

Scrotal Ulceration: A Complication of Hyperthermic Intraperitoneal Chemotherapy and Subsequent Treatment With Dimethyl Sulfoxide

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PRACTICE POINTS

- Scrotal ulceration following hyperthermic intraperitoneal chemotherapy has been reported only a few times in the literature and is likely underreported. The presentation in all reported cases was similar, with a delay in symptom onset of weeks to months, involvement of the anterior scrotum, and pain.
- Dimethyl sulfoxide, used in other vesicant reactions, may have a role in mitigating tissue damage. Alternatively, methods to prevent sequestration of vesicants in the potential space of the tunica vaginalis layers can be employed.

To the Editor:

A 54-year-old man with a history of stage IV appendiceal carcinoid adenocarcinoma treated approximately 3 months prior with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) presented to our clinic with scrotal pain of 5 days' duration. He had no history of genital herpes, topical contactants, other cutaneous lesions on the body, fever, or chills. On physical examination the patient had an erythematous, purpuric, indurated, tender plaque on the left anterolateral and anterior midline of the scrotum (Figure 1). No other areas of acral purpura or livedoid cutaneous changes were identified. There was no inguinal lymphadenopathy. Biopsy was performed for histologic examination

as well as tissue culture. Histology demonstrated epidermal necrosis without evidence of vasculitis. Tissue culture was unremarkable.

Two days after clinic evaluation, the patient presented to the emergency department with progression of the lesions, and he was admitted to the hospital for pain control. Computed tomography of the pelvis showed bilateral



FIGURE 1. Scrotal ulceration 5 days after symptom onset, with 2 prominent areas of involvement on the left anterolateral and anterior midline of the scrotum with retiform purpura that connected the 2 sites. Erythema and induration surrounded these foci of involvement.

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The authors report no conflict of interest.

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hydroceles without evidence of abscess. Ultrasonography showed scrotal thickening without abscess or fluid collection. On day 5 in the hospital, a regimen of topical 60% dimethyl sulfoxide (DMSO) was applied every 8 hours to the affected area. The patient experienced notable pain relief and a decrease in erythema within 7 hours of application (Figure 2). This regimen was continued for 7 days with improvement in surrounding erythema and pain; however, the patient's pain persisted in the areas of necrosis. Fourteen days following completion of therapy (27 days following presentation), the patient underwent debridement and partial scrotal resection for eschar removal. Histologic examination of the debrided scrotal tissue showed necrosis extending into the dermis and no evidence of vasculitis.

Our case demonstrates a unique presentation of scrotal necrosis secondary to mitomycin C (MitC) extravasation subsequently managed with DMSO. Imaging and biopsy findings effectively ruled out

infection or vasculitis and led us to consider extravasation reactions that typically occur at peripheral intravenous (IV) infusion sites. Suspected cases of scrotal necrosis following HIPEC with MitC have been reported in the literature, along with hypothesized pathophysiology.¹⁻³

In consideration of the proposed pathophysiology, individuals with hydroceles may be more likely to experience this complication due to an abnormal but not uncommon communication between the intraperitoneal cavity and the scrotum via a patent processus vaginalis. The location of necrosis on the anterior scrotum remains unexplained. It may be a consequence of the anatomic location of the hydrocele, a collection of fluid within the tunica vaginalis. The tunica vaginalis is composed of an inner visceral and outer parietal layer, enveloping the testis at the anterior border but not the superior or posterior border. Thus, sequestration of MitC in a hydrocele would correlate anatomically to necrosis of the anterior wall of the scrotum.

Akhavan et al¹ proposed the testes are unaffected because of the presence of the tough fibrous coat of the tunica albuginea that directly adheres to the testes, in addition to the adjacent visceral layer of the tunica vaginalis. These 2 layers separating the testes and the hydrocele may provide a double barrier of protection for the testes.¹

According to a PubMed search of articles indexed for MEDLINE using the terms *scrotal or cutaneous, pain or ulceration*, and *HIPEC or hyperthermic intraperitoneal or mitomycin C*, 4 cases of scrotal necrosis as a suspected complication of HIPEC have been reported.¹⁻³ In 2015, Abdul Aziz et al² reported a case of scrotal eschar presenting 67 days after HIPEC. Silva et al³ presented a similar case 9 days after HIPEC. Akhavan et al¹ reported 2 cases of scrotal eschar presenting at 3 and 4 months following HIPEC. All cases involved the anterior scrotum with erythema and pain progressing to an eschar. No fever or other systemic signs or symptoms were reported, cultures were negative, and treatment with antibiotics was ineffective. Conservative managements failed, and excision of the necrotic area with primary closure produced resolution of pain. Histology showed epidermal and dermal necrosis.^{1,3} The remarkably similar presentation of these patients following HIPEC with MitC in the absence of an identifiable alternative etiology supports an extravasation reaction.

Hyperthermic intraperitoneal chemotherapy involves installation of high-concentration chemotherapeutics into the peritoneal cavity at the conclusion of surgical cytoreductive therapy. Cell cycle-nonspecific agents such as MitC commonly are used for this procedure.⁴ It is classified as a vesicant, which is the designation given to drugs known to produce the most severe extravasation reactions of skin ulceration and necrosis.^{5,6} Symptoms typically include an early area of localized edema, erythema, and severe pain that progresses to superficial soft tissue and skin necrosis.⁷ Unfortunately, no well-studied antidote exists for MitC, though empirical



FIGURE 2. A, Scrotal ulceration 10 days after symptom onset, prior to the application of 60% dimethyl sulfoxide. Purpura progressed to areas of eschar and increased in surface area of surrounding erythema and induration. B, Seven hours after the first application of 60% dimethyl sulfoxide.

guidelines suggest therapeutic management with DMSO and ice packs.^{6,8}

Dimethyl sulfoxide is thought to work as a free radical scavenger as well as a solvent that facilitates diffusion of chemotherapeutics through tissues and thus down a concentration gradient, ideal in the circumstance of an extravasation reaction.⁸ Topical DMSO has been studied as a nonsurgical treatment in a small number of patients to prevent progression to necrosis following MitC extravasation.^{5,7} However, these cases only report extravasation reactions from IV infiltration.^{5,7,9} Dimethyl sulfoxide is rapidly absorbed and acts as a theoretical carrier for MitC as well as other topical substances.^{5,10,11} Caution is advised when using topical lidocaine or steroids in combination with DMSO, as they will be rapidly absorbed systemically. Patients also should be informed about a mild local burning sensation after DMSO application and a garliclike odor of the breath, which have occurred in 5.5% and 27.5% of patients, respectively (N=144).⁵ Dimethyl sulfoxide has no known toxic side effects but can cause erythema, pruritus, and very rarely allergic contact dermatitis.^{5,12} Abdul Aziz et al² postulated that DMSO might be used as a method to prevent the progression of necrosis in symptomatic patients following HIPEC with MitC. Reports of its use on the scrotum are absent in the current available literature.

Treatment with DMSO was attempted in our patient with limited success secondary to delayed recognition and lack of supporting literature for DMSO treatment of scrotal necrosis. Treatment was delayed by 11 days after the onset of symptoms, which is far beyond the recommendation of starting within 10 minutes.⁸ Irreversible tissue necrosis had already occurred as evidenced by the presence of eschar. However, it seems apparent that DMSO provided some benefit given the clear improvement in erythema and pain 7 hours after application (Figure 2). It is unknown to what extent the necrosis would have progressed if not treated with DMSO.

Scrotal necrosis following HIPEC with MitC is a rare and incompletely understood but important chemotherapy reaction. The presentation is fairly specific with the presence of intractable and constant scrotal pain along with erythema and induration progressing to eschar. Although DMSO has been found to be effective for certain vesicant extravasation reactions at IV sites, it is not well

studied for MitC, and no reports exist regarding its use on the scrotum. The presented characterization and explanation of the pathophysiology of this entity will aid in early recognition and timely institution of topical mitigating agents such as DMSO, which may prevent progression to scrotal necrosis and need for surgical debridement. More effective strategies may be geared toward prevention with thorough washout following HIPEC, preprocedural radiologic imaging or intraoperative visualization of the patent processus vaginalis, internal inguinal canal plugs, and patient education with anticipatory guidance should a reaction occur.²

REFERENCES

1. Akhavan A, Yin M, Benoit R. Scrotal ulcer after intraperitoneal hyperthermic chemotherapy. *Urology*. 2007;69:778.E9-E10.
2. Abdul Aziz NH, Wang W, Teo MC. Scrotal pain and ulceration post HIPEC: a case report. *J Gastrointest Cancer*. 2015;46:60-63.
3. Silva F, Avancini J, Criado P, et al. Scrotum ulcer developed after intraperitoneal hyperthermic chemotherapy with mitomycin-C [published October 21, 2012]. *Bjui International*. doi:10.1002/BJUIw-2012-019-web.
4. González-Moreno S, González-Bayón LA, Ortega-Pérez G. Hyperthermic intraperitoneal chemotherapy: rationale and technique. *World J Gastrointest Oncol*. 2010;15:68-75.
5. Bertelli G, Gozza A, Forno GB, et al. Topical dimethyl sulfoxide 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. Prevention and management of extravasation of cytotoxic drugs. *Drug Saf*. 1995;12:245-255.
7. Alberts DS, Dorr RT. Case report: topical DMSO for mitomycin-C-induced skin ulceration. *Oncol Nurs Forum*. 1991;18:693-695.
8. Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al; ESMO Guidelines Working Group. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. *Ann Oncol*. 2012;23 (suppl 5):167-173.
9. Ludwig CU, Stoll HR, Obrist R, et al. Prevention of cytotoxic drug induced skin ulcers with dimethyl sulfoxide (DMSO) and alpha-tocopherole. *Eur J Cancer Clin Oncol*. 1987;23:327-329.
10. Groel JT. Dimethyl sulfoxide as a vehicle for corticosteroids. a comparison with the occlusive dressing technique. *Arch Dermatol*. 1968;97:110-114.
11. Simon LS, Grierson LM, Naseer Z. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis [published online April 19, 2009]. *Pain*. 2009;143:238-245.
12. Nishimura M, Takano Y, Toshitani S. Systemic contact dermatitis medicamentosa occurring after intravesical dimethyl sulfoxide treatment for interstitial cystitis. *Arch Dermatol*. 1988;124:182-183.