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【 CASE REPORT 】

Complete Response to Eribulin in a Patient with Unresectable Liposarcoma: A Case Report and Implications of New Biomarkers

Hajime Nakamura[1], Kohichi Takada[1], Makoto Emori[2], Naotaka Hayasaka[1] and Shintaro Sugita[3]

Abstract:
We herein report a rare case of unresectable liposarcoma that showed a complete response to eribulin. Furthermore, a low expression of phosphorylated AKT (p-AKT) on an immunohistological evaluation was observed. This result is consistent with our previous preclinical study that demonstrated the significance of p-AKT signaling for eribulin resistance in multiple subtypes of soft tissue sarcoma (STS) cells. This case highlights the potential benefits of eribulin as well as the mechanism underlying resistance to eribulin in patients with unresectable or metastatic STS, especially liposarcoma.

Key words: eribulin, liposarcoma, phosphorylated AKT

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Introduction

Soft tissue sarcoma (STS) is a rare disease that accounts for around 1% of all malignancies in adults (1). Despite adequate locoregional treatment, such as surgery, 40% to 50% of patients with STS develop metastatic disease (1, 2). When metastases are detected, the standard therapy used in response is based on chemotherapy aimed at extending the survival and palliative care (3). However, the prognosis for unresectable or metastatic (UM)-STS is extremely poor, with an overall survival (OS) of less than 1.2 years after the diagnosis (4). There is thus a strong need for novel strategies to treat STS.

Doxorubicin is the only approved first-line therapy for patients with UM-STS and has been used for more than 40 years (5). It has been difficult to develop new drugs because of the heterogeneity of STS, which has over 50 recognized histological subtypes (6). Recently, three new drugs (pazopanib, trabectedin, and eribulin) were introduced for patients with UM-STS who had been previously treated with doxorubicin (7-9). Notably, eribulin was the only drug shown to improve the OS in patients with liposarcoma or leiomyosarcoma compared to dacarbazine in a phase III trial (9).

Eribulin is currently considered a key drug in patients with UM-STS because liposarcoma is one of the most common types of sarcomas in adults. In practice, in Japan, it is approved for all subtypes of UM-STS previously treated with chemotherapy containing anthracycline. However, eribulin only extends the OS by about two months, and no patient has shown a complete response (CR) under eribulin treatment (9).

We herein report an excellent case of unresectable liposarcoma that showed a CR with eribulin. This case also highlights the mechanism underlying resistance to eribulin in UM-STS from a molecular biology perspective.

Case Report

A 61-year-old man was referred to our hospital because abdominal ultrasound and computed tomography (CT) re-

[1]Department of Medical Oncology, Sapporo Medical University School of Medicine, Japan, [2]Department of Orthopedics, Sapporo Medical University School of Medicine, Japan and [3]Department of Surgical Pathology, Sapporo Medical University School of Medicine, Japan
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Correspondence to Dr. Kohichi Takada, ktakada@sapmed.ac.jp

vealed a tumor with a maximum diameter of 70 mm in the perinephric space. Abdominal ultrasound showed a solid heterogenous hypoechoic tumor with internal vascularity that is typical of STS near the left kidney (Fig. 1). Furthermore, CT showed a slightly and heterogeneously enhanced tumor whose exact origin was uncertain in the perinephric space (Fig. 2a-f). However, it was difficult to diagnose the tumor using only imaging examinations. Therefore, a percutaneous ultrasound-guided biopsy was performed, and the histological evaluation of a biopsy specimen revealed a dedifferentiated liposarcoma of Fédération Nationale des Centres de Lutte Contre le Cancer grade 2. No clinical or radiographic evidence of distant metastases was found.

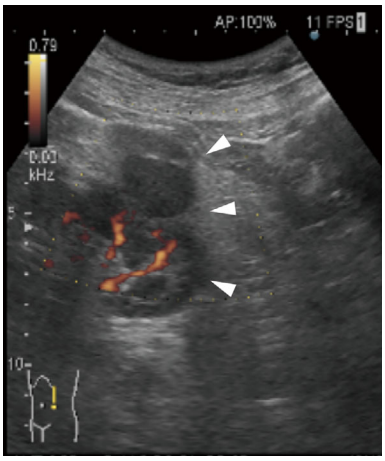

Figure 1. An abdominal ultrasound image at the initial diagnosis. A heterogenous hypoechoic tumor with internal vascularity (arrowheads) is located near the left kidney.

Resection of the tumor and a segment of the descending colon that was invaded by the tumor was conducted in a curative setting. The final pathological diagnosis was a dedifferentiated liposarcoma. This was identical to the preoperative diagnosis, since both cyclin-dependent kinase 4 and mouse double minute-2 positive immunostaining was noted, although lipid droplets were not found within the tissue (Fig. 3a-e). The patient was discharged from our hospital 31 days after surgery. However, he presented with local recurrence in the left iliopsoas muscle nine months after surgery (Fig. 4a). Initially, we had considered further surgery, but this was judged to be too risky and invasive because of the location of the relapsed site. We decided to administer chemotherapy with doxorubicin (30 mg/m^2 per day on days 1-2). The treatment was repeated every three weeks for four times in total.

However, the relapsed site continued to grow despite the treatment (Fig. 4b). Eribulin (1.4 mg/m^2 per day on days 1 and 8 of a 21-day cycle) as second-line treatment was thus administered 12 months after surgery. CT was performed after three cycles of eribulin treatment, showing slight shrink-

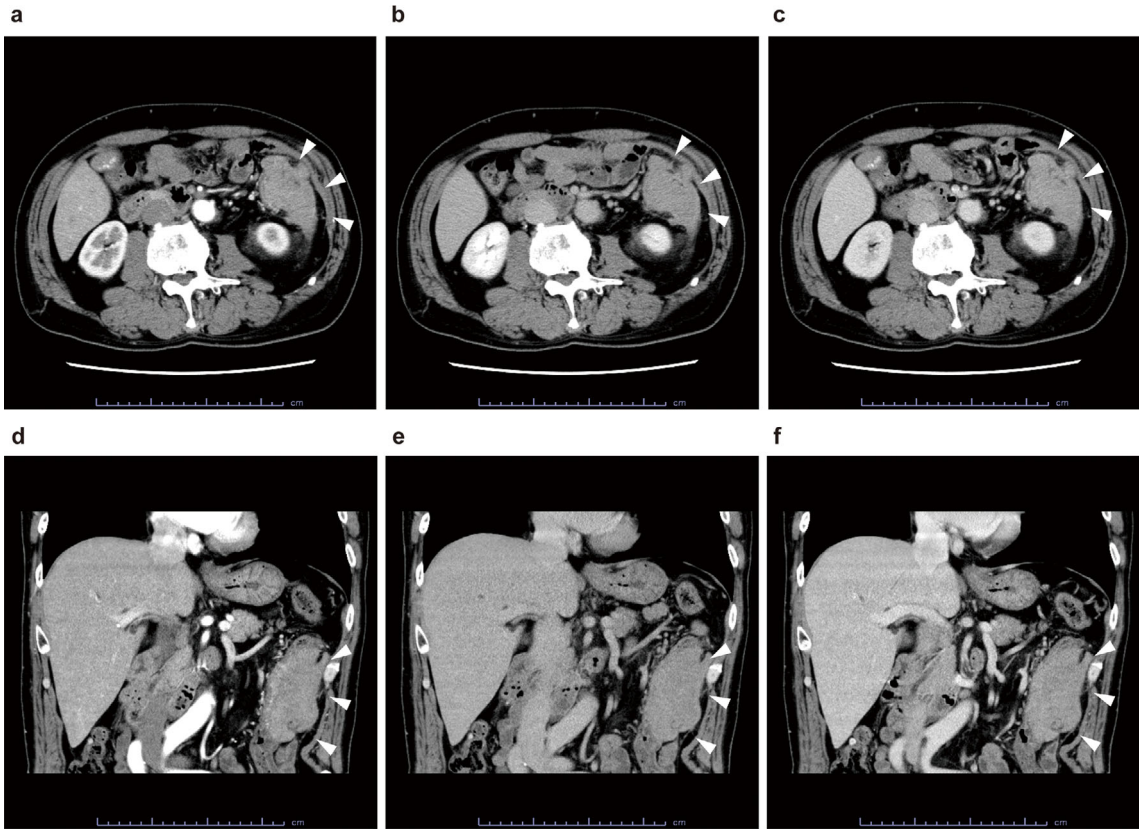

Figure 2. Computed tomography images at the initial diagnosis. A tumor (arrowheads) is located in the perinephric space and is extensively invading the descending colon. (a-c) Axial images, a: arterial phase, b: portal phase, c: delayed phase, (d-f) coronal images, d: arterial phase, e: portal phase, f: delayed phase.

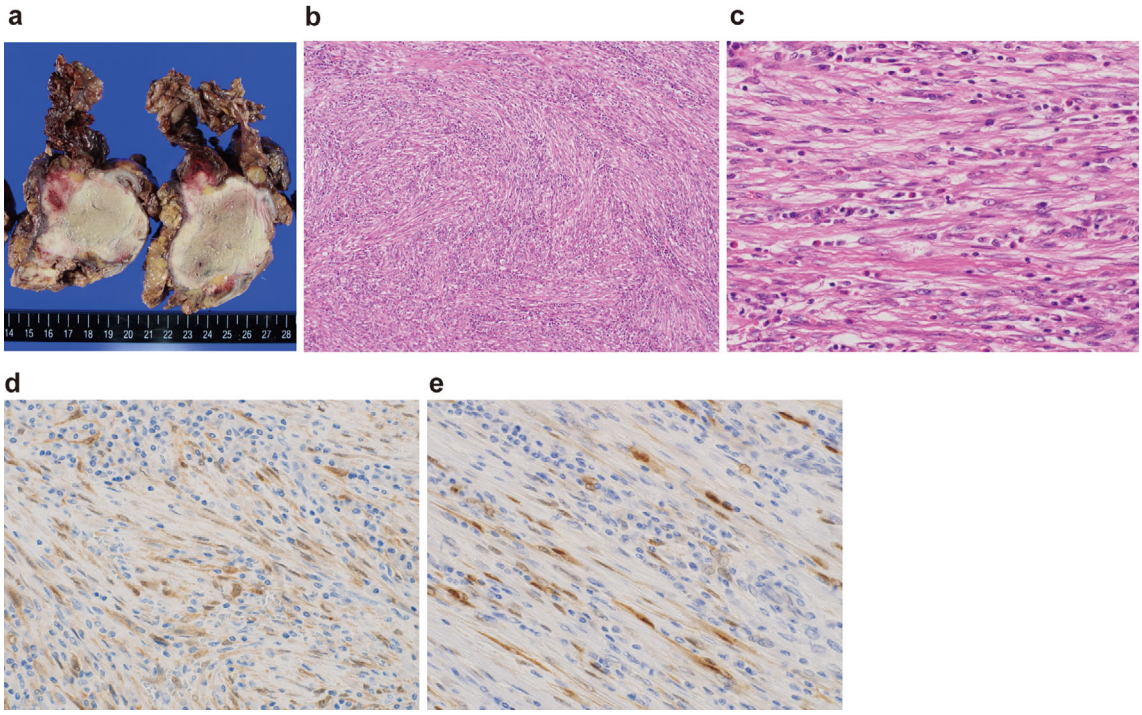

Figure 3. **Pathological findings including immunohistochemical staining. (a) Macroscopic view of the resected specimen. (b-c) Hematoxylin and Eosin staining. b: a distant view (×100), c: a near view (×400). Immunostaining for (d) cyclin-dependent kinase 4 (positive) and (e) mouse double minute-2 (positive).**

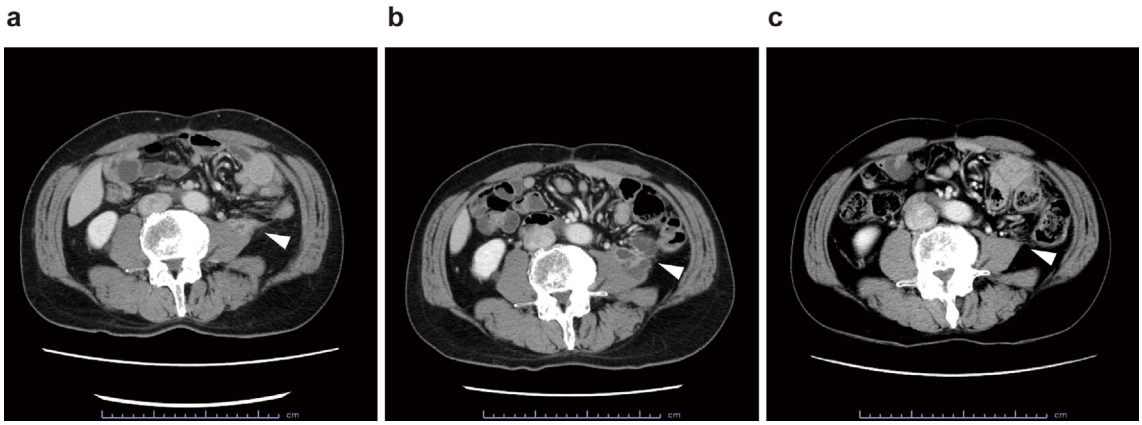

Figure 4. **Time course of changes in computed tomography during treatment. (a) A metastatic site was detected in the left iliopsoas muscle (arrowhead). (b) Three months (four cycles) after the administration of doxorubicin. (c) Eleven months (14 cycles) after the administration of eribulin.**

age of the relapsed site. We continued the eribulin treatment, and periodic evaluations with CT revealed that the relapsed site had gradually decreased in size. No new distant metastases appeared during eribulin treatment. Finally, the relapsed site disappeared after 14 cycles of eribulin treatment (Fig. 4c).

We continued the eribulin treatment without a dose reduction for 20 cycles in total. The patient has since maintained a CR without any serious adverse events. At the time of writing, eribulin treatment has been stopped for nearly 18 months with no recurrence.

Discussion

Eribulin is a synthetic analog of the marine natural product halichondrin B, which interferes with microtubule dynamics (10). It was first approved in the United States as a treatment for patients with metastatic breast cancer in 2010. It was also approved for the treatment of patients with unresectable liposarcoma who received prior chemotherapy containing anthracycline in 2016. This approval was based on a randomized phase III clinical trial demonstrating an advan-

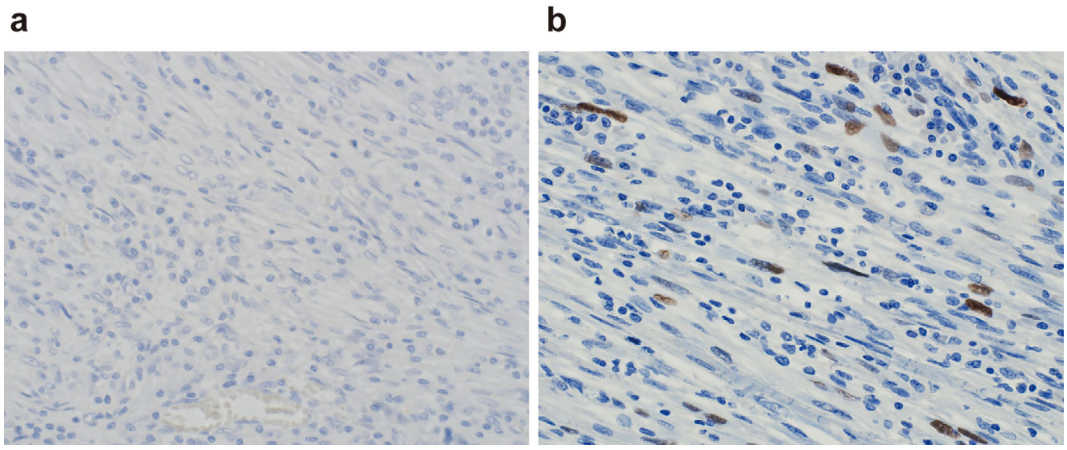

Figure 5. Pathological findings with immunohistochemical staining of phosphorylated AKT (p-AKT) and TP53. Immunostaining for (a) p-AKT (negative) and (b) TP53 (focal positive).

tage with regard to the OS for patients with liposarcoma or leiomyosarcoma treated with eribulin compared with those treated with dacarbazine as second-line therapy. However, the clinical outcomes with eribulin may not be sufficient to fully address the needs of patients with unresectable liposarcoma.

To our knowledge, this is the first report of a CR case of liposarcoma treated with eribulin. A few reports have described a good therapeutic effect being observed in patients with unresectable breast cancer treated with eribulin, but the underlying mechanism was not fully elucidated (11, 12). We previously revealed that increased phosphorylated AKT (p-AKT) in sarcoma tissue was associated with eribulin resistance in multiple subtypes of STS cells (13). In that study, we first established stable STS cell lines with resistance to eribulin and screened the phosphorylation status of a panel of kinases using a phospho-kinase array. Based on the findings, we focused on p-AKT and, using Western blotting, found that its protein expression was increased in STS cells with eribulin resistance compared to parental cells. Therefore, we evaluated the expression of p-AKT by immunohistochemistry in the case presented here.

As expected, the expression of p-AKT was not detected, which implies an association with a high sensitivity to eribulin (Fig. 5a). Furthermore, a high level of p-AKT was reportedly associated with a poor prognosis in STS (14). Based on these findings, we postulate that p-AKT is a potential predictive factor of eribulin sensitivity and the prognosis. In the future, we suggest that the level of p-AKT in tumor tissue be determined before the administration of eribulin. In addition, several molecular changes have been described, including *TP53* in leiomyosarcoma, which may have a potential impact on the survival of patients treated with eribulin (15). We also revealed the increased expression of TP53 with immunohistological staining in this case (Fig. 5b). An alteration in this gene might also have influenced the excellent clinical response of the patient.

In summary, several molecular alterations, including p-AKT, in STS might have been associated with the excellent sensitivity to eribulin in the present case. As a disease, STS appears heterogeneous and has a complex genetic background with multiple gene expression alterations and mutations (16). Further studies are needed in order to develop a molecular biological approach that improves the treatment outcome in patients with UM-STS.

The authors state that they have no Conflict of Interest (COI).

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