CASE REPORT

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EXTRAVASATION OF PEGYLATED-LIPOSOMAL DOXORUBICIN: FAVORABLE OUTCOME AFTER IMMEDIATE SUBCUTANEOUS ADMINISTRATION OF CORTICOSTEROIDS

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ABSTRACT

A massive extravasation of pegylated-liposomal doxorubicin (Doxil®) accidentally occurred, affecting the right forearm of a 54-year-old woman with metastatic ovarian cancer who was receiving an intravenous infusion of the drug. In accordance with the institutional guidelines for vesicant drugs, a corticosteroid preparation was immediately injected subcutaneously into the surrounding tissues. Clobetasol propionate and an ice pack were then topically applied to the affected region. There were no serious complications at the extravasation site, such as tissue necrosis or severe pain, and only a transient erythema of the skin and desquamation remained after 2 months.

Key Words: Extravasation, Liposomal doxorubicin, Chemotherapy, Ovarian cancer

INTRODUCTION

Extravasation refers to the unintended leakage of a liquid formulation of a drug from blood vessels into surrounding tissues. Extravasation of anticancer drugs administered by intravenous infusion constitutes a serious adverse event associated with chemotherapy. In particular, the extravasation of drugs with vesicants, such as anthracyclines, can cause necrosis of the surrounding tissues, often requiring surgical procedures. In addition to careful observation during treatment, a better understanding of the risks of tissue damage triggered by extravasation is essential to ensure the safety of patients who receive cancer chemotherapy.

The package insert of Doxil® (pegylated-liposomal doxorubicin) cautions that this preparation is an irritant. However, medical procedures for the management of extravasation reactions and their actual outcomes have not been well documented.[1-4] We describe here a patient in whom extravasation of a large volume of Doxil® was successfully treated by an immediate subcutaneous corticosteroid injection.

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CASE REPORT

A massive extravasation of a Doxil® Injection (Janssen Pharmaceutical, Tokyo, Japan) accidently occurred during an intravenous infusion of the drug in a 54-year-old woman with heavily treated metastatic ovarian cancer. She had previously received four courses of the same regimen without any extravasation.

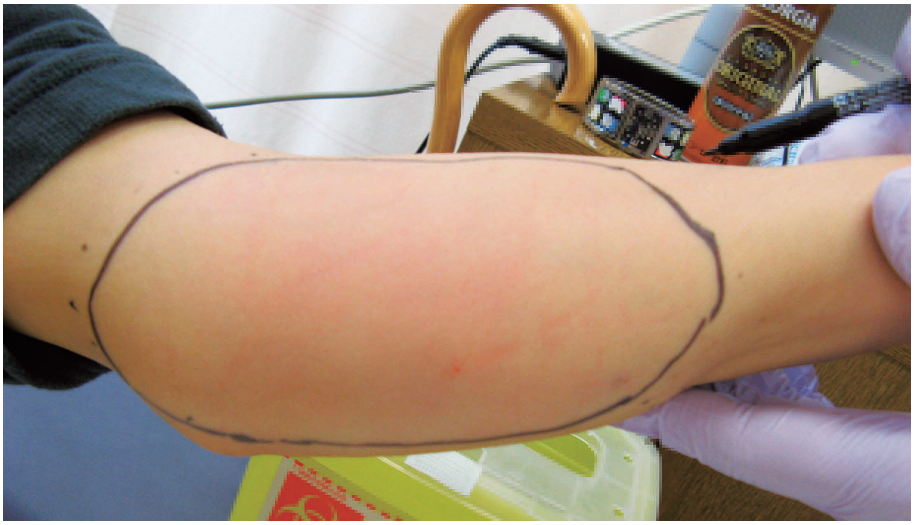

Fig. 1 Immediately after the extravasation of Doxil®. The extravasation site was remarkable, and the skin was partially red.

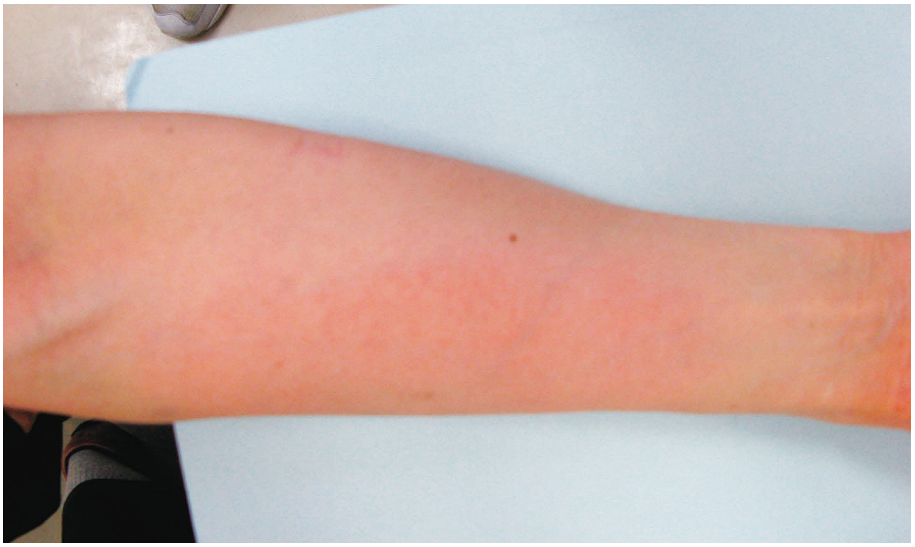

Fig. 2 Three days after extravasation. The swelling had decreased, and erythema of the extravasation site had become faint.

The patient was scheduled to receive an intravenous infusion of 75 mg of Doxil® in a 250 ml 0.9% NaCl solution, delivered *via* a 24-gauge cannula (SurFlo® I. V. Catheters, Terumo, Tokyo, Japan) placed in the right forearm. Before and at the beginning of the infusion, oncology nurses in the outpatient chemotherapy unit confirmed good patency of the vein by checking the blood backflow; a free flow of the infusion solution was also confirmed. Extravasation occurred after about 35 mg of pegylated-liposomal doxorubicin had been infused. The patient reported a swelling (10 x 20 cm) with mild erythema gradually spreading around the infusion cannula placed in the right forearm (Fig. 1). She experienced no pain, but did feel numbness. In accordance with the institutional guidelines for the management of the extravasation of vesicant drugs, the infusion was terminated immediately, and less than 0.1 ml of the infusion solution and a small amount of blood were slowly aspirated back through the original cannula with the use of a disposable syringe. After removal of the original cannula, 200 mg of corticosteroid (Solu-Cortef®, Pfizer, Tokyo, Japan) and 50 mg of lidocaine (1% Xylocaine®, AstraZeneca, Tokyo, Japan) diluted with 0.9% NaCl solution to a total volume of 20 ml were injected subcutaneously *via* a 27-gauge needle into the extravasation site and surrounding tissues. The affected site was then topically applied with clobetasol propionate (Dermovate Ointment®, GlaxoSmithKline, Tokyo, Japan) and cooled with an icepack for 30 minutes.

Three days after extravasation the swelling decreased, and erythema of the extravasation site became faint. The color was most likely caused by the extravasated doxorubicin (Fig. 2). Four weeks after extravasation, the erythema had faded, and a mild epithelial desquamation remained around the extravasation site (Fig. 3). By two months after extravasation the erythema had resolved, and the wound had healed with no apparent sequela. There were no serious complications such as tissue necrosis or ulceration.

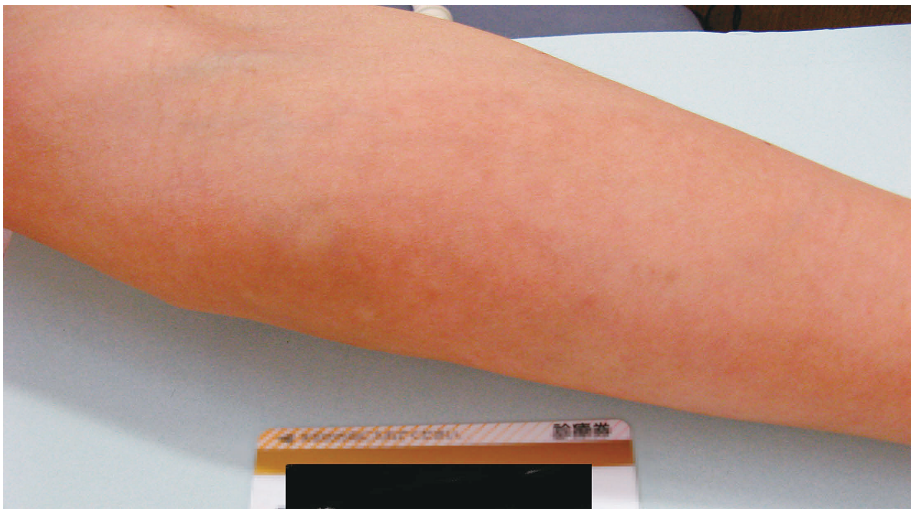

Fig. 3 Four weeks after extravasation. The erythema had faded, with mild epithelial desquamation remaining around the extravasation site.

DISCUSSION

This case report provides valuable information on the characteristics and successful management of extravasation reactions caused by Doxil®, an intravenous anticancer drug used to treat refractory ovarian cancer. This preparation contains doxorubicin encapsulated in pegylated-liposomes (STEALTH® liposomes). In contrast to conventional liposomes, the introduction of this novel delivery system allows pegylated-liposomal doxorubicin to evade detection and destruction by the body's immune system. The drug thus remains in the systemic circulation for a prolonged period, with an elimination half-life of approximately 55 hours. Though doxorubicin is thought to be preferentially released from the pegylated-liposomes into tumor tissues, the exact mechanism involved is not fully understood. Owing to a modification of the formulation, extravasated Doxil® is categorized as an irritant, even though doxorubicin *per se* is a well-known vesicant.

Although the package insert states that Doxil® is an irritant, we took all necessary precautions and administered all the treatments currently available in Japan because the extravasation was massive, and doxorubicin *per se* is classified as a vesicant. Other antidotes, such as dimethyl sulfoxide (DMSO), hyaluronidase, or dexrazoxane, have been used to treat extravasation reactions, but they are not currently approved in Japan.[5,6] Although the mechanism by which corticosteroids ameliorate extravasation reactions remains unclear, these drugs have been used to manage extravasation injury caused by various drugs. In our patient, an immediate subcutaneous corticosteroid injection apparently contributed to preventing tissue necrosis and other potentially serious complications.

Conflicts of interest

We have no conflicts of interest to declare.

REFERENCES

1) Lokich J. Doxil extravasation injury: a case report. *Ann Oncol*, 1999; 10: 735–736.
2) Masoorli S. Extravasation injuries associated with the use of central vascular access devices. *J Vasc Access Devices*, 2003; 8: 21–23.
3) Madhavan S, Northfelt DW. Lack of vesicant injury following extravasation of liposomal doxorubicin. *J Natl Cancer Inst*, 1995; 87: 1556–1557.
4) Laufman LR, Sickle-Santanello B, Paquelet J. Liposomal doxorubicin extravasation. *Community Oncology*, 2007; 4: 464–465.
5) Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, Del Mastro L, Garrone O, Rosso R, Dini D. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. *J Clin Oncol*, 1995; 13: 2851–2855.
6) Bertelli G, Dini D, Forno GB, Gozza A, Silvestro S, Venturini M, Rosso R, Pronzato P. Hyaluronidase as an antidote to extravasation of Vinca alkaloids: clinical results. *J Cancer Res Clin Oncol*, 1994; 120: 505–506.