the poison®

CASE SERIES

Doxorubicin extravasation: Case series

María L. Melina[1]*, Antonella Milano Gil[1] and Patricia C. Docampo[2]

[1] Central Aeronautical Hospital, Buenos Aires, Argentina.
[2] National Poison Center (CNI) - 'Prof. Alejandro Posadas' National Hospital, El Palomar, Buenos Aires, Argentina.
laumelina@yahoo.com.ar

Submitted: 02/04/2024 - Accepted: 05/12/2024 - Published: 31/01/2025 - DOI: https://doi.org/10.62129/YKKZ6693

ABSTRACT

Background. One of the most severe complications arising from the IV administration of certain cytostatic drugs is the extravasation into adjacent tissue, which causes local irritation, tissue necrosis, and may even result in amputation of the affected limb. According to the literature, the incidence of extravasations in peripheral intravenous administration ranges from 0.1 to 6%.

Clinical cases. Three patients presented suffering from doxorubicin extravasation while undergoing chemotherapy treatment. General measures were applied in all cases, and in one case dimethyl sulfoxide (DMSO) was applied topically as an antidote for 24-48 hrs. All three had favorable responses.

Conclusions. Extravasation is a potentially serious complication of doxorubicin infusion. It is key to adhere to safe chemotherapy administration guidelines in order to prevent issues, as well as to continuously train staff.

Key words: *Extravasation; Chemotherapy; Doxorubicin; Dimethyl sulfoxide; DMSO.*

Doxorubicin (hydroxydaunorubicin or adriamycin) is a chemotherapy medication in the anthracycline family used to treat various cancers, including breast cancer, bladder cancer and hematolymphoid tumors. One of the serious complications that may occur during the IV administration of some cytostatic drugs is the extravasation into adjacent tissue. *Extravasation* refers to the unintended, inadvertent or accidental leakage of IV-administered drugs to perivascular and subcutaneous spaces.[1,2]

Doxorubicin is a vesicant that can cause serious and long-lasting injury to tissue, as well as necrosis. Symptoms can appear immediately after extravasation or after several days or weeks, causing local pain or irritation, mild erythema, pruritus, or edema. Over time, erythema and pain may intensify, resulting in discoloration and skin induration, desquamation and blistering. Significant extravasation may cause necrosis, eschars, and ulcers affecting subcutaneous tissue. Indolent ulcers lack granulation tissue formation and peripheral re-epithelialization.

The actual incidence of extravasation is unknown due to underreporting of cases. The estimated prevalence of extravasation caused by IV-administration of chemotherapy drugs is 0.1-6%, and 0.3-4.7% when administered via central venous catheter.[3] Three cases of doxorubicin extravasation are presented in the following paragraphs, registered in the Oncohematology Service of the Central Aeronautical Hospital of the City of Buenos Aires, Argentina.

CLINICAL CASES

Three cases of doxorubicin extravasation were studied. The following variables were considered: sex, underlying condition, puncture site, type of catheter, drug, instance of the chemotherapy protocol during which the lesion took place, clinical presentation, and treatment.

Clinical case 1

65-year-old female patient, diagnosed with breast cancer. Doxorubicin extravasation occurred on the dorsal side of her left hand, during the third cycle of treatment. Her symptoms were pain, necrotic ulcer, affection to tendinous tissue and functional impairment. Antibiotics, corticosteroids and analgesics were administered as treatment, and subsequent reconstructive surgery was required (Fig. 1).

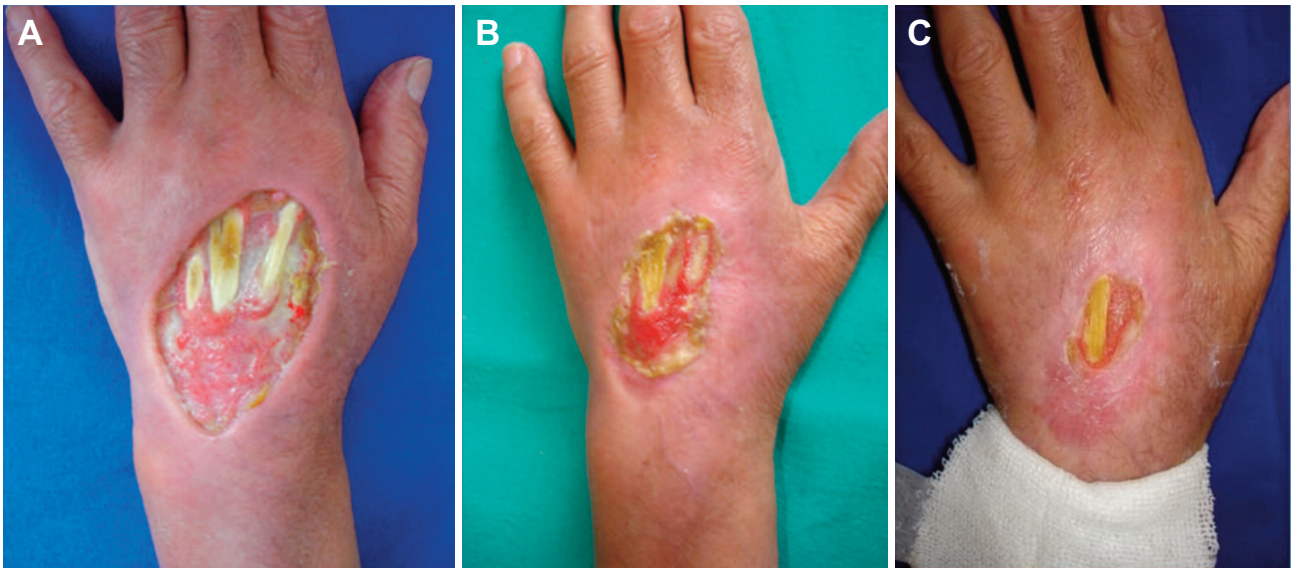

Figure 1 (A, B and C). A necrotic ulcer can be observed in the dorsal part of the left hand, with defined edges and affection to tendinous tissue.

Clinical case 2

53-year-old male patient, suffering from non-Hodgkin lymphoma (NHL). Doxorubicin extravasation occurred on the dorsal side of his left hand, during the fifth cycle of treatment. He presented pain, a necrotic ulcer and affection to tendinous tissue (Fig. 2). Treatment with antibiotics, corticosteroids, and analgesics was administered, and later required reconstructive surgery.

Clinical case 3

72-year-old female patient diagnosed with NHL. Doxorubicin extravasation occurred on the left forearm, during the third cycle of treatment. Upon physical examination, she presented local pain, edema, dispersed papules, erythema and desquamation (Fig. 3), and later developed a necrotic ulcer. Topical treatment was administered, using dimethyl sulfoxide (DMSO) 99%, antibiotics and corticosteroids.

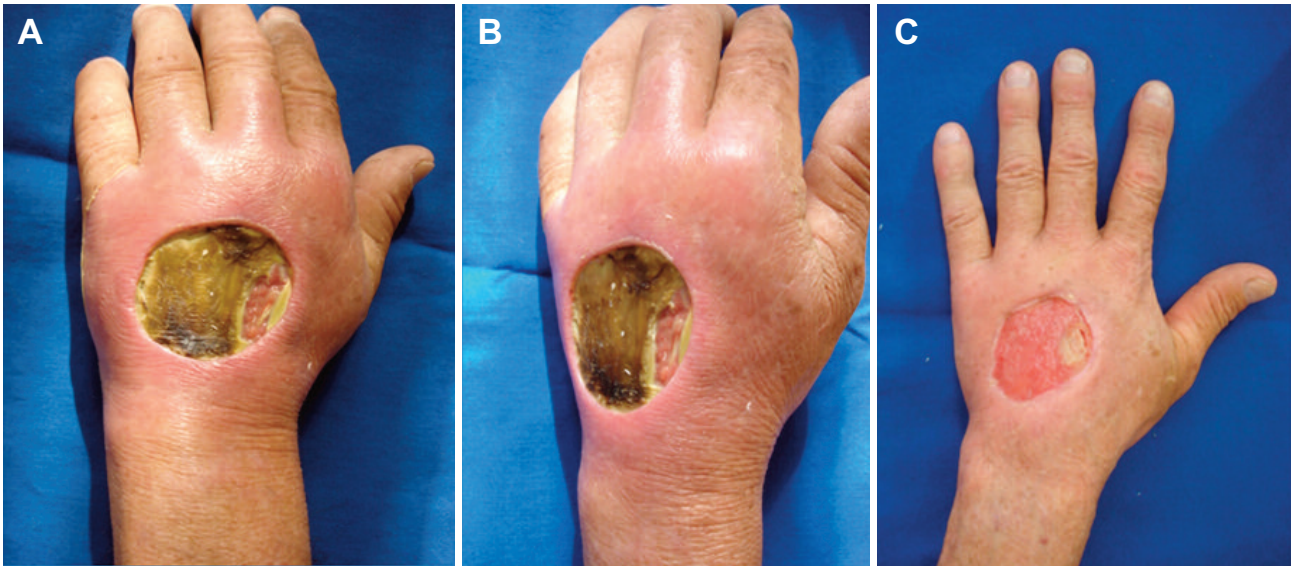

Figure 2 (A, B and C). A necrotic ulcer can be observed in the dorsal part of the left hand, with defined edges, affection to tendinous tissue and fibrinous tissue inside the lesion.

www.thepoisonjournal.com | Cite as: Poison 2025; 2(1):14-17 | DOI: 10.62129/YKKZ6693

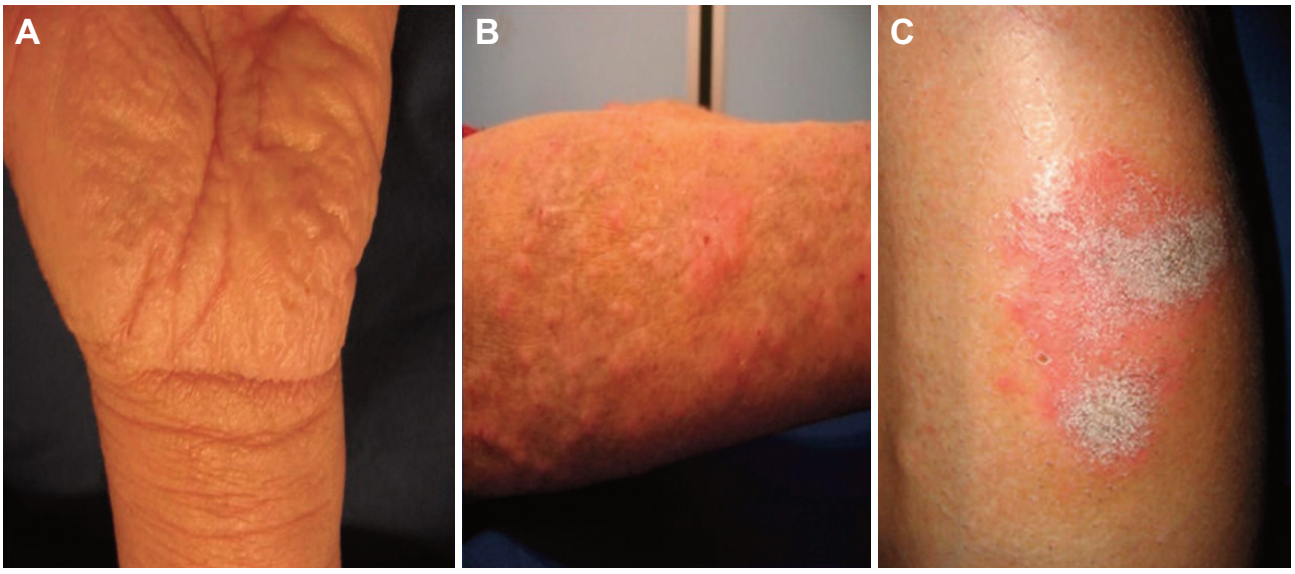

Figure 3 (A, B and C). Edema, erythema and papules can be observed in the left forearm, later developing erythematous plaques and desquamation.

In all three cases a necrotic ulcer lesion was observed, with a shorter recovery time in case 3, after DMSO was administered. The three patients received antibiotic treatment, as well as daily cleansing, surgical interventions and kinesiology rehabilitation due to the loss of sensitivity and movement in the affected limb.

DISCUSSION

Doxorubicin extravasation may cause from local irritation and tissue necrosis to limb amputation, one of the most feared adverse effects. The most relevant aspect when dealing with the administration of cytostatics is the prevention of lesions, training the staff involved and applying careful and standardized drug-administration techniques.[4-6] Any service where this type of agent is infused should have therapeutic algorithms aimed at treating extravasation, as well as kits with materials and medications necessary to treat such cases.[7] When preventive measures are insufficient and extravasation of a vesicant drug occurs, general and specific measures must be implemented.

General measures

Firstly, the infusion of the drug must be stopped immediately, and the equipment and/or system used for the perfusion must be disconnected and removed. The line must be kept in place, with the needle or cannula *in situ* and the limb immobilized. Then, the residual liquid must be removed through the line, aspiring gently. If any subcutaneous blister is observed, its content must be removed using a 1 mL syringe and a fine needle (25G), changing the needle for each blister. The affected limb should be raised to improve venous return and minimize the edema, and a cold compress should be applied. This therapy should be applied for the first hour (as much as the patient endures), and then 3-4 times a day for 15-20 minutes -without interrupting night-time rest-, for 48-72 hrs. Cold therapy induces local vasoconstriction, reducing the distribution of the drug to other areas and, thusly, may reduce the size of the lesion, in addition to reducing pain and inflammation. This approach reduces the absorption of doxorubicin, cisplatin, bleomycin, carmustine, mitomycin, and mitoxantrone, and its synergy with DMSO is confirmed.

Specific measures

While keeping the catheter in place, DMSO 99% can be administered. It is a dissolving antidote that penetrates tissue and eliminates free radicals and enhances the clearance of extravasated drugs, especially anthracyclines and mitomycin. It is applied topically by covering an area twice the size of the affected area, 2 drops per 4cm^2 (≈ 1-2 mL, or 20-40 drops per 7.5 cm by 7.5 cm gauze) for 15-20 minutes, 3-4 times a day, for 7-14 days. This treatment must be started within 10 minutes of the extravasation and left to dry without bandages.[8]

Regarding evidence on the efficacy of DMSO, there are

no randomized clinical trials. Despite initially discouraging results in animal studies,[9] in the 1980s a prospective pilot study of 20 patients showed clinical benefit in the treatment of anthracycline extravasation.[10] Topical application of DMSO was performed immediately after the extravasation, covering twice the affected area. The treatment was repeated twice a day for 14 days. There was no ulceration and no surgical intervention was required. In 1995, a study of the cases of 144 patients treated with DMSO after the extravasation of different chemotherapy drugs was published, including doxorubicin (n = 11).[11] In these cases, DMSO 99% was applied topically, four drops per 10 cm^2 of skin surface, twice over the affected area, and was left to dry without bandages. The treatment was administered within 10 minutes of the extravasation in 84% of patients, and repeated every 8 hrs. for a week. Only 1 patient developed ulceration after epirubicin extravasation. It is important to note that DMSO may cause local erythema, which may lead to an incorrect assessment of the tissue damage.

Other considerations

It is important to apply antibiotic treatment if bacterial superinfection occurs, providing patients with written proscriptions, as it happened in our cases. Documenting the extravasation in the medical history is crucial, as it allows for a proper evaluation of the applicability and efficacy of the institutional protocol for such cases.

Lastly, patients must be informed about post-treatment care before being discharged.[12] It is recommended that patients are periodically examined, every 24-48 hrs. during the first week and on a weekly basis afterwards, until symptoms have disappeared. If necessary, referral to a plastic surgeon is advised.

CONCLUSIONS

Extravasation is a serious complication of doxorubicin chemotherapy. The implementation of therapeutic and diagnostic algorithms, as well as continuously training staff involved in these treatments is crucial for preventing complications and long-term sequels.

Conflicts of interest
The authors declare no conflicts of interest.

REFERENCES

1 Hadaway L. Infiltration and extravasation. AJN Am J Nurs. 2007 Aug;107(8):64-72. Available from https://doi.org/10.1097/01.naj.0000282299.03441.c7. Erratum in: Am J Nurs. 2007 Oct;107(10):15
2 Dougherty L. IV therapy: recognizing the differences between infiltration and extravasation. Br J Nurs. 2008;17(14):896-901. Available from: https://doi.org/10.12968/bjon.2008.17.14.30656
3 Kreidieh FY. Overview, prevention and management of chemotherapy extravasation. World J Clin Oncol. 2016;7(1):87. Available from: https://doi.org/10.5306/wjco.v7.i1.87
4 Mader I, Fürst-Weger P, Mader R, Nogler-Semenitz E, Wassertheurer S. Extravasation of Cytotoxic Agents. Vienna: Springer Vienna; 2010. Available from: https://doi.org/10.1007/978-3-211-88893-3
5 Wengström Y, Margulies A. European Oncology Nursing Society extravasation guidelines. Eur J Oncol Nurs. 2008; 12(4):357-61. Available from: https://doi.org/10.1016/j.ejon.2008.07.003
6 WOSCAN Cancer Nursing and Pharmacy Group. Chemotherapy extravasation guideline, 2009 [cited 2024 Dec 8]. 24 p. Available from: https://hemonc.org/w/images/b/b3/BeatsonWestScotlandExtravasation.pdf
7 Pattison J. Managing cytotoxic extravasation. Nurs Times. 2002;98(44):32-4. PMID: 12451746. Available from: https://pubmed.ncbi.nlm.nih.gov/12451746/
8 SEFH. SOCIEDAD ESPAÑOLA DE FARMACIA HOSPITALARIA. Prevención y tratamiento de extravasaciones de fármacos antineoplásicos. Madrid; 2020. 50 p. Available from: https://gruposdetrabajo.sefh.es/gedefo/images/stories/documentos/2020/monografia_extravasaciones.pdf
9 Dorr RT, Alberts DS. Failure of DMSO and vitamin E to prevent doxorubicin skin ulceration in the mouse. Cancer Treat Rep. 1983;67(5):499-501. PMID: 6850665. Available from: https://pubmed.ncbi.nlm.nih.gov/6850665
10 Olver IN, Aisner J, Hament A, Buchanan L, Bishop JF, Kaplan RS. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. J Clin Oncol. 1988;6(11):1732-5. Available from: https://doi.org/10.1200/jco.1988.6.11.1732
11 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 Nov;13(11):2851-5. Available from: https://doi.org/10.1200/jco.1995.13.11.2851
12 Pérez Fidalgo JA, García Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO–EONS Clinical Practice Guidelines. Ann Oncol. 2012;23:vii167—vii173. Available from: https://doi.org/10.1093/annonc/mds294