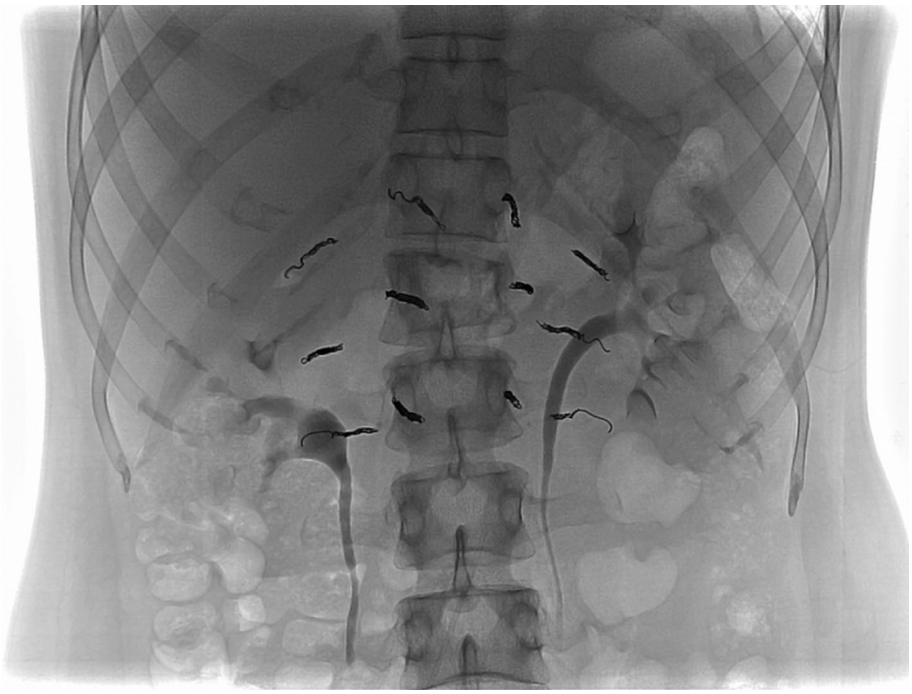

Fig. 5 Preoperative tumor embolization. Preoperative embolization of bilateral segmental arteries at three levels was performed 3 days before total en bloc spondylectomy

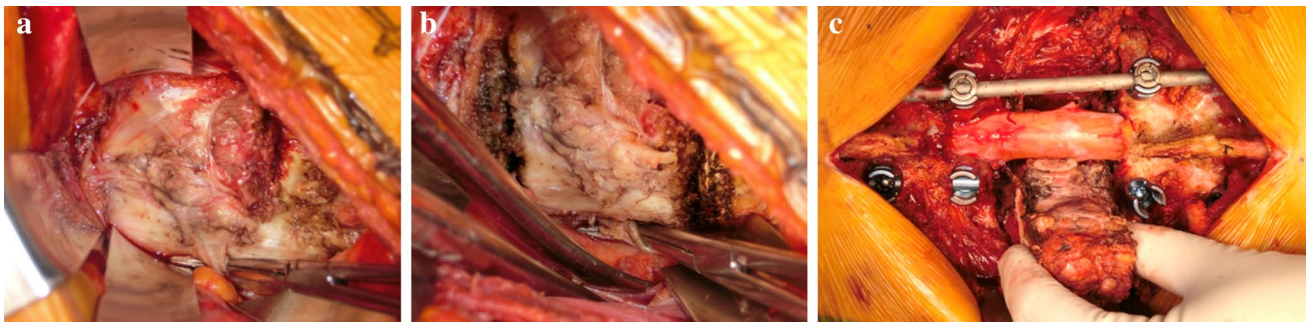

Fig. 6 Intraoperative photographs. Left anterolateral retroperitoneal approach to dissect segmental arteries from the left lateral aspect of the vertebral body. Bilateral segmental vessels of L1 were cut and ligated through this approach: left (**a**) and right (**b**) segmental artery. L1 vertebral body was removed en bloc posteriorly (**c**)

Pathological findings of resected L1

Histological analysis of L1 body sections was performed. Pathological analysis revealed metastasis of uterine leiomyosarcoma. Immunohistochemistry showed that the majority of cells were αSMA-, caldesmon-, desmin-, ER-, and PgR-positive, but negative for CD34, S-100, and EMA. Partial tumor necrosis and obstructing material used in preoperative embolization were detected in the resected specimen (Fig. 7).

Postoperative course

No postoperative complications occurred, and she walked independently 2 weeks after surgery. Five days after TES, chest CT scan demonstrated decreased solitary lung mass size to 16 × 18 mm without receiving any adjuvant treatment (Fig. 4b). Forty-two days after TES, lobectomy of solitary lung metastases was performed. Tumor necrosis was detected in resected lung metastasis, and the ratio of tumor necrosis compared to the whole area of the tumor was approximately 18% (Figs. 8, 9a). Infiltration of CD8+ T lymphocyte into tumor tissue for L1, lung metastasis, and uterus as primary lesion was histologically evaluated (Fig. 9a, b). A rabbit polyclonal antibody against CD8 (1:100, ab101500; Abcam, Cambridge, UK) was used as the primary antibody. Antimouse or rabbit IgG conjugated with peroxidase-labeled polymers (EnVision; Dako, Carpinteria, CA, USA) was used as the secondary antibody. Immunological study revealed

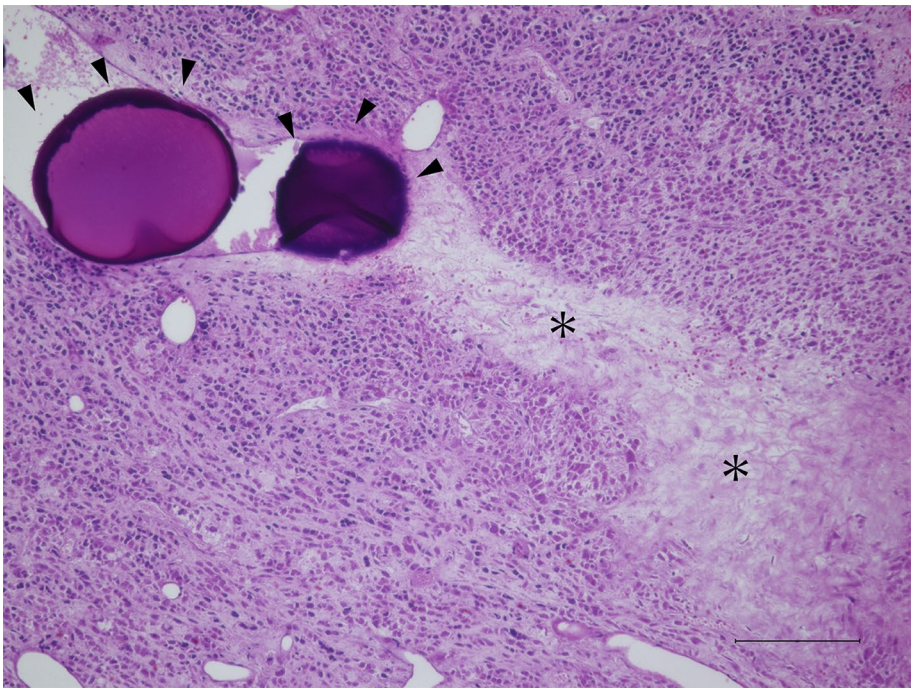

Fig. 7 Pathological findings of the resected tumor (hematoxylin and eosin staining). Tumor necrosis and obstructing material were detected in the resected specimen. Black arrowhead indicates obstructing material. Asterisk indicates tumor necrosis. Scale bar corresponds to 200 μm

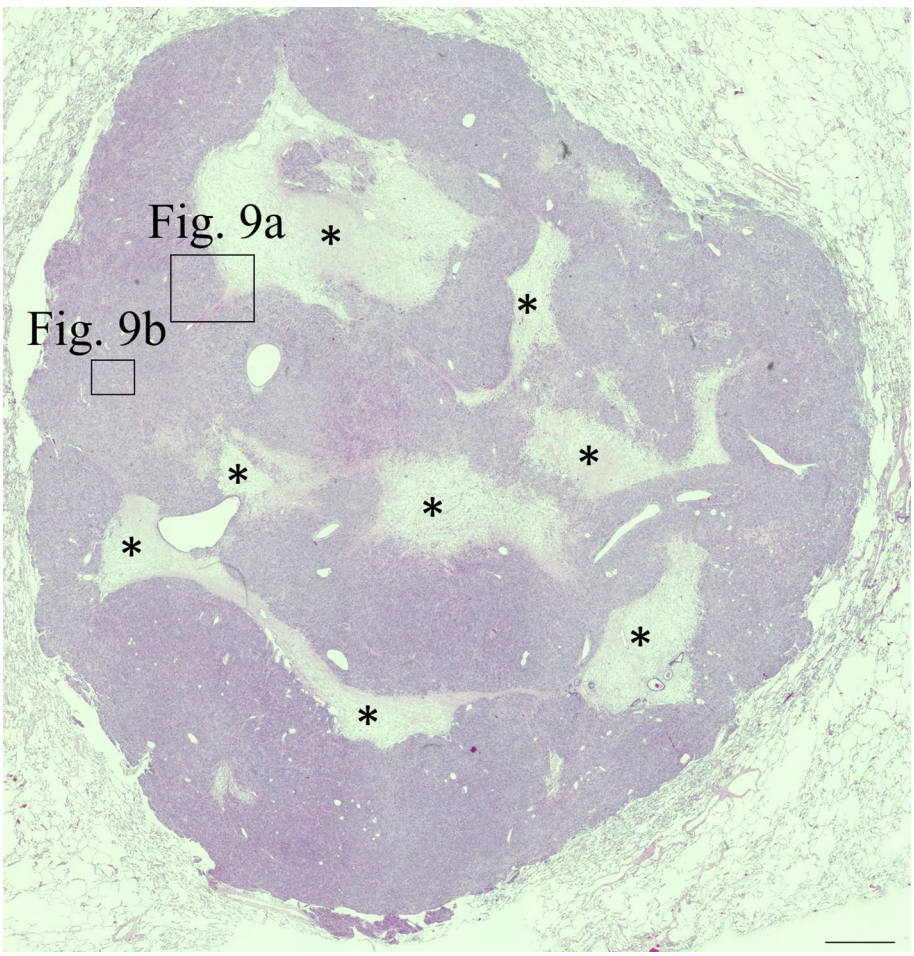

Fig. 8 Histological analysis of resected shrunk lung metastasis (hematoxylin and eosin staining). The asterisk indicates tumor necrosis. The ratio of tumor necrosis compared to the whole area of the tumor was approximately 18%. Scale bar corresponds to 1000 μm

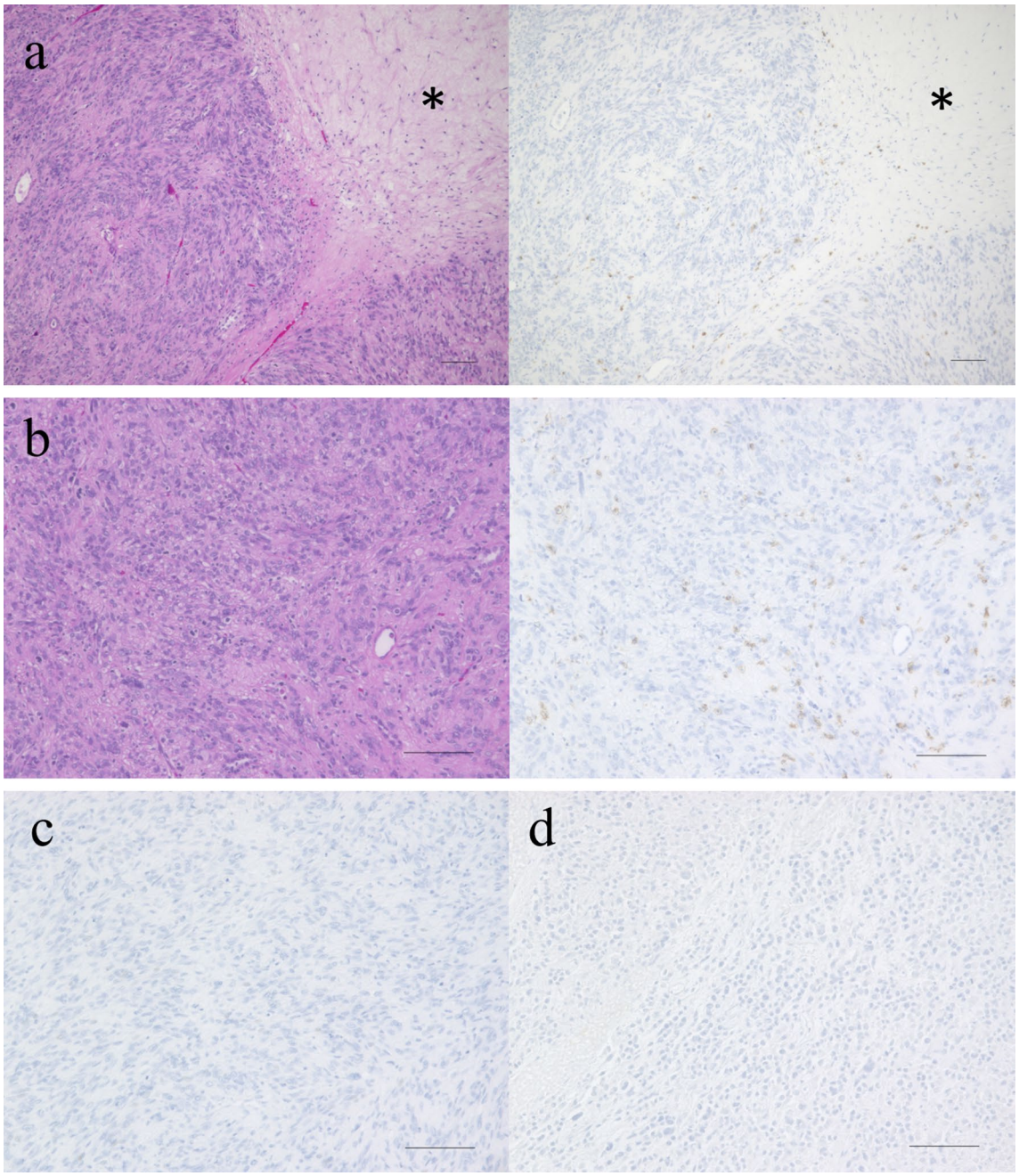

Fig. 9 Histological analysis of resected shrunk lung metastasis (**a**, **b**), primary legion of uterus (**c**), and L1 vertebral body (**d**) (hematoxylin and eosin staining and CD8 immunostaining). The asterisk indicates tumor necrosis. Histologically evaluated determined significantly increased infiltration of CD8+ T lymphocyte in shrunk lung metastasis (**a**, **b**), and no infiltration in both primary uterine lesion (**c**) and L1 vertebral body (**d**). Scale bar corresponds to 100 μm

significantly increased CD8+ T lymphocyte infiltration into tumor tissue in shrunk lung metastasis. On the other hand, slight infiltration in L1 or primary uterine lesion was observed (Fig. 9c, d). Total number of CD8+ cells per ten high power fields was 347 cells (lung metastasis), 9 cells (L1), and 15 cells (primary uterine lesion). Six months after TES, activities of daily living were normal with no evidence of local recurrence or distant metastasis. One year after TES, however, lung CT revealed occurrence of another lung metastasis, and molecular-targeting therapy (pazopanib) was initiated. Postoperative radiography and CT demonstrated that the reconstructed spine was well-maintained (Fig. 10).

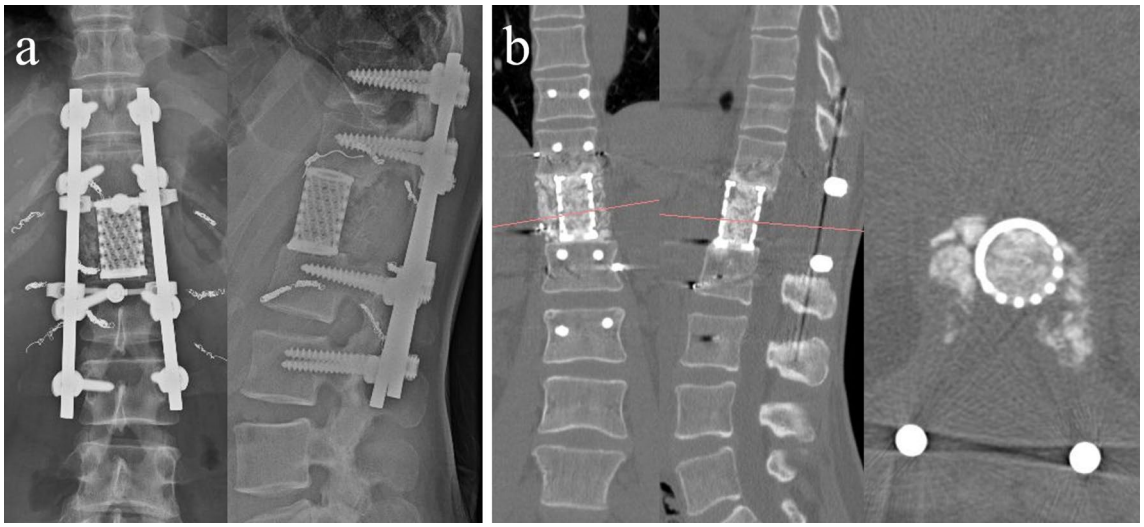

Fig. 10 Postoperative radiological findings 1 year after total spondylectomy. Postoperative radiography and computed tomography demonstrated that the reconstructed spine was well-maintained. A large amount of excess frozen autograft was placed around the cage

Discussion

Spinal metastatic leiomyosarcoma is rare, with only three case series and few case reports published [7–9]. Due to its rarity, disease management is based on clinical case reports, clinical status, and patient survival, which are considered for palliative purposes. There are no current recommendations for adjuvant therapies; however, most spinal metastatic leiomyosarcoma cases received radiation or chemotherapy [7–9]. Radiation in spinal metastasis controls local symptoms and preserves neurological function; however, radioresistant and infiltrative growth pattern of the sarcoma, and difficulty in delivering optimal doses, causes high recurrence rate. For example, stereotactic radiosurgery has a local control rate of 84–88% in metastatic spinal sarcomas [10, 11]; however, failure in metastatic leiomyosarcoma yielded high recurrence rate (32%) compared to other sarcoma types overall (21%) [12]. While efficacy of radiation in spinal metastatic leiomyosarcoma is limited, chemotherapy efficacy still lacks evidence; thus, surgeries are the best treatment, when feasible. Survival from spinal metastatic leiomyosarcoma varies from weeks to up to 13 years [7, 8]. We expected long survival in this patient because she had single-level spinal involvement and single lung metastasis that suited the metastasectomy. Thus, aggressive approaches, including TES of L1 and lobectomy of solitary lung metastases, were performed.

Reconstruction using tumor-bearing autograft treated with liquid nitrogen in patients with malignant bone tumor is safe and effective [13] with no reported local recurrences. Advantages of frozen autografts include: low cost; osteoinductive and osteoconductive properties; good fit between graft and host bone; no disease transmission, immunological rejection, or harmful denatured substances; early revitalization; and cryoimmunological effects [14–16]. Possible induction of systemic antitumor immune response from reimplantation of destroyed tumor tissue treated with liquid nitrogen was observed in a murine model [17] and patient with osteosarcoma who was concurrently treated with dendritic cell therapy [18].

This reconstruction technique has been concurrently performed in TES at our institute since 2010. This technique eliminates graft harvest-site morbidity, decreases blood loss, and shortens surgical time [19]. Our institute previously reported three cases of carcinoma with regression of lung or lymph node metastasis following TES using tumor-bearing frozen autograft for reconstruction, combined with preoperative spinal embolization [20–22]. The present study is the first case of sarcoma showing clinical response of cryoimmunology using this reconstruction technique in TES, combined with preoperative embolization. Further, in 60 TES cases that used this combined reconstruction technique and preoperative embolization, mean IL-12 and IFN-γ relative concentrations significantly increased after TES [23].

Metastatic tumor regression with infiltration of CD8+ T cells in the metastatic tumor tissue is considered as enhancement of immune response. CD8+ T lymphocytes play a central role in immunity to cancer through their capacity to kill malignant cells upon recognition by T cell receptor (TCR) of specific antigenic peptides [24]. To our knowledge, this is the first report to demonstrate lung metastases regression with increased CD8+ T lymphocyte infiltration into tumor tissue following the combined treatment method. Many studies reported immunologic effect resulting in the rejection of secondary tumor challenges following cryoablation in animal model [25–28]. However, CD8 infiltration into the

metastatic tumor was not observed after cryotreatment alone. Cryotreatment-induced metastatic antitumor activity with CD8 infiltration into the metastatic tumor was observed after cryotreatment combined with CTLA-4-blocking antibodies such as ipilimumab in the mouse prostate cancer model [29]; however, the results of their cryoablation study indicate that in their system, cryoablation alone had no effect on secondary tumor growth or T cell infiltration into secondary tumors [29].

The contribution of preoperative embolization in reducing intraoperative blood loss and its clinical importance are reported in palliative surgery for spinal metastasis, which violates the tumor vessels in such a highly vascular condition [30]. However, the contribution of preoperative embolization in reducing intraoperative blood loss in free margin excision such as total en bloc spondylectomy is unclear. In general, surgeons do not need to reduce the tumor vascularity in free margin excision surgery. To our knowledge, there have been no reports suggesting the efficacy of preoperative embolization prior to free margin excision for spinal metastasis. In our institution, spinal embolization is routinely performed 1–3 days before total en bloc spondylectomy, to reduce the risk of unexpected intraoperative bleeding due to the injury of segmental arteries and vein, and to prepare for unexpected intralesional tumor resection.

Preoperative embolization of spinal metastatic tumor can also enhance antitumor immune response. The efficacy of embolization-stimulated antitumor immunological response was mainly reported in transcatheter arterial embolization for hepatocellular carcinoma and renal embolization for renal cell carcinoma. To our knowledge, there have been no reports presenting the efficacy of embolization-stimulated antitumor immunological response for spinal metastasis. This case report is the first report indicating the potential of embolization-stimulated antitumor immunological effect for spinal metastasis. In patients with renal cell carcinoma, preoperative renal artery embolization significantly enhanced systematic antitumor response [31] and elongated survival compared to nephrectomy alone [31, 32]. They concluded that embolization may lead to stimulation of the immune system in the following mechanism: close off blood supply to the tumor leads to necrosis which gives a chance to enhance antigenicity of cancer cells and evoke the potential amplification of the immune system. In hepatocellular carcinoma, transcatheter arterial embolization also enhanced antitumor immune response via the same mechanism [33, 34]. Duan et al. reported that transcatheter arterial embolization combined with radiofrequency ablation activates CD8+ T cell infiltration surrounding residual tumors in the rabbit liver tumors. They concluded that in the rabbit liver tumor model, TAE + RFA activated the highest number of CD8+ T cells surrounding residual tumors [34]. In the present case, partial tumor necrosis was observed in resected L1 tumor after preoperative tumor embolization, potentially indicating embolization-stimulated antitumor immunological response. The combination of preoperative tumor embolization with TES using tumor-bearing frozen autograft caused necrosis and collapse of a large quantity of tumor cells, thereby releasing a large amount of tumor-related antigens, which may have stimulated the antitumor immune response. Li et al. reported that transcatheter renal arterial embolization combined with cryoablation enhances systematic immune response. In the reports, transcatheter renal arterial embolization combined with cryoablation contributes to reduce the percentage of Treg cells and improve the immune situation of patients with renal cell carcinoma, which consequently increase tumor necrosis rate and prolong the patients' survival duration [35]. As shown in our case, this combined treatment for spinal metastasis can improve short-term outcome for the patients with spinal metastasis. However, the long-term effect can be limited. Further investigation of this combined therapy as a new therapy for spinal metastasis is warranted.

Conclusion

The combination of preoperative spinal tumor embolization and TES using tumor-bearing frozen autograft provided both a local radical cure and systemic antitumor immunological enhancement in this case, although the long-term effect can be limited.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient described in the study.

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