Skin and soft tissue disorders caused by trabectedin extravasation: A case report

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Abstract. Trabectedin extravasation can cause significant soft tissue disorders. Early surgical intervention has been recommended in the event of chemotherapeutic extravasation; however, treatment tends to remain conservative. Trabectedin is a vesicant drug that is associated with a risk of delayed tissue damage; therefore, leaks should be promptly stopped. Complications associated with central venous (CV) ports include infection, catheter damage and obstruction, which can lead to trabectedin extravasation. In the present case report, a 61-year-old woman who received trabectedin treatment for multiple liver and lung metastases is described. Extravasation developed from a CV port in the right chest during the third course of treatment and swelling was the only apparent symptom at that time. Trabectedin was immediately discontinued and she was administered steroids subcutaneously. Erythema, induration and tenderness appeared on day 1 after extravasation, but skin symptoms were not subsequently exacerbated. The central region of the erythema became crusted ~1 month after extravasation. When the skin condition had settled at 2 months post-extravasation, the patient underwent port removal, debridement and port reattachment.

Introduction

Soft tissue sarcomas (STS) are rare tumors that account for <1% of cancers in adults. Leiomyosarcoma (LMS) accounts for 10-20% of STS, is associated with a poor prognosis, a high tendency toward distant recurrence, and decreased disease-free survival rates (1). Systemic chemotherapy is considered for advanced STS. Doxorubicin either alone or combined with ifosfamide has served as first-line chemotherapy. However, newer drugs such as trabectedin, pazopanib and eribulin have proven effective against advanced STS including LMS after the failure of first-line anthracycline-based chemotherapy (2).

Trabectedin was tolerated well in clinical trials (3). The most prevalent grade 3/4 adverse events were neutropenia (37%) and elevated serum aspartate transaminase/alanine transaminase levels (13 and 26%, respectively) followed by elevated creatine phosphokinase (5.3%) and rhabdomyolysis (1.2%). The incidence of death caused by drug-related adverse events was low (2.1%). Trabectedin extravasation has been reported to cause serious soft tissue damage (4-7). A characteristic feature of trabectedin extravasation is the paucity of associated symptoms such as pain, swelling and redness during and immediately after extravasation. Therefore, patients and medical staff often overlook the early stages of extravasation; hence, detection and treatment may be delayed, which exacerbates soft tissue damage. Delayed skin and soft tissue disorders can take days to weeks to develop after trabectedin extravasation.

In the present case report, a patient who developed skin and soft tissue disorders due to trabectedin extravasation is presented. The Institutional Review Board at Mie University Graduate School of Medicine waived the need for written informed consent owing to the nature of the study. The patient provided written informed consent to the collection of her data and associated images for research purposes and the publication of the present case report.

Case report

A 61-year-old woman was diagnosed with retroperitoneal LMS that was resected at another hospital. Lung metastasis developed one year later and she was referred to Mie University Hospital for further treatment on January 2020. An indwelling central venous (CV) port was deployed into the left subclavian vein and the patient underwent seven courses of chemotherapy using doxorubicin. Thereafter, eribulin was administered as second-line chemotherapy. However, this failed and was replaced with trabectedin. Trabectedin was continuously infused intravenously (i.v.) into the CV port for 5 h. A total of 5 h after trabectedin administration, the i.v. infusion device alarm indicated a leak from the CV port at the right chest wall. Skin symptoms other than swelling were not evident at that time; however, trabectedin

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Table I. The course of events after extravasation of TRB.

1st day of TRB administration	Patient report TRB leakage after 5 h administration. → Discontinue administration immediately. Local injection of steroids at the leakage area. (Solcoteph™ 100 mg + Lidocaine 5 ml)
Post leakage	
Day 1	Topical steroids applied to the leakage area.
Day 2	Only mild redness at the CV port area, no pain, discharged from hospital.
Day 5	Expansion of the erythematous area and tenderness appear. Thereafter, the disease milder. (Painkillers and antimicrobials were not used.)
Day 62	Skin symptoms have settled and surgery is performed. CV port removed and leak area debridement performed. A new CV port was constructed in the left chest wall.
Day 66	TRB administered from new CV port.
Day 70	Discharged without problems in the post-operative course.

TRB, trabectedin; CV, central venous.

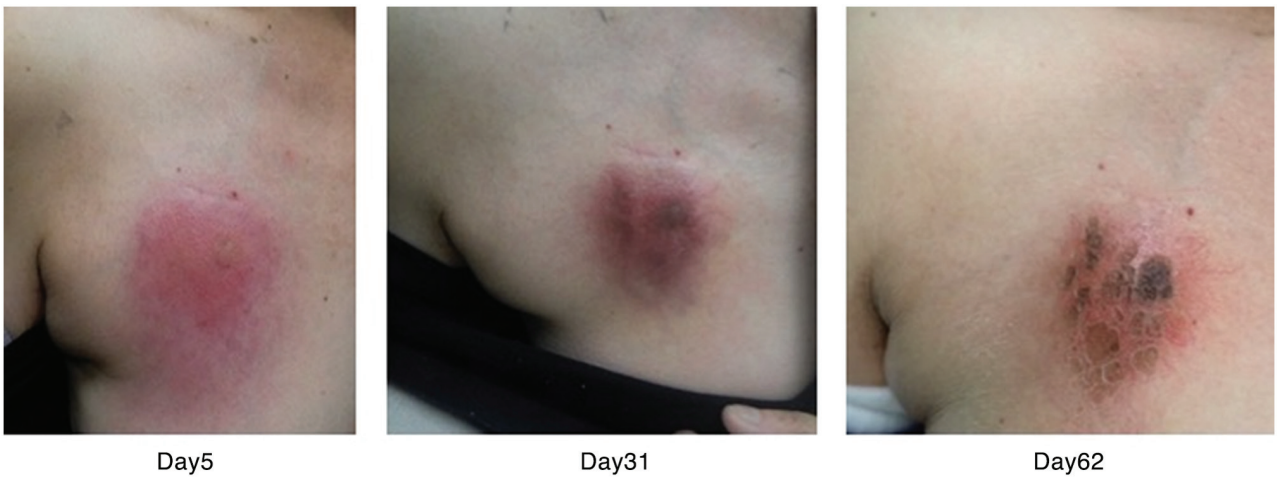

Figure 1. Macroscopic findings after trabectedin extravasation. Day 5 (left), day 31 (middle), and day 62 (right).

was immediately discontinued and a steroid hydrocortisone sodium succinate (100 mg) was injected subcutaneously (s.c.) around the CV port. Topical clobetasol propionate was started on day 1 after the leak was recognized, as erythema, induration and tenderness were observed. Although skin symptoms were not exacerbated, the erythematous area expanded by day 5 after the leak was determined. A total of 1 month after extravasation, the central region of the erythematous area had become crusted. As the skin condition had subsided, the CV port was removed and necrotic soft tissue was debrided 62 days after extravasation (Fig. 1; Table I). Soft tissue flap and skin graft were not necessary. The CV port and catheter that were removed were not damaged.

Necrotic changes of soft tissue were not grossly visible in the subcutaneous tissue on the surface of the resected area (Fig. 2), but microscopic necrotic changes were evident in the subcutaneous tissue around the insertion site of the port. These consisted of extensive subcutaneous fat necrosis with some fibrosis and fibrin deposition. The presence of a small amount of foam cells indicated mild inflammatory cell infiltration (Fig. 3). Trabectedin was continued from a new indwelling CV port positioned at left chest wall. The patient succumbed to sarcoma 21 months after trabectedin administration.

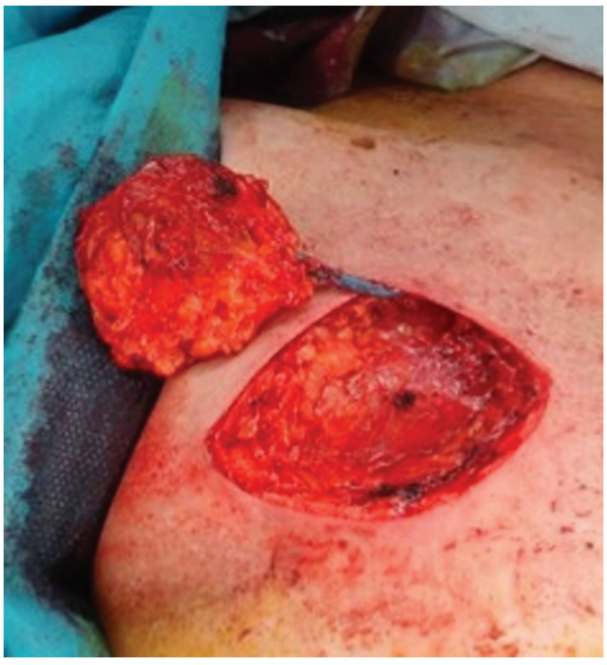

Figure 2. Intraoperative gross findings. No visible necrotic changes were observed in the soft subcutaneous tissue on resected surface.

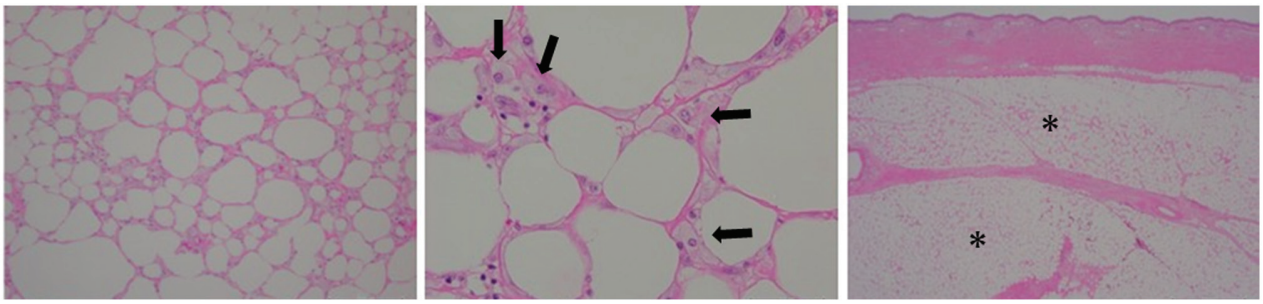

Figure 3. Histological analysis of lesion stained with hematoxylin-eosin. Left and middle panel show fat necrosis and foam cell infiltration (black arrow). Inflammatory cell infiltrates other than foam cells are scarce. Right panel shows extensive necrosis of subcutaneous fat (*) and poor inflammatory cell infiltration.

Discussion

The classification of cytotoxic with regard to their subcutaneous toxicity was classified into three categories (6): first, non-vesicant substances which do not cause local irritations; second, irritant substances which can cause local pain, swelling and local irritations but do not result in necrosis; and third, vesicant substances including trabectedin (8), which may induce ulcerations and necrosis. Extravasations of vesicants may result in scar formation and damage of skin and soft tissue requiring surgical interventions. Severe skin and soft tissue disorders are associated with trabectedin extravasation (4-7), the initial characteristic of which is scant subjective symptoms. Trabectedin should be immediately discontinued if extravasation is suspected. Ward staff and patients should be informed to prevent and detect extravasation as early as possible to minimize the occurrence of skin and soft tissue disorders. Trabectedin is administered *via* a central vein often with an indwelling CV port. Most trabectedin leaks are caused by issues with the CV port and puncture, or by the catheter. Although the cause of the leak in our patient was not evident, septal deterioration may have been involved. Issues with the puncture site of the CV port include a puncture needle that is short, bent, anatomically unsuitable, or a needle that floats owing to swelling after CV port deployment. Puncture site fixation problems include dislodged needles due to patient movement, including those while asleep. Catheter problems include deterioration, a bent route, breakage (0.3-2.9%) and occlusion due to thrombus such as a fibrin sheath (0.6-1.7%) (1,9-12).

The clinical course after extravasation is difficult to predict and is dependent on several factors such as the amount of extravasated drug, the cytotoxic in the affected tissue and vesicant potential of the drug (6). Previous studies recommend early surgical intervention after trabectedin extravasation; however, treatment tends to be conservative (13,14). Trabectedin is a vesicant drug (8) and it has been suggested that leaks should be promptly dealt with owing to risk of delayed tissue disorders (15). Trabectedin extravasation caused tissue disorders in 4 (0.4%) of 950 patients in a clinical trial using CV administration (16). Verboom *et al* (17) reported CV access-related adverse events after trabectedin infusion in 127 patients with STS. The most frequently adverse events at the venous access devices site were erythema (30.7%), pain (28.3%), inflammation (11.8%) and thrombosis (11.0%). Of 127 patients, extravasation developed in one (0.8%). Therefore, trabectedin extravasation may be uncommon. However, skin disorders have developed owing to trabectedin extravasation after debridement and skin grafting (4). After extravasation, trabectedin was immediately discontinued and topical and s.c. injected steroids were started on the following day. It is presumed that early discontinuation of trabectedin and additional treatment prevented extensive skin disorders requiring a skin graft or flap. After the skin symptoms at the extravasation site had subsided, the CV port was removed and the skin was debrided. Pathological assessment identified extensive necrosis at the site of the trabectedin extravasation. Yoshimi *et al* (18) reported pathological findings of necrosis without inflammatory cell infiltration, which was consistent with our patient. Haslik *et al* (5) reported that a pathological characteristic of trabectedin extravasation is necrosis with various degrees of cellular infiltration similar to those of other cytotoxic vesicants. It is difficult to determine whether a skin lesion is due to infection around CV port or trabectedin extravasation. Pathological findings of cell necrosis facilitate differentiation between infection and extravasation. Nonetheless, early biopsy of erythema far from the site of an implanted CV port site is recommended as surgery and ulcers can induce cell infiltration. In conclusion, a trabectedin leak was promptly observed and treatment was promptly implemented to protect soft tissue. However, our patient underwent additional treatment as using the same CV port after extravasation would possibly impose further extravasations and infection. Patients and medical staff should be continuously educated about the risk of symptom-free trabectedin extravasation to ensure a rapid response.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TN, TH and KA treated the patient and provided follow-up care. YM and TN drafted the manuscript. YM, TN, HY and MH prepared the figures and table, and confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Institutional Review Board at Mie University Graduate School of Medicine waived the need for written informed consent owing to the nature of the study.

Patient consent for publication

The patient provided written informed consent for publication of her data and associated images.

Competing interests

The authors declare that they have no competing interests.

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