Acta Med. Okayama, 2021
Vol. 75, No. 4, pp. 533-538

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Tumor Lysis Syndrome due to Eribulin Administration for Metastatic Undifferentiated Pleomorphic Sarcoma of the Buttock

Hiroyuki Tsuchie*, Naohisa Miyakoshi, Hiroyuki Nagasawa, and Yoichi Shimada

Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita 010-8543, Japan

Tumor lysis syndrome (TLS) is a complication of cancer treatment that requires urgent intervention. It is extremely rare in the treatment of soft tissue sarcoma (STS) of the limbs or trunk, and there are currently no reports of TLS occurrence from eribulin therapy. We report the case of a 78-year-old woman with an undifferentiated pleomorphic sarcoma on the right buttock. We initiated chemotherapy with intravenous eribulin mesylate. Deterioration of renal function, mild hyperkalemia, hyperuricemia, hypocalcemia, and hyperphosphatemia were confirmed on examination, suggesting the presence of TLS. We present an extremely rare case of TLS from eribulin for STS.

Key words: tumor lysis syndrome, eribulin, soft tissue sarcoma, cancer chemotherapy, metastasis

Tumor lysis syndrome (TLS) is a severe complication of cancer treatment that requires immediate and urgent intervention. It is extremely rare in the treatment of soft tissue sarcoma (STS). Presently, there are no reports of TLS in STS of the limbs or trunk as a result of the chemotherapeutic agent eribulin.

Herein, we describe the first case of TLS occurring during treatment of STS of the trunk with eribulin, along with a review of the available literature. The patient and her family were informed of our intent to submit the data from this case for publication, and gave their consent.

Case Presentation

A 78-year-old woman presented at our outpatient clinic due to a mass and mild pain in the right buttock that had persisted for three months. She had a history of breast cancer, which had been diagnosed 28 years ago, and a liver abscess one year ago, but no relapses. She had since been treated solely for hypertension and hypothyroidism. Physical examination revealed a hard firm lump in the right gluteal area. Magnetic resonance imaging (MRI) showed a large tumor (maximum diameter: 79 mm) spreading under the buttock and within the gluteus medius. This tumor showed an iso signal intensity on T1-weighted images (Fig. 1A) and a low-to-high intensity on T2-weighted images (Fig. 1B-C). Since we suspected STS, a needle biopsy was performed to sample the buttock tumor. Histopathologic examination revealed spindle-shaped mesenchymal cells showing nuclear swelling and irregularity. The increased chromatin in the nucleus showed dense proliferation and a storiform pattern (Fig. 2). Therefore, a diagnosis of undifferentiated pleomorphic sarcoma (UPS) was made.

Positron-emission tomography (PET)/computed tomography (CT) demonstrated ^{18}F-FDG uptake in the buttock tumor, along with uptake in the lymph nodes of the right groin and left neck areas (Fig. 3A-C). A needle biopsy was performed of the right groin, but not the left neck; histopathologic examination demonstrated

Received October 22, 2020; accepted February 19, 2021.
*Corresponding author. Phone: +81-18-884-6148; Fax: +81-18-836-2617
E-mail: tuchikiti@yahoo.co.jp (H. Tsuchie)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

pathological features similar to the tumor in the buttock, confirming the presence of UPS here as well. Therefore, the sarcoma was considered to be stage IV according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system [1].

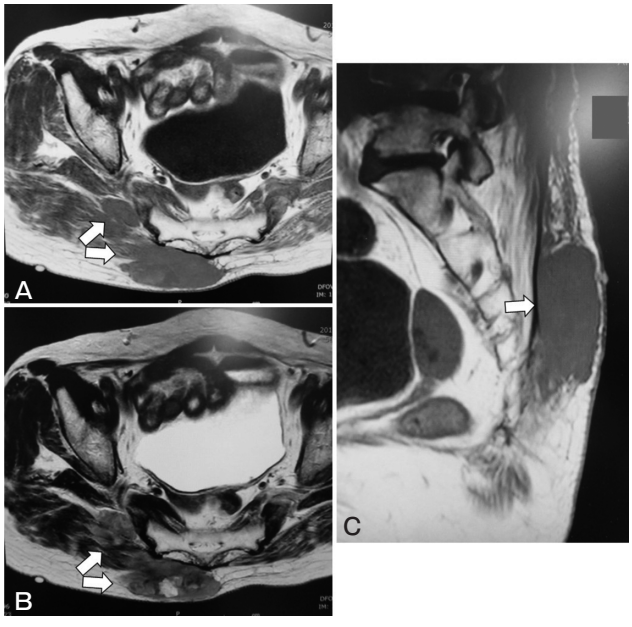

Fig. 1 Magnetic resonance imaging (MRI) with axial views of T1-weighted **(A)** and T2-weighted **(B)** images, and an axial view **(C)** of the buttock. The tumor revealed an iso signal intensity on T1-weighted images and a low-to-high intensity on T2-weighted images, as indicated by the white arrows.

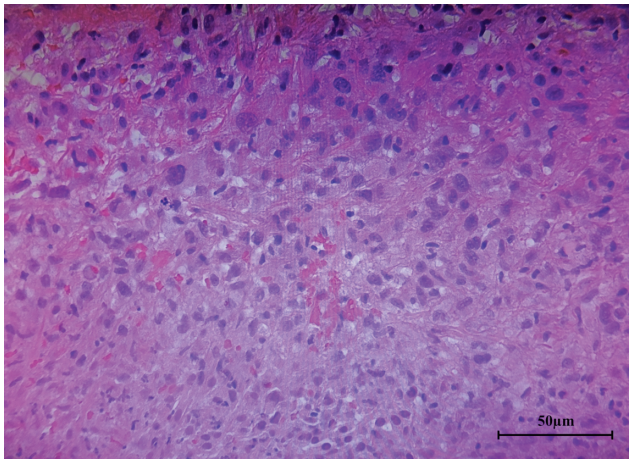

Fig. 2 Histopathological findings by a needle biopsy from the buttock tumor visualized with hematoxylin and eosin (H&E) staining (×400). Histopathologic examination demonstrated spindle-shaped mesenchymal cells showing nuclear swelling and irregularity, as well as increased chromatin in the nucleus with dense proliferation.

After 6 weeks of 60 Gy curative radiation therapy for the tumor of the buttock, we initiated chemotherapy with intravenous eribulin mesylate (Halaven®; Eisai, Tokyo) to control the exacerbation of the primary and metastatic lesions. Although this medicine is generally used at 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle, we administered 0.98 mg/m^2 on days 1 and 8 of a 28-day cycle due to the patient's advanced age. The CT at 2 months after the initial PET-CT scan, just before the start of eribulin administration, showed shrinkage of the tumor of the right buttock (maximum diameter: 69 mm), but revealed new metastatic lesions on the right inguinal lymph node and in the liver (Fig. 4A-B).

During the first course of chemotherapy, the laboratory examination on day 15 showed only a slight reduction in the white blood cell count, and no other abnormalities were found (Table 1). The white blood cells spontaneously recovered, and the second course was started

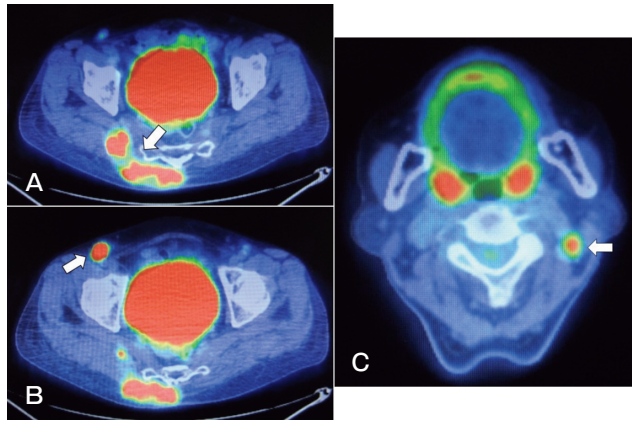

Fig. 3 Positron-emission tomography (PET)/computed tomography (CT) with axial views. PET-CT images showed ^{18}F-FDG uptake in the buttock tumor **(A)** as well as in the lymph nodes of the right groin **(B)** and left neck **(C)**, as indicated by the white arrows.

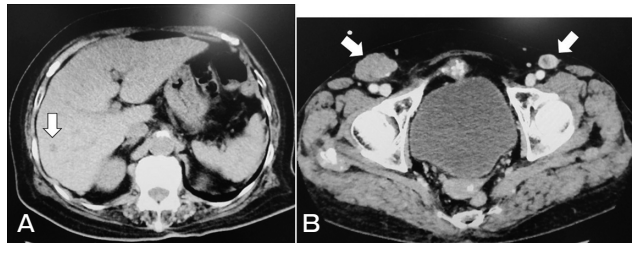

Fig. 4 Computed tomography (CT) with axial views of abdomen **(A)** and groin **(B)** at 2 months after the PET-CT scan. CT showed one small metastatic lesion in the liver (A) and swollen inguinal lymph nodes on both sides (B), as indicated by the white arrows.

Table 1 Timeline of laboratory findings during eribulin administration

Parameter	Normal range	First cycle		Second cycle					
		Day 1	Day 15	Day 1	Day 15	Day 19	Day 20	Day 21	Day 22
BUN (mg/dL)	8–20	18.8	15.8	15.9	11.0	37.8	62.7	47.4	40.7
CRE (mg/dL)	046–0.79	0.62	0.78	0.57	0.72	2.14	2.82	1.43	1.11
UA (mg/dL)	2.3–7.0	4.5	–	–	–	9.3	12.3	11.6	10.9
Ca (mg/dL)	8.8–10.1	9.1	9.6	9.2	9.7	9.5	8.5	7.7	7.9
IP (mg/dL)	2.7–4.6	3.1	–	–	–	–	6.0	3.2	2.9
Potassium (mmol/L)	3.6–4.8	3.6	3.5	3.8	3.7	4.9	4.6	3.6	4.0
LDH (U/L)	124–232	192	206	258	486	653	1250	1047	1140
AST (U/L)	13–30	19	25	26	67	124	500	231	242
ALT (U/L)	7–23	17	26	25	138	195	430	366	326
γ-GTP (U/L)	9–32	28	46	57	444	572	474	502	555
T-Bil (mg/dL)	0.4–1.5	0.6	0.8	0.7	–	2.6	2.6	3.5	4.4
WBC (μL)	3300–8600	4700	1900	6200	2800	8500	11000	15500	15600
CRP (mg/dL)	0.00–0.14	0.46	–	–	3.66	5.33	5.29	5.25	5.30

BUN, blood urea nitrogen; CRE, creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; Ca, calcium; IP, inorganic phosphate; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; T-Bil, total bilirubin; WBC, white blood cell; CRP, C-reactive protein.

as scheduled, according to the 28-day cycle. On day 16 of the second course, the patient experienced a loss of appetite and fatigue. After day 16, she could not eat at all, and she visited our hospital on day 19. Examination revealed that her renal function had deteriorated (blood urea nitrogen (BUN): 37.8 mg/dL; creatinine (CRE): 2.14 mg/dL), and she had mild hyperkalemia (potassium: 4.9 mmol/L). Deterioration of the liver function was also confirmed (aspartate aminotransferase (AST): 124 U/L; alanine aminotransferase (ALT): 195 U/L; γ-glutamyl transpeptidase: 572 U/L; and total bilirubin: 2.6 mg/dL). Her vitals were as follows: temperature of 36.5°C , heart rate of 81 beats per minute, blood pressure of 89/35 mmHg, and 97% oxygen saturation on room air.

She was admitted to the hospital and received volume resuscitation (3000 mL/day) and administration of furosemide for hypotension and prerenal acute kidney injury. Her blood pressure recovered to 133/70 mmHg on the day after admission, but her renal and liver function worsened (BUN: 62.7 mg/dL; CRE: 2.82 mg/dL; AST: 500 U/L; and ALT: 430 U/L). In addition, hyperuricemia (uric acid: 12.3 mg/dL), hypocalcemia (calcium: 8.5 mg/dL), and hyperphosphatemia (inorganic phosphate: 6.0 mg/dL) were observed. At this point, a CT showed more prominent swelling of the liver compared to the CT image taken two months previously, and multiple liver and spleen metastases were evident (Fig. 5). We consulted with a nephrologist who suggested a diagnosis of TLS due to the presence of hyperuricemia, hyperphosphatemia, hyperkalemia, and renal dysfunction. We also consulted with a liver physician who pointed out the exacerbation of liver function due to the destruction of metastatic liver lesions using anticancer drugs. Continuous intravenous hydration and furosemide administration to maintain urine output improved the renal function, hyperuricemia, and hyperphosphatemia, but the find-

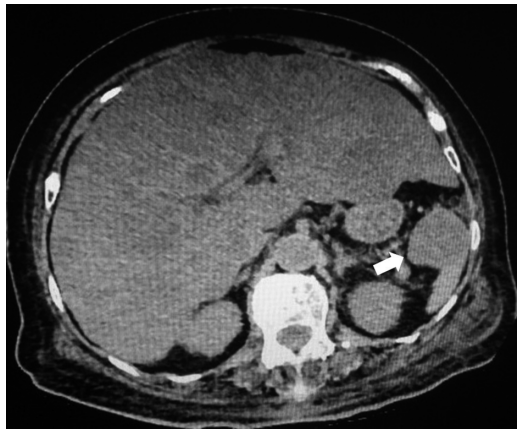

Fig. 5 Computed tomography (CT) with axial views of the abdomen on day 20 of the second cycle. CT showed more prominent swelling of the liver compared to the CT image taken two months previously, and multiple liver metastases and spleen metastases (arrow) were observed.

ings of cholestasis continued to worsen. Hypoxemia and consciousness disorder appeared gradually on day 22. Given the patient's poor prognosis overall, her family opted for palliative care with continuous intravenous injection of morphine and she passed away on day 23.

Discussion

TLS is an oncological emergency characterized by rapid and extensive destruction of tumor cells, and resulting in hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia [2]. TLS presents with symptoms such as nausea, anorexia, fatigue, and diarrhea, and in severe cases, it causes renal dysfunction, convulsion, and arrhythmia, which may lead to sudden death. Laboratory TLS (LTLS) is diagnosed when the laboratory examination values of 2 or more parameters, including serum levels of uric acid, phosphate, and potassium, are abnormal in patients undergoing chemotherapy [3]. In addition to LTLS, clinical TLS (CTLS) is diagnosed if there are clinical symptoms such as renal dysfunction, arrhythmia, and convulsions. In our case, hyperkalemia improved immediately with volume resuscitation; however, hyperuricemia and hyperphosphatemia persisted, indicating a diagnosis of LTLS. In addition, renal dysfunction was also present, suggesting a diagnosis of CTLS. According to a previous report, the six-month mortality rate in patients with TLS and an acute renal injury approaches 66%, and TLS is considered a medical emergency in such cases [4].

The treatment for TLS is a large volume infusion to maintain urine volume, and the use of diuretics such as furosemide, depending on the urine volume. In addition, uric acid production inhibitors such as allopurinol or febuxostat may be used, although they will have no immediate effect. In our case, TLS showed a gradual improvement with high volume infusion and diuretics. However, hepatic and biliary enzymes continued to rise. We believe that the rapid increase in liver and spleen metastases due to the weak effect of eribulin, combined with the effects of the partial necrosis of liver metastases, resulted in the patient's death.

TLS most commonly occurs in the initial therapy against rapidly proliferating hematological malignancies such as acute lymphoid leukemia and Burkitt's lymphoma. It is very rarely encountered in the treatment of solid tumors [5]. Among the solid tumors that do develop TLS, small cell cancer and hepatocellular carcinoma are relatively common, whereas sarcomas are distinctly uncommon. The risk factors for TLS development in solid tumors are as follows: large tumor burden; extensive metastases; high tumor cell proliferation rate; high sensitivity to anticancer therapy; and increased lactate dehydrogenase (LDH) levels [6,7]. In the present case, some of these risk factors, such as high proliferative ability due to rapid progression, multiple metastases, and a high level of LDH, may have affected the onset of TLS.

Only 10 cases of TLS have been reported in sarcoma (Table 2) [6-14]. Patients with a solid tumor usually develop TLS after intensive chemotherapy, which is known as treatment-induced TLS, but TLS can sometimes appear before the treatment, which is referred to as spontaneous TLS, especially in cases of bulky tumors with wide necrotic areas [13,14]. In our present case, because TLS occurred after eribulin administration, we considered that it was treatment-induced. However, the possibility of spontaneous TLS cannot be ruled out, since eribulin was not effective. In the past, 7 in 10 cases of sarcoma that developed TLS were treatment-induced [6-12]. In most of these cases, the primary tumor was located in the abdomen, including the retroperitoneal cavity, and most patients were at high risk for TLS because they had multiple metastases in the abdominal cavity, lymph nodes, and liver, and large tumor size [6-10,12]. On the other hand, only 1 of these cases was suspected of having STS [11]. This case was an alveolar rhabdomyosarcoma, which is a high-grade sarcoma, and the risk of TLS was considered high because the cancer had spread widely to the bone marrow and lymph nodes. In our case, multiple lymph node metastases and liver metastases occurred. In general, metastasis of STS occurs most often in the lung, and only rarely in the lymph nodes and liver [15-21]. This is considered to be one of the reasons for the rarity of reports of TLS in STS.

Eribulin is a structurally modified analog of halichondrin B, originally isolated from the marine sponge *Halichondria okadai*, and it works as a microtubule inhibitor. It exerts its antimitotic effects by inhibiting the formation of mitotic spindles, arresting the cell cycle at the G2/M phase [22]. It may be used for the treatment of advanced/metastatic breast cancer or certain metastatic/unresectable sarcomas. Hematological toxicity, including neutropenia and leukopenia, is a

Table 2 Literature review of clinical presentation and treatment of sarcoma with tumor lysis syndrome

Case	Author/year	Age	Sex	Location	Size (cm)	Histological diagnosis	Chemotherapy	Metastasis
1	Qian KQ. /2009 [6]	44	M	Retroperitoneal	21	Soft tissue sarcoma	Cisplatin, Adriamycin, Dacarbazine	None
2	Ahmed Z. /2019 [7]	71	M	Abdominal cavity	19	Undifferentiated endometrial stromal sarcoma	Paclitaxel, Carboplatin	Omentum, bowel, gastric, pancreas
3	Khan J. /1993 [8]	9	M	Abdominal cavity	N/A	Rhabdomyosarcoma	Carboplatin, Epirubicin, Vincristine	Lung
4	Gold JE. /1993 [9]	66	M	Stomach	N/A	Leiomyosarcoma	Cyclophosphamide, Autolymphocyte therapy	Liver
5	Hiraizumi Y. /2011 [10]	36	F	Abdominal cavity	N/A	Uterine epithelioid leiomyosarcoma	Vincristine, Actinomycin-D, Cyclophosphamide	Lung
6	Sanford E. /2016 [11]	8	M	Posterior to the L5 vertebral body	N/A	Alveolar rhabdomyosarcoma	Vincristine, Irinotecan	Bone marrow, lymph node
7	Pabon C. /2018 [12]	Middle-age	F	Uterus	12	Leiomyosarcoma	Eribulin	Liver, soft tissue, lymph node, lung
8	Bien E. /2010 [13]	14	M	Unknown	N/A	Ewing sarcoma	None	Lymph node, subcutaneous, peritoneum
9	Bien E. /2010 [13]	14	F	Parietal	N/A	Rhabdomyosarcoma	None	None
10	Catania VE. /2017 [14]	65	F	Abdominal cavity	N/A	Extraskeletal osteosarcoma	None	Lung
11	Present case	78	F	Buttock	7.9	Undifferentiated pleomorphic sarcoma	Eribulin	Lymph node, liver, spleen

frequent side effect that requires caution. In addition, side-effects such as liver dysfunction, gastrointestinal manifestations, and peripheral neuropathy have been reported [23]. Ours is only the second case of eribulin-induced TLS, and the first case of eribulin-induced TLS during treatment of STS of the limbs or trunk. The previous report of TLS caused by eribulin was a case of leiomyosarcoma of the uterus with lymph node and liver metastases [12]; similar to our present case, that patient also developed distant metastases. Since eribulin is metabolized in the liver, there is a risk of liver damage. Thus, it cannot be ruled out that our patient's existing liver metastases may have affected the breakdown of eribulin, resulting in dysfunction. Although eribulin was used at a reduced dose in our case, older age may have also affected the onset of TLS. When eribulin is used in patients with STS, caution is necessary, particularly in elderly patients with multiple metastases, including those in the liver and lymph nodes.

In conclusion, we have presented the first case of TLS from treatment with eribulin for STS of the trunk. Although TLS is very rare in STS, caution should be exercised when using eribulin in older people with multiple metastases.

References

1. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds): AJCC Cancer Staging Handbook, 8th ed. New York: Springer, 2017.
2. Cairo MS, Coiffier B, Reiter A and Younes A: TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol (2010) 149: 578–586.
3. Howard SC, Jones DP and Pui CH: The tumor lysis syndrome. N

Engl J Med (2011) 364: 1844–1854.
4. Darmon M, Guichard I, Vincent F, Schlemmer B and Azoulay E: Prognostic significance of acute renal injury in acute tumor lysis syndrome. Leuk Lymphoma (2010) 51: 221–227.
5. Vodopivec DM, Rubio JE, Fornoni A and Lenz O: An unusual presentation of tumor lysis syndrome in a patient with advanced gastric adenocarcinoma: case report and literature review. Case Rep Med (2012) 2012: 468452.
6. Qian KQ, Ye H, Xiao YW, Bao YY and Qi CJ: Tumor lysis syndrome associated with chemotherapy in primary retroperitoneal soft tissue sarcoma by ex vivo ATP-based tumor chemo-sensitivity assay (ATP-TCA). Int J Gen Med (2009) 2: 1–4.
7. Ahmed Z, Barefah A, Wasi P, Jones G and Ramsay J: Tumour lysis syndrome in a patient with undifferentiated endometrial stromal sarcoma. Gynecol Oncol Rep (2019) 28: 41–43.
8. Khan J and Broadbent VA: Tumor lysis syndrome complicating treatment of widespread metastatic abdominal rhabdomyosarcoma. Pediatr Hematol Oncol (1993) 10: 151–155.
9. Gold JE, Malamud SC, LaRosa F and Osband ME: Adoptive chemoimmunotherapy using ex vivo activated memory T-cells and cyclophosphamide: tumor lysis syndrome of a metastatic soft tissue sarcoma. Am J Hematol (1993) 44: 42–47.
10. Hiraizumi Y, Kamoi S, Inde Y, Kurose K, Ohaki Y and Takeshita T: A case of tumor lysis syndrome following chemotherapy for a uterine epithelioid leiomyosarcoma with focal rhabdomyosarcomatous differentiation. J Obstet Gynaecol Res (2011) 37: 947–952.
11. Sanford E, Wolbrink T, Mack J and Rowe RG: Severe Tumor Lysis Syndrome and Acute Pulmonary Edema Requiring Extracorporeal Membrane Oxygenation Following Initiation of Chemotherapy for Metastatic Alveolar Rhabdomyosarcoma. Pediatr Blood Cancer (2016) 63: 928–930.
12. Pabon C, Esnakula AK and Daily K: Tumour lysis syndrome following eribulin for metastatic uterine leiomyosarcoma. BMJ Case Rep (2018) 11: e224576.
13. Bien E, Maciejka-Kapuscinska L, Niedzwiecki M, Niedzwiecki M, Stefanowicz J, Szolkiewicz A, Krawczyk M, Maldyk J, Izycka-Swieszewska E, Tokarska B and Balcerska A: Childhood rhabdomyosarcoma metastatic to bone marrow presenting with disseminated intravascular coagulation and acute tumour lysis syndrome: review of the literature apropos of two cases. Clin Exp Metastasis (2010) 27: 399–407.
14. Catania VE, Vecchio M, Malaguarnera M, Madeddu R, Malaguarnera G and Latteri S: Tumor lysis syndrome in an extraskeletal osteosarcoma: a case report and review of the literature. J Med Case Rep (2017) 11: 79.
15. Riad S, Griffin AM, Liberman B, Blackstein M, Catton C, Kandel RA, O'Sullivan B, White LM, Bell RS, Ferguson PC and Wunder JS: Lymph node metastasis in soft tissue sarcoma in an extremity. Clin Orthop Relat Res (2004) 426: 129–134.
16. Behranwala KA, A'Hern R, Omar AM and Thomas JM: Prognosis of lymph node metastasis in soft tissue sarcoma. Ann Surg Oncol (2004) 11: 714–719.
17. Fong Y, Coit DG, Woodruff JM and Brennan MF: Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg (1993) 217: 72-77.
18. Billingsley KG, Lewis JJ, Leung DH, Casper ES, Woodruff JM and Brennan MF: Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer (1999) 85: 389–395.
19. Nakamura T, Matsumine A, Matsubara T, Asamuma K, Niimi R, Uchida A and Sudo A: Retrospective analysis of metastatic sarcoma patients. Oncol Lett (2011) 2: 315–318.
20. Kane JM, Finley JW, Driscoll D, Kraybill WG and Gibbs JF: The treatment and outcome of patients with soft tissue sarcomas and synchronous metastases. Sarcoma (2002) 6: 69–73.
21. Vezeridis MP, Moore R and Karakousis CP: Metastatic patterns in soft-tissue sarcomas. Arch Surg (1983) 118: 915–918.
22. Setola E, Noujaim J, Benson C, Chawla S, Palmerini E and Jones RL: Eribulin in advanced liposarcoma and leiomyosarcoma. Expert Rev Anticancer Ther (2017) 17: 717–723.
23. Kobayashi E, Naito Y, Asano N, Maejima A, Endo M, Takahashi S, Megumi Y and Kawai A: Interim results of a real-world observational study of eribulin in soft tissue sarcoma including rare subtypes. Jpn J Clin Oncol (2019) 49: 938–946.