

Mitomycin extravasation injury: A case series



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INTRODUCTION

Mitomycin C (MMC) is a DNA-alkylating chemotherapeutic agent mostly used in the treatment of adenocarcinomas of the gastrointestinal tract.¹ Due to its toxicity, inadvertent extravasation of this medication can cause local skin and soft tissue injury. Acute symptoms are mild with erythema, swelling, and pain.² Weeks later, indolent ulcerations can appear with severe local necrosis, resembling doxorubicin extravasation.³ Additionally, rare cases of delayed MMC extravasation reactions have been reported occurring months after infusion and are typically associated with an identifiable effector that alters vascular permeability such as radiation therapy, sunburn, or alcohol.³⁻⁵

Despite the long-reported cutaneous sequela of extravasated vesicant chemotherapeutics, the pathophysiology remains unknown. Therefore, there are no known therapeutic targets for antidotal intervention, and trialed medical management has been largely ineffective.¹ Although some report successful treatment with pyridoxine and dimethylsulfoxide,⁶ with or without α -tocopherol,^{1,2,7,8} many cases require surgical excision and split-thickness grafts to restore function and prevent structural damage.² Improved infusion techniques and fewer extravasation reactions may have contributed to a paucity of literature over the last 2 decades. Consequently, dermatologists must remain aware of this now infrequently seen and already rare manifestation. We present a cluster of 4 cases of MMC extravasation injury, which highlights the varied array of time courses and locations of the disease.

Abbreviations used:

IV: intravenous
 MMC: mitomycin C

CASE SERIES

Case 1

A 51-year-old woman with anal cancer treated with radiotherapy and concurrent capecitabine and MMC presented to the dermatology clinic with a fixed, bound down ulcer with black eschar and surrounding erythema and induration on the dorsal side of the left forearm (Fig 1, A). She reported that the lesion developed after a minor arm trauma 3 weeks prior. She was seen in the emergency department and treated with cephalexin for a presumed infection but without improvement. Additional history revealed that the lesion developed at the site where she had received MMC infusion 4 months prior, during which she experienced burning and pain at the intravenous (IV) access site. A punch biopsy showed an ulcer with subjacent dermal necrosis and a mixed inflammatory infiltrate, including lymphocytes, eosinophils, and neutrophils. The epidermis adjacent to the ulcer was intact and without atypia. The adjacent dermis demonstrated fibrosis with conspicuous reactive atypia in the fibroblasts and necrosis and squamous metaplasia of the eccrine epithelium (Fig 1, B). Special stains for microorganisms revealed only yeast on the surface. Tissue cultures were negative. The patient experienced slow, yet complete,

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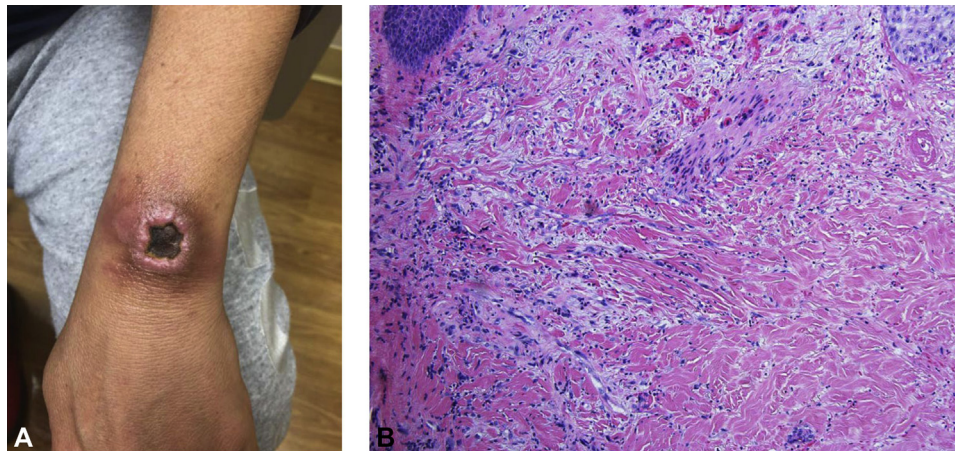


Fig 1. Case 1: Mitomycin extravasation reaction. **A**, Fixed, bound down ulcer with black eschar and surrounding erythema and induration on the dorsal side of the left forearm. **B**, The dermis demonstrated necrosis and fibrosis with reactive atypia of fibroblasts. (**B**, Hematoxylin-eosin stain; original magnification: **B**, $\times 10$.)

resolution over the following 3 months with appropriate wound care.

Case 2

A 64-year-old man with HIV and anal cancer treated with radiotherapy and concurrent capecitabine and MMC was hospitalized for a wound on his right forearm that reportedly began as a painful pustule and failed to resolve with IV vancomycin and piperacillin/tazobactam. The lesion developed 1 month after the patient's last MMC infusion near the site of administration. The evaluation revealed an indurated, purpuric retiform plaque with an erythematous border and central angulated ulceration and eschar (Fig 2, A). A punch biopsy showed an ulcer with minimal inflammation of the reticular dermis, fibrin thrombi, necrosis and squamous metaplasia of eccrine epithelium, and dermal fibrosis with reactive changes in fibroblasts (Fig 2, B). Fungi were seen only on the surface. Tissue cultures were negative. The lesion healed over the following 3 months with gentamicin ointment.

Case 3

A 77-year-old woman with anal cancer treated with radiotherapy and concurrent capecitabine and MMC was admitted for progressively enlarging ulcers on the right hand and dorsal side of the forearm, which began 1 month prior. Although tissue cultures were negative, multiple biopsies and magnetic resonance imaging scans were suggestive of an infectious process. She was treated with vancomycin and piperacillin/tazobactam but without improvement. Following discharge, the patient was seen in a

dermatology clinic where she provided the additional history that she experienced a “pinching” sensation at the site of MMC infusion 3 months prior. On the dorsal side of the right hand, there was an erythematous, indurated, tender ulcer with a central irregularly shaped eschar and erythema tracking linearly up the inner forearm to a similar, smaller lesion (Fig 3, A). An excisional biopsy demonstrated an ulcerated epidermis with underlying dermal necrosis; reactive fibroblasts and fibrosis; and a mixed-cell inflammatory infiltrate of lymphocytes, histiocytes, neutrophils, and eosinophils (Fig 3, B). Periodic acid–Schiff, acid-fast bacilli, and Gram stains were negative for microorganisms. Both lesions healed over the ensuing months with gentamicin ointment.

Case 4

A 70-year-old woman with anal cancer treated with radiotherapy and concurrent capecitabine and MMC was hospitalized for right hand pain and swelling. She noted that a wound first appeared after the IV placement during an admission for weakness 2 months prior, although she had also received MMC infusion at the same site 3 weeks before that. The patient had 2 well-demarcated, round ulcers with surrounding hyperpigmentation on the dorsal side of the wrist and hand. A punch biopsy demonstrated fibrin thrombi, minimal to no inflammation, dermal fibrosis with occasional reactive fibroblasts, necrosis of eccrine epithelium, and fat necrosis. She was prescribed mupirocin ointment and experienced a complete resolution.

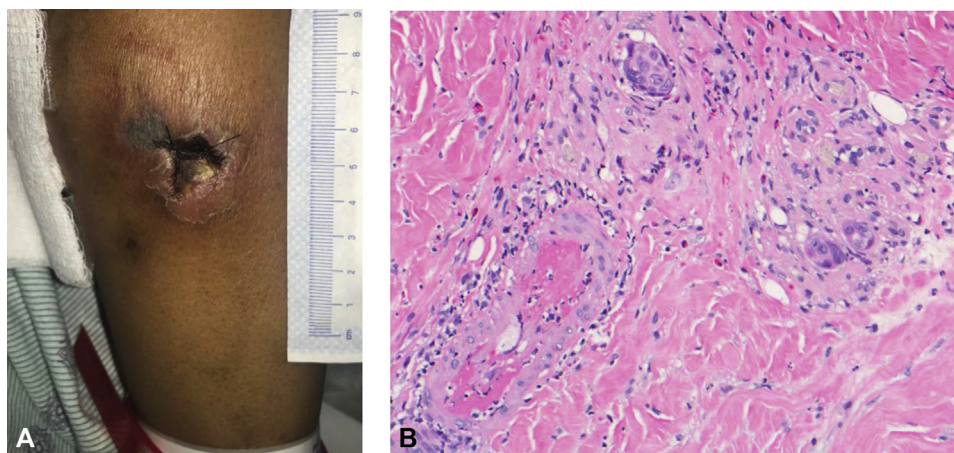


Fig 2. Case 2: Mitomycin extravasation reaction. **A**, Indurated, erythematous plaque with a central angulated ulceration and overlying eschar. Stitches at the site of the first biopsy. **B**, Within the dermis, there is necrosis, fibrosis with reactive atypia in fibroblasts, occasional thrombi, squamous metaplasia of eccrine epithelium, and minimal inflammation. (**B**, Hematoxylin-eosin stain; original magnification: **B**, $\times 20$.)

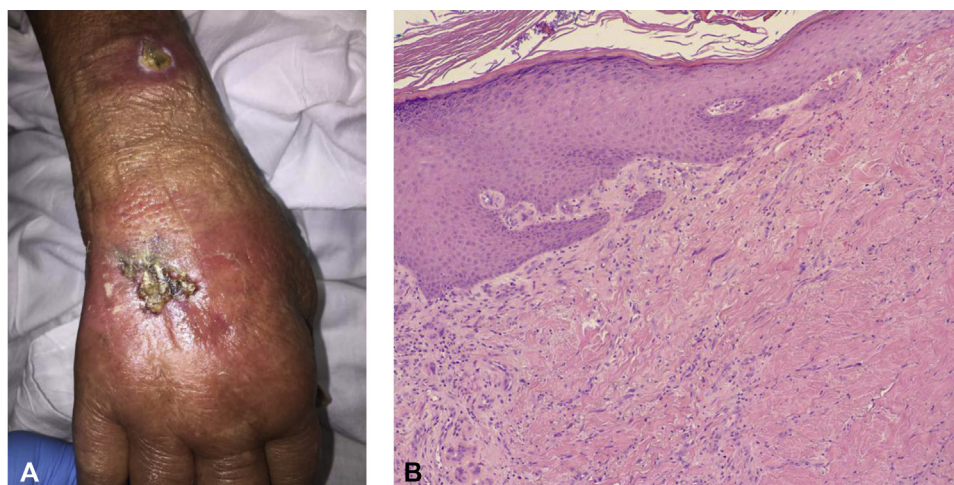


Fig 3. Case 3: Mitomycin extravasation reaction. **A**, Erythematous and indurated ulcer with a central irregularly shaped eschar as well as erythema tracking linearly up the inner forearm to a similar yet smaller lesion. **B**, Adjacent to the ulcer, there were reactive changes in the epidermis; dermal fibrosis with reactive atypia in fibroblasts; and a relatively sparse inflammatory cell infiltrate of lymphocytes, histiocytes, neutrophils, and eosinophils. (**B**, Hematoxylin-eosin stain; original magnification: **B**, $\times 10$.)

DISCUSSION

As a diagnosis of exclusion, occurring in only 0.1% to 6% of MMC recipients,⁹ extravasation reactions are difficult to diagnose. Accordingly, when this hearty necrotic process appeared in a cluster of cases, an infectious process was strongly favored with suspicion for a batch of medication contaminated with an infectious agent. Surprisingly, tissue cultures revealed no signs of infection. Biopsies revealed predominantly tissue necrosis with reactive changes in the fibroblasts, squamous metaplasia of the

eccrine epithelium, and occasionally thrombi with comparatively minimal inflammation, which supported the concern for a physical or toxic insult.⁴ Chemotherapeutic agents can accumulate within the eccrine glands by being secreted through sweat, thereby inducing squamous metaplasia of the eccrine glands and ducts. In our cases, however, mitomycin extravasated into the dermis and the same metaplastic phenomenon was observed. This was a unique finding that may be secondary to regeneration after MMC-induced injury.¹⁰ The

clinical factors supporting the diagnoses included lesion development at the site of MMC infusion, administration via IV push, and reported symptoms of irritation at the affected site during infusion by 2 patients despite documented adherence to evidence-based vesicant precautions. An exhaustive investigation of all patients who received the agent over the previous year found no explanation for the delayed reactions.

In all cases, the patients received 2 infusions of MMC approximately 1 month apart. Regarding the time course of the disease, the initial symptom onset of cutaneous changes ranged from 3 weeks to 4 months following the last MMC administration. Although extravasation reactions classically manifest after 3 to 6 weeks, delayed injury has also been reported,⁵ which is postulated to be secondary to MMC's ability to chronically bind tissue DNA and induce the destruction of the surrounding healthy cells. Additionally, delayed necrosis has been attributed to a "recall mechanism" that causes a symptomatic flareup of a previously indolent extravasated drug.⁴ Despite subclinical venous irritation acutely, an inciting local or distant event provokes MMC reactivation and tissue necrosis thereafter.¹¹ This phenomenon was demonstrated in 2 of our patients: 1 patient with accidental trauma and another with an unrelated peripheral IV placement. Awareness of extravasation remains paramount as immediate cessation of infusion and aspiration may prevent injury.¹² If an injury does occur, the cutaneous disease is typically managed conservatively with antibacterial creams, topical dimethylsulfoxide, and optimized wound care. However, a more serious disease may necessitate surgical intervention with debridement and skin grafting.²

In conclusion, MMC extravasation injury is a rare yet debilitating cutaneous adverse event. The lack of extravasation symptoms during the administration can be misleading and prevent timely detection, particularly when the documentation of the infusion site is absent. Although oncologic care teams have

the responsibility to be aware of its possibility to prevent and manage accidental extravasation, when not detected at the time of administration, dermatology plays a vital role in diagnosis and management. Educating patients on signs of potential tissue injury is also essential so that they promptly seek medical assistance to avoid long-term sequelae.

Conflicts of interest

None disclosed.

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