

[CASE REPORT]

Skin Necrosis Due to the Extravasation of Irritant Anticancer Agents

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Abstract:

A 70-year-old man with malignant lymphoma was subjected to a fourth course of chemotherapy using gemcitabine and cisplatin. During the intravenous infusion of anticancer agents, pain and redness was observed at the site of insertion. The patient was subsequently treated with the strongest topical steroids and topical cooling agents. However, 2 weeks later, the affected area turned yellow, and the histopathological findings revealed skin necrosis of the entire dermis layer. It took two and a half months to cure the lesion. Close attention should be paid to the development of skin necrosis even when irritant anticancer agents such as gemcitabine and cisplatin are administered.

Key words: skin necrosis, extravasation, anticancer agent, gemcitabine, cisplatin

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Introduction

An extravasation of an anticancer agent consists of a leakage (extravasation) of an intravenously-administered anticancer agent outside the blood vessel, or the infiltration of the extravascular space by the drug; and the surrounding tissues. It causes various symptoms, such as reddening, swelling, pain, a burning sensation, erosion, bullous formation, ulceration, and necrosis (1). The severity of tissue injury may vary depending on the type of anticancer agent, which can be classified as vesicants, irritants, and non-vesicants (2). Irritant anticancer agents may cause transient inflammation with swelling, redness, and pain at the site of extravasation, but rarely cause skin necrosis. We herein we report our experience with a case of skin necrosis due to the extravasation of two irritant anticancer agents, gemcitabine and cisplatin.

Case Report

The patient was a 70-year-old man. An area of pain and redness measuring 5×4 cm in size was found in the medial part of his left forearm, where he had received an intravenous infusion of anticancer agents. The patient was therefore

referred to the dermatology department of the hospital (Fig. 1). Seven years prior to his admission, the patient had been diagnosed with malignant lymphoma (diffuse large B-cell lymphoma). Since then, he had received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and cyclophosphamide, pirarubicin, vincristine, and prednisone (THP-COP) therapy; however, half-a-year before his admission, gemcitabine, dexamethasone, and cisplatin (GDP) therapy (3) (a combination chemotherapy that includes gemcitabine, dexamethasone and cisplatin) had been initiated. He had no particular medical or family history. When the patient was on his fourth course of chemotherapy, an intravenous line was established in the medial side of the forearm and was secured with an indwelling 22 G intravenous cannula. Intravenous infusions were performed continuously in the following order: dexamethasone (40 mg diluted in 100 mL 0.9% saline) was administered for 30 minutes, followed by gemcitabine hydrochloride (1,500 mg diluted in 250 mL 5% glucose) for 2 hours, and then cisplatin (110 mg diluted in 500 mL 0.9% saline) for 6 hours. As a premedication, palonosetron was injected intravenously as an antiemetic 30 minutes before the start of chemotherapy.

After the infusion of cisplatin was complete, an intrave-

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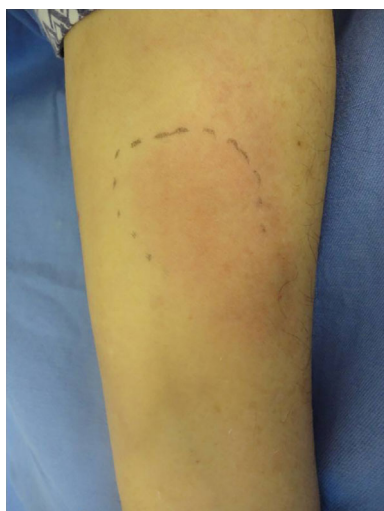


Figure 1. One day after the extravasation of the intravenous infusion. Erythema with tenderness was observed.



Figure 2. Two weeks after the extravasation of the intravenous infusion. The center of the lesion was observed to have turned yellow.

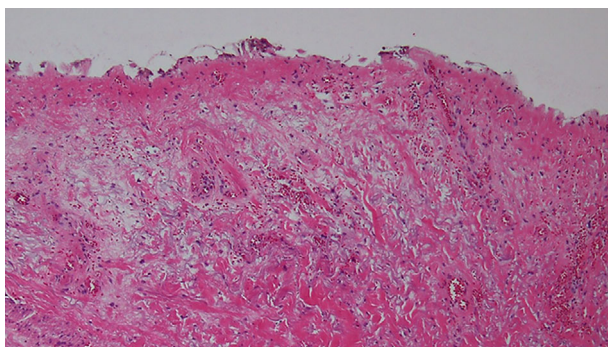


Figure 3. The histopathological findings (Hematoxylin and Eosin staining). Necrosis of the entire dermis layer was observed.



Figure 4. One month after the extravasation of the intravenous infusion. Leukonecrosis with disintegration was observed.

nous infusion of normal saline solution was attempted but failed, and redness and tenderness were found proximal to the site at which the indwelling intravenous cannula had been inserted. The needle was therefore removed, and was replaced with a peripheral venous line on the right forearm. Localized cooling and the application of a clobetasol topical ointment were carried out, and the patient was examined by dermatologists the next day. After consulting the dermatology department, the topical preparation continued to be administered; however, 2 weeks later, the lesion turned yellow (Fig. 2), and a histopathological examination of samples obtained from the center of the lesion showed that necrosis had developed in the whole dermis layer (Fig. 3). There was no further expansion of the extent of the necrosis (Fig. 4), and the lesion was eventually cured with conservative treatment at approximately two and a half months after the patient's first visit (Fig. 5).

Discussion

Malignant neoplasms are among the leading causes of death in the Japanese population; and in recent years, an increasing number of patients have been receiving cancer chemotherapy in the outpatient setting. Health professionals are required to provide safe and comfortable chemotherapy. Among the adverse events that are likely to occur during the administration of an anticancer agent, the one that should absolutely be avoided is the extravasation of the drug solution.

The GDP regimen is an effective salvage therapy for relapsed or refractory malignant lymphoma. Gemcitabine is an antipyrimidine that inhibits DNA synthesis and suppresses the growth of cancer cells. It is widely used in the treatment of malignant lymphoma and other types of cancers, including non-small-cell lung cancer, urothelial carcinoma, pancre-



Figure 5. Two and a half months later. The lesion was cured, with scar formation.

atic cancer, biliary tract cancer, and bladder cancer.

An administration time of 60 minutes or longer is associated with an incidence of myelosuppression and impairment of the liver function; thus, as a precaution, it is recommended that the drug be administered within 30 minutes (4). In the present case, it took 2 hours to administer the drug because of mild pain at the insertion site. No previous studies have reported an association between the administration time of gemcitabine and its extravasation; however, several studies have shown that the administration of gemcitabine led to the occurrence of conditions such as skin necrosis, venous thrombosis, and vasculitis (5, 6). While the cause remains unclear, gemcitabine has a low pH, which may induce vascular toxicity. In addition, if the administration time is too long, the integrity of the vein may be impaired, causing injury to the endothelial cells, and as a result, inflammation and infiltration may be more likely to occur.

Cisplatin is a platinum-containing drug, and previously reported cases have shown that an extravasation of high concentrations of cisplatin (≥ 0.75 mg/mL) aggravated the tissue damage and led to necrosis (7, 8). Meanwhile, the extravasation of low concentrations of cisplatin has been reported to be accompanied by inflammatory symptoms, such as redness and swelling, but it rarely causes tissue necrosis. Bairey et al. pointed out that even with low concentrations of the drug, an immediate recall phenomenon may occur as a result of repeated administration, which may lead to severe tissue necrosis (9). In the case described in our study, the concentration of cisplatin was as low as 0.21 mg/mL. The necrosis of the surrounding tissues may have occurred when tissues that had been damaged by gemcitabine were exposed to cisplatin. Further verification will need to be carried out in the future.

Regarding treatments after the extravasation of anticancer drugs, in Japan, the extravasation of large quantities of irritant anticancer agents is often treated with local steroid in-

jections, but in the case described in the present study, an unknown amount of the drug was extravasated, and the patient was not given any local injection of steroids; however, instead, the patient was treated with cooling and topical steroids. In other countries, a local injection of a specific antidote (sodium thiosulfate) is considered to be effective for the treatment of an extravasation of cisplatin; however, because the antidote's clinical efficacy has not been fully elucidated, it has not yet been approved for insurance coverage in Japan (10). Although the use of dexrazoxane, which has an inhibitory effect on tissue damage due to the extravasation of anthracycline anticancer agents, recently received insurance coverage in Japan, its inhibitory effects have not been reported in relation to cisplatin and gemcitabine. Experience with a greater number of cases will provide high-level evidence that will help in drug development or in establishing treatment methods that are effective for treating the extravasation of cisplatin and gemcitabine.

Skin necrosis due to the extravasation of anticancer agents causes limitations in activities of daily living; and may later lead to difficulty in conducting chemotherapy itself. In some cases, it may potentially affect the prognosis. Based on the findings in the present case, extreme caution is needed regarding the administration time as well as the intravenous line through which the drug is administered when treating elderly patients who have been repeatedly subjected to multidrug combination chemotherapy.

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

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