Case Report

Accidental Extravasation of Mitomycin C into the Subcutaneous Tissue

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Abstract

Introduction
Mitomycin C (MMC) is a common chemotherapeutic agent used to treat a variety of solid tumors. Cutaneous adverse events are rare, but MMC is a known vesicant reported to cause tissue necrosis and sloughing, erythema, and ulceration if incorrectly infused into the subcutaneous tissue. Definitive treatment of extravasation injuries due to MMC depends on the severity of the cutaneous manifestation, which includes stopping the infusion, removing the catheter, or possible debridement.

Case Presentation
We present the case of a 70-year-old female with extensive soft-tissue injury secondary to extravasation of MMC that required hospital admission and surgical intervention to remove the implantable venous access device.

Conclusion
Extravasation injuries caused by vesicant drugs, such as MMC, often present as local skin irritation and inflammation. MMC extravasation may present a wide range of skin and soft tissue manifestations, ranging from erythema to ulcerations to necrosis. This rare but potentially detrimental complication of chemotherapy infusions should be recognized in cancer patients.

Keywords
mitomycins/adverse effects; mitomycin; extravasation of diagnostic and therapeutic materials; vesicant; antineoplastic agents; necrosis; soft tissue injuries; chemotherapy

Introduction
Mitomycin C (MMC) is a powerful DNA-alkylating chemotherapeutic agent used to treat solid tumors.[1] This drug is a part of several different treatment protocols for breast, bladder, cervical, colorectal, and anal cancers. Known as a potent vesicant (a drug that can result in tissue necrosis or blister formation), MMC may cause serious and painful skin and soft tissue injuries if extravasated into the subcutaneous tissue. Symptoms typically begin as soon as the infusion begins, but MMC has been reported to cause symptoms weeks or months after the infusion.[2] MMC extravasation may present a wide range of skin and soft tissue manifestations, from erythema to ulcerations to necrosis.[3] It is important to practice antibiotic stewardship when considering the differential diagnosis, as these injuries are not due to infection. We present a case of accidental extravasation of MMC into the subcutaneous tissue presenting as a large, painful area of erythema with superficial ulcerations.

Case Presentation
A 70-year-old, obese woman presented to the emergency department (ED) due to a week of worsening right-sided chest wall pain and skin changes. She had a history of anal cancer and

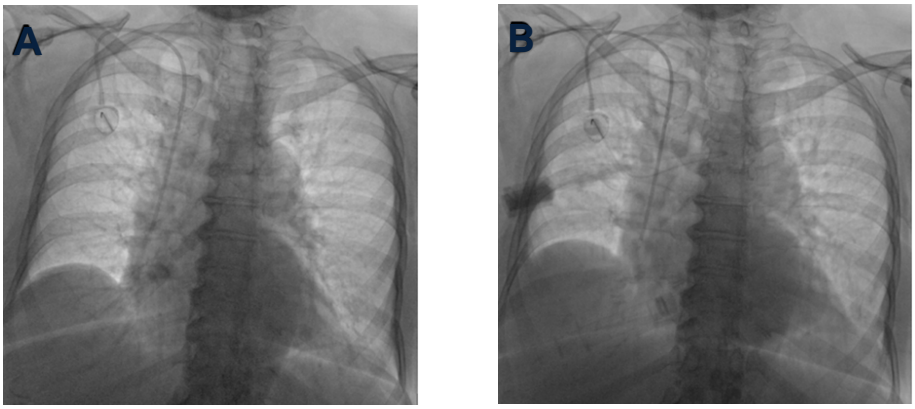

Figure 1. A. A chest x-ray shows normal curvature of the catheter. **B.** An injection of contrast demonstrates no evidence of leakage or extravasation.

was actively undergoing chemotherapy with MMC. The patient reported that symptoms began during a recent chemotherapy session a week prior. Before the infusion, the patient stated that the implantable venous access device (port) site was flushed with saline and blood was drawn from the site without any problems. When the infusions began, however, the patient experienced a burning sensation that extended up to her right shoulder and down into her right breast. The infusion was immediately stopped. Interventional radiology was consulted to evaluate the port. Ten milliliters of an undiluted iopamidol contrast agent were injected into the port, demonstrating no leakage or extravasation (**Figure 1**). Over the next week, the patient felt increasing pain, erythema, and induration throughout the right chest wall, including the breast and overlying skin ulcerations. The worsening pain and skin changes prompted the patient to present to the ED.

The patient denied fever, chills, or shortness of breath. Upon our initial examination, the erythema and induration extended superiorly to the right shoulder, medially to the sternum, laterally to the mid-axillary line, and inferiorly to the right nipple (**Figure 2**). Small, superficial blisters were noted at the lateral chest wall (**Figure 3**). The patient reported severe pain to light touch. The patient was afebrile, and her vital signs were otherwise unremarkable. Her white blood cell count was within normal limits at 7.1 x 10^3 per uL (normal range: 5.0-12.0 x 10^3 per uL). A computed tomography (CT) scan of the chest showed inflammation of the soft tissues overlying the right breast and the port partially flipped, lying at an oblique angle under the skin (**Figure 4**).

The patient was admitted for observation and port removal. Her skin was monitored for signs of tissue necrosis. After 2 days of observation, the skin showed a marked decrease in erythema, and the superficial ulcerations showed no

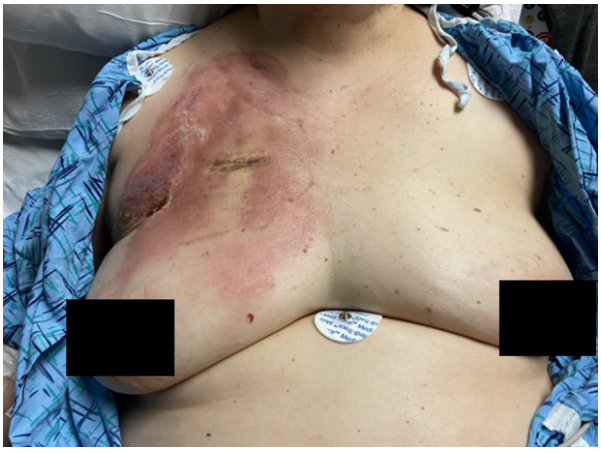

Figure 2. Gross examination shows extensive erythema of the right chest wall surrounding the port site.

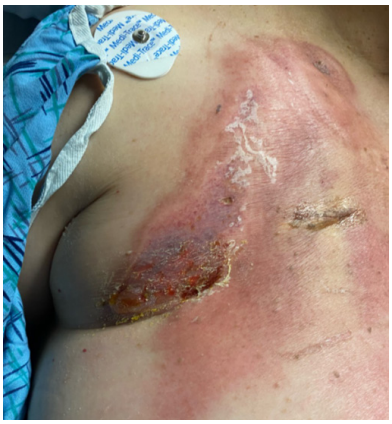

Figure 3. Superficial ulceration and blistering were noted at the superior-lateral chest wall.

signs of necrosis. On hospital day 3, the port was removed. At the time of removal, it was noted that there was extensive soft tissue inflammation surrounding the port pocket. The port was removed without complications, and the patient tolerated the procedure well. The patient had a peripherally inserted central catheter (PICC) placed prior to discharge to receive her final dose of chemotherapy. The patient was discharged on postoperative day 1 (hospital day 4) with a plan to follow up with her oncologist to complete her chemotherapy regimen.

Discussion

Chemotherapy infusion carries a wide range of potential complications. Intravenous (IV) therapeutic agents have been classified into 5 categories based on their potential cutaneous adverse events: neutrals, exfoliants, inflammitants, irritants, and vesicants.[4] Vesicants are the most injurious class due to their ability to induce tissue necrosis. They are further divided into 2 sub-categories: DNA-binding or DNA-non-binding. DNA-binding vesicants, such as MMC, are more potent vesicants with the most severe risk profile of the IV chemotherapies, as they can cause irreversible disability and disfigurement.[3]

Extravasation of chemotherapeutic agents is a multi-factorial adverse risk event. Patient-related risk factors include age, vein fragility, lymphedema, and obese body habitus. Prolonged duration and increased rate, volume, and concentration of the chemotherapy all increase the risk of extravasation.[4] Implementation of central venous access device (CVAD) infusion protocols have resulted in dramatic reductions in extravasation.[5] There is still a reported risk of 0.26% to 4.7% due to malposition, port rotation, thrombosis, fragmentation, or migration. In the case of our patient, the port was malpositioned. The extravasation was likely related to an iatrogenic injury secondary to a misplaced needle due to the suboptimal port position.

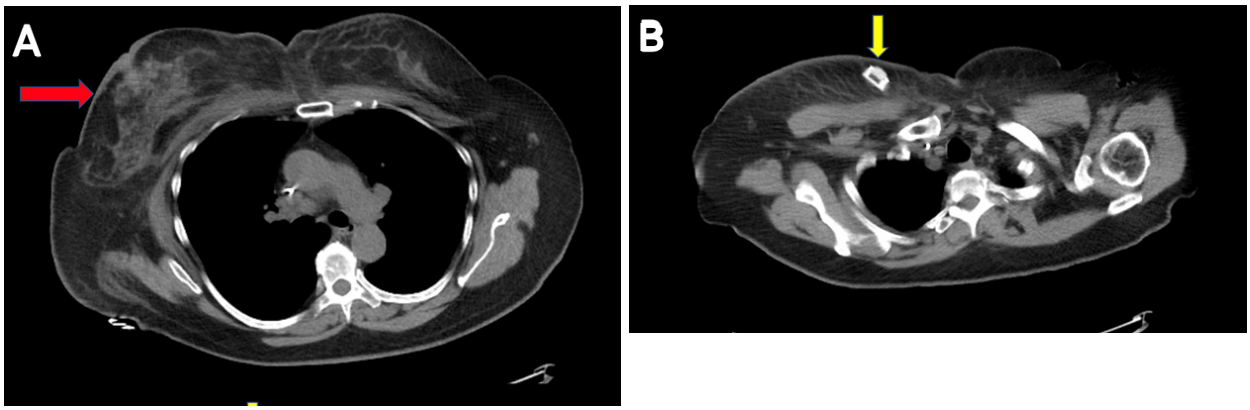

Figure 4. An axial view CT scan of the chest shows, **A.** right-sided cellulitis of the breast and chest wall (red arrow), and **B.** the port lying obliquely under the skin (yellow arrow).

Prompt detection of extravasation is crucial in preventing extensive tissue damage. A burning sensation in the adjacent region to the infusion site is the most common symptom and indicates an immediate cessation of the infusion.[4] As the inflammatory response mounts, the cutaneous symptoms may be mild with erythema, swelling, and pain.[3] Patients receiving chemotherapy are at a higher risk of developing multi-drug-resistant infections.[6] Therefore, clinicians must practice excellent antibiotic stewardship by correctly identifying the underlying etiology to initiate the proper treatment.[3] This practice is essential for both short and long-term patient outcomes.[3]

Protocols for chemotherapy infusion should include properly assessing CVAD patency by utilizing saline flushes or confirming blood aspirate before initiating the medication.[4] If resistance is noted, further troubleshooting and evaluation should precede the scheduled infusion. If patency cannot be confirmed prior to the infusion, other methods of central venous access may be considered, including PICC line placement. The CVAD should be carefully palpated prior to needle insertion to ensure proper placement and continuously monitored upon infusion induction.[4]

Once an extravasation injury is detected and the infusion halted, the treatment is tailored to the specific type of chemotherapy. In the case of vesicant extravasation with MMC, cold compresses may be applied to the affected area for up to 20 minutes 4 times daily for the first 24-48 hours. Dimethylsulfoxide (DMSO) may be applied topically to promote systemic absorption of MMC.[4] DMSO induces an anti-inflammatory and vasodilatory response by binding free radicals. If the injury progresses to tissue necrosis or the patient experiences persistent pain, CVAD removal and surgical debridement are the definitive treatments.[4]

Conclusion

MMC is a common chemotherapeutic agent used in the treatment of many cancers. Extravasation injuries caused by vesicant drugs, such as MMC, often present as local skin irritation and inflammation. We hope our case presentation and discussion bring awareness and recognition to a rare but potentially detrimental complication of chemotherapy infusions.

Conflicts of Interest

Drs Chung, Walterscheid, Lopez-Vera, and Rashid declare that they have no conflicts of interest.

Dr Liang reports personal fees from UpToDate outside the submitted work.

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