

# Proximal-type epithelioid sarcoma in pubic region expressing L-type amino acid transporter 1: A case report

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## Abstract

Proximal-type epithelioid sarcoma is an aggressive malignant soft-tissue neoplasm, a “proximal” variant of epithelioid sarcoma, resistant to multimodal therapy and involved in early tumor-related death. Pertinent treatments are, therefore, continually being explored. A 24-year-old woman with nonmetastatic proximal-type epithelioid sarcoma, originating subcutaneously on the right side of the vulva, underwent surgical resection; the lesion recurred, however, leading to death 3 months after the second surgery. Here described is a case of proximal-type epithelioid sarcoma expressing L-type amino acid transporter 1 (LAT1) that transports essential amino acids and *p*-borono-L-phenylalanine (BPA)—the chemical compound used in boron neutron capture therapy (BNCT)—and is highly expressed in many malignant tumors. Recently, LAT1 has drawn attention, and relevant treatments have been studied—LAT1 inhibitor and BNCT. LAT1 expression in proximal-type epithelioid sarcoma may lead to cogent treatments for the disease.

## Keywords

Epithelioid sarcoma, proximal-type, L-type amino acid transporter 1 (LAT1), CD98, LAT1 inhibitor, boron neutron capture therapy (BNCT), *p*-borono-L-phenylalanine (BPA)

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## Introduction

Epithelioid sarcoma (ES), a rare soft-tissue tumor described by Enzinger<sup>1</sup> evincing an incidence of 0.02 per 100,000 in Europe<sup>2</sup> is divided into two clinicopathological subtypes: classic ES (or distal type) and proximal ES (PES). The latter described as a variant of ES by Guillou et al.<sup>3</sup> is encountered in almost half of the classic ES.<sup>4</sup> PES is observed primarily at axial locations—pelvic or genital regions—in middle-aged or older patients. PES is more aggressive than classic ES, of poorer prognosis, with the 5-year overall survival (OS) rate being 57% versus 77% for the latter; it also has a tendency to distant metastasis.<sup>4</sup> A multi-institutional case series has shown a more moderate response to chemotherapy with anthracycline- and gemcitabine-based regimens than to pazopanib<sup>2</sup>; nevertheless, wide local resection is still the main treatment for primary localized ES.

Recently proposed are some new treatments involving L-type amino acid transporter 1 (LAT1),<sup>5</sup> that is, together with the heavy chain of cell surface antigen CD98, expressed on cell membranes of various malignant tumors. Because

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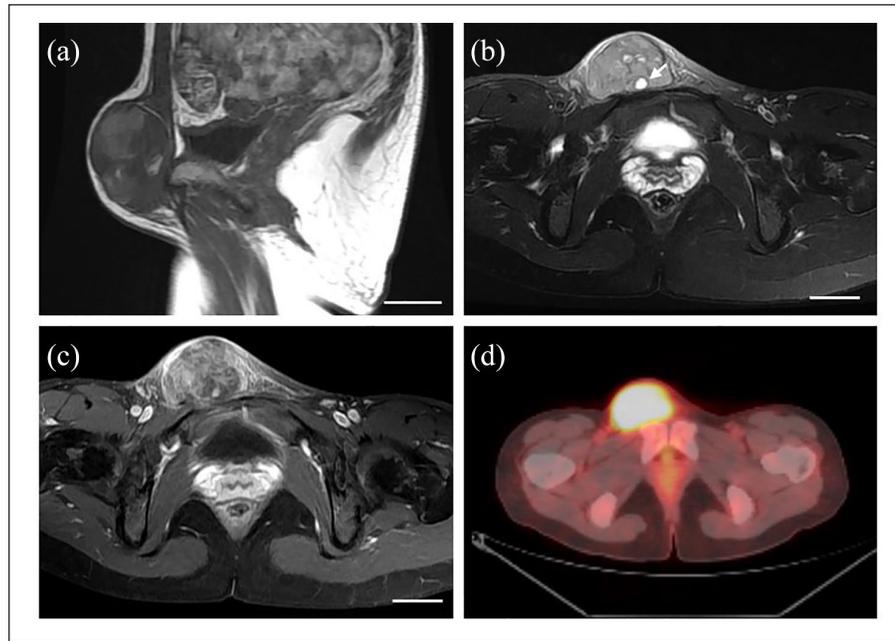
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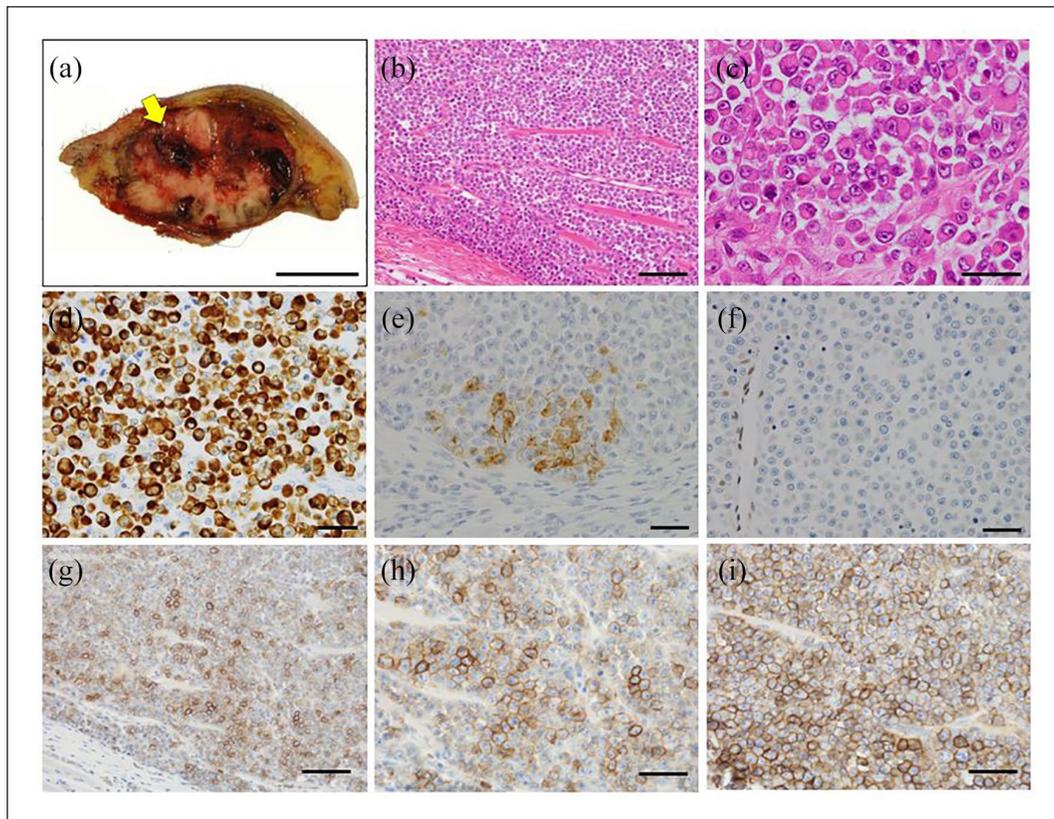
**Figure 1.** Imaging studies. (a) MRI on T1-weighted (T1W) sagittal image. (b) MRI on T2-weighted (T2W) fat suppression axial image with a blood spot (white arrow). (c) MRI on gadolinium-enhanced T1W fat suppression axial image. (d)  $^{18}\text{F}$ -FDG PET/CT. FDG uptake by the tumor ( $\text{SUV}_{\text{max}}$  7.8). Bars indicate 3 cm.

LAT1 promotes the transport of essential amino acids into tumor cells for their growth,<sup>6</sup> a LAT1 inhibitor is foreseen as a new therapeutic agent. LAT1 has also been involved in the incorporation of *p*-borono-L-phenylalanine (BPA), the chemical compound used in boron neutron capture therapy (BNCT).<sup>7</sup> BNCT is a method that induces a nuclear reaction between neutrons and boron atoms ( $^{10}\text{B}$ ) to selectively destroy cancer cells within tumors without impairing normal cells. Ascertaining whether or not LAT1 is expressed on tumor cell membranes is a prerequisite to determining the potency of these treatments. In the present study, the expression of LAT1 and CD98 was assessed by immunohistochemical analysis of surgical specimens from the trunk of a 24-year-old woman with PES. Approval for the study was obtained from the Hyogo Cancer Center Internal Review Board. Discussed in this study is a case of PES expressing LAT1 and the potentiality of new relevant treatments.

### Case report

A 24-year-old woman with a rapidly growing painful mass recognized in her right genital region was referred to our hospital. The tumor was a well-defined solid mass firmly adhering to the fascia with no inflammation, originating subcutaneously to the right of the vulva. Magnetic resonance imaging (MRI) demonstrated a well-circumscribed  $5.3 \times 3.5 \times 6.3$  cm lobulated, subcutaneous soft-tissue tumor, displaying low signal intensity on a T1-weighted (T1W) sagittal image (Figure 1a), a high signal intensity on

a T2W fat suppression axial image and a blood spot (Figure 1b). A gadolinium-enhanced T1W fat suppression axial image disclosed a heterogeneously enhanced tumor (Figure 1c).  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) showed the highest uptake of FDG by the tumor mass—the maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) of 7.8 (Figure 1d)—but no metastasis was observed. The diagnosis of PES was reached by histological examination of needle biopsy specimens. Since the tumor was a nonmetastatic, well-defined and resectable subcutaneous solid mass, the patient first underwent wide local excision of the primary tumor. Macroscopically, the resected mass revealed a well-defined, grayish-white lobulated solid tumor, with bleeding inside the mass, adhering to the fascia in the subcutaneous space (Figure 2a). Microscopically, the tumor was composed predominantly of round epithelioid cells, including cells with rhabdoid features, but no necrotic area (HE staining; Figure 2b, c). Immunohistochemical analysis revealed tumor cells positive for cytokeratin (Figure 2d), EMA (Figure 2e) and CD34, but lacking expression of integrase interactor 1 (INI1), also known as SMARCB1 (Figure 2f). Furthermore, both LAT1 and CD98 were subjected to immunohistochemical analyses, as described.<sup>8</sup> Both LAT1 (Figure 2g, h) and CD 98 (Figure 2i) were diffusely and strongly expressed on tumor cell membranes. Although a second local, wide excision was carried out 3 months after the first surgery and post-operative radiation therapy was administered to forestall local recurrence, metastasis ensued with several lesions spreading



**Figure 2.** Histopathology of the tumor. (a) Macroscopic image of the resected tumor. Scale bar, 3 cm. The yellow arrow shows a blood spot within the tumor. (b) HE staining. Diffuse proliferation of epithelioid tumor cells. Scale bar, 100  $\mu$ m. (c) HE staining. Many tumor cells show rhabdoid features. Scale bar, 40  $\mu$ m. Immunohistochemical images show tumor cells positive for cytokeratin (d) and EMA (e), but negative for INI1 (f) (INI1 is retained in nuclei of endothelial cells). Scale bar, 40  $\mu$ m. (g) Diffuse expression of LAT1 in tumor cells. Scale bar, 100  $\mu$ m. Both LAT1 (h) and CD98 (i) are observed on only tumor cell membranes. Scale bar, 50  $\mu$ m.

subcutaneously in the vicinity of the abdominal wall and around the surgical wound. The patient declined further treatment and died 3 months after the second surgery.

## Discussion

PES has been identified as an aggressive subtype of ES; both are of aggressive clinical behavior and distinct pathological characteristics. PES, resistant to multimodal therapy, is marked by early tumor-related death.<sup>3,9</sup> Tumors of the variant develop mainly in the pelvis, perineum and genital tract, are deep-seated and tend to occur in older adults than does classic ES. Even for patients with localized PES and demonstrating a low survival rate due to a high tendency toward metastatic spread,<sup>4</sup> the main treatment is still wide surgical resection. Therefore, new treatment methods are required.

Microscopically, PES, which often grows in a multinodular pattern, comprises large epithelioid carcinoma-like cells with marked cytological atypia, vesicular nuclei and prominent nucleoli. As in our present case, rhabdoid features are also frequently observed (Figure 2c), and loss of INI1 function (Figure 2f) is the most common alteration found in both

types of ES.<sup>10</sup> Our diagnosis of PES was reached based on those criteria.

A retrospective study of a multi-institutional case series has postulated that with a moderate effect of cytotoxic chemotherapy, the objective response is 22% with anthracycline-based and 27% with gemcitabine-based therapy for advanced ES.<sup>2</sup> Recently, tazemetostat, a selective EZH2 inhibitor developed from the fact that loss of INI1 function in ES induces oncogenic dependence on transcriptional repressor EZH2, has provided a 25% objective response as a first-line treatment with few serious side effects.<sup>11</sup> Thus, the search for and development of new therapeutic agents are still ongoing.

Other INI-1 deficient vulvar tumors, such as myoepithelial carcinoma,<sup>12</sup> myoepithelioma-like tumors<sup>13</sup> and yolk sac tumors<sup>14</sup> can also be targets for the EZH2 inhibitor. Notably, the association between LAT1 and EZH2 has been described through a study, using lung cancer cell lines, demonstrating that the expression of LAT1 is regulated by EZH2.<sup>15</sup> Therefore, LAT1 expression in these INI-1 deficient vulvar tumors requires further study.

LAT1, generally not detected in normal tissues, is expressed in numerous cancer cells,<sup>16</sup> and observed in several sarcomas.<sup>17</sup> Several studies have described the therapeutic

potential of LAT1 expression in tumor cells: endothelial LAT1 has been described as a novel key player in tumor angiogenesis in human pancreatic ductal adenocarcinoma that is responsive to few treatment methods; also, the therapeutic inhibition of LAT1 has been suggested as an ideal option to potentiate antiangiogenic therapies.<sup>18</sup> LAT1 has been shown as involved in the development of bladder cancer, a common disease worldwide, which could be receptive to new treatments with LAT1 inhibitors.<sup>19</sup> Analysis of cancer cell proteomes and phosphoproteomes with the use of biliary tract cancer cell lines has induced LAT1 obstruction by LAT1 inhibitors suggesting that the antitumor effect of the combined use of LAT1 inhibitors and cell cycle-related kinase inhibitors could signify new cancer treatments.<sup>20</sup> As a method very similar to BNCT, targeted  $\alpha$ -therapy (TAT) combined with a LAT1 inhibitor has selectively destroyed tumor cells by delivering  $\alpha$ -emitters with high linear energy transfer (LET)  $\alpha$ -particles to tumors while sparing damage to surrounding tissues.<sup>21</sup> Based on the above studies, assessment of LAT1 expression in tumor tissues is essential for the implementation of new potentially effective cancer treatments.

Immunohistochemical analysis has demonstrated diffuse expression of LAT1 in four cases of ES, as in our clinical case, without precise data on the subtypes of ES.<sup>17</sup> Although the subtype of ES is nonspecific, the above observations suggest that the expression of LAT1 in ES reflects a feature of ES. On the other hand, whereas our PES case showed strong and diffuse expression of CD98, the four cases<sup>17</sup> showed weak expression of CD98. It is unclear whether this high expression of both LAT1 and CD98 in PES is specific to PES or related to BPA uptake. Further study in this regard is warranted. Thus, in the present case, the expression of LAT1 in PES, disclosed for the first time by immunohistochemical analysis, was involved in intracellular uptake of both essential amino acids required for cell proliferation and BPA required for BNCT. Therefore, LAT1 expression in PES becomes highly significant when contemplating new therapies. Indeed, a LAT1-selective inhibitor has provided promising outcomes against biliary tract cancer in a phase I clinical trial comprising patients with advanced solid tumors.<sup>22</sup> On the other hand, the propitious outcome of BNCT with the use of BPA has been demonstrated in not only cancers but also sarcoma.<sup>23</sup> Indeed, a clinical case of clear cell sarcoma that responds to no effective treatment other than surgical excision, but displayed strong LAT1 expression, was locally and completely controlled by BNCT.<sup>8</sup> These data suggest that the potency of the LAT1 inhibitor and the efficacy of BNCT show potential as new treatments for patients with PES. LAT1 expression requires further study aimed at its implementation into these new treatments.

Tumor cells can escape from the immune response by ligation of programmed cell death protein 1 (PD-1) with PD-1 ligand 1 (PD-L1) that activates an immune checkpoint

leading to T cell dysfunction. Recently, immunotherapy with the use of immune checkpoint inhibitors has been shown in clinical trials as significantly effective in various types of cancer.<sup>24</sup> Conversely, sarcomas have not seen the same benefits from immunotherapy as seen in other malignancies.<sup>25</sup> Of three cases of ES, however, the therapeutic effect of the PD-L1 antibody on metastatic and unresectable sarcoma has been demonstrated in one ES that displayed a partial response.<sup>26</sup> Also, a case of ES, which did not respond to conventional chemotherapy and an EZH2 inhibitor, responded completely to a combination of immune checkpoint inhibitors.<sup>27</sup> The development of new treatment methods for ES is currently progressing rapidly; therefore, further study on relevant treatment strategies is warranted.

To date, the main treatment method for primary PES has been total surgical resection; in recent years, however, treatment methods with the use of EZH2 inhibitors and immunotherapy have also been proposed. Here, furthermore, we described a case of PES expressing LAT1; this expression is of clinical interest in that, as a target of both LAT1 inhibitors and BNCT, it may potentially be a key to new and effective therapies.

#### Author note

Toshihiro Akisue is now affiliated to Department of Rehabilitation Science, Kobe University Graduate School of Health Sciences, Kobe, Japan.

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#### Declaration of conflicting interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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#### Ethical approval

Ethical approval to report this case was obtained from the Hyogo Cancer Center Internal Review Board (Akashi, Japan; approval number G-190).

#### Informed consent

Written informed consent was obtained from the patient.

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