Gemcitabine-Induced Pseudocellulitis

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PRACTICE **POINTS**

- Gemcitabine is a nucleoside analogue used to treat a variety of solid and hematologic malignancies.
- Gemcitabine-induced pseudocellulitis is a rare cutaneous side effect of gemcitabine therapy.
- Early recognition of pseudocellulitis may prevent unnecessary exposure to broad-spectrum antibiotics.

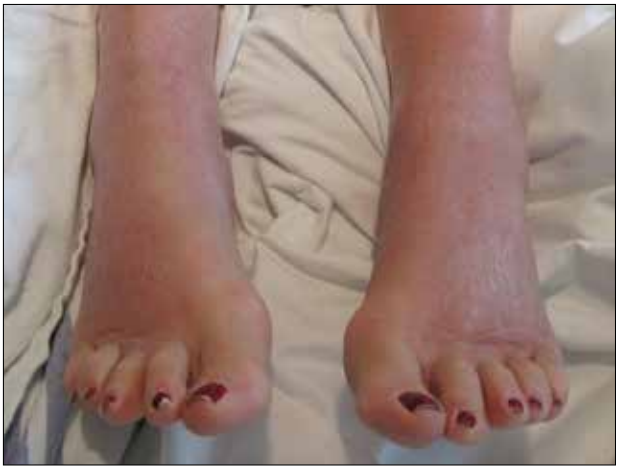
To the Editor:

Gemcitabine is a nucleoside analogue used to treat a variety of solid and hematologic malignancies. Cutaneous toxicities include radiation recall dermatitis and erysipelaslike reactions that occur in areas not previously treated with radiation. Often referred to as pseudocellulitis, these reactions generally have been reported in areas of lymphedema in patients with solid malignancies.[1-6] Herein, we report a rare case of gemcitabine-induced pseudocellulitis on the legs in a patient with a history of hematologic malignancy and total body irradiation (TBI).

A 61-year-old woman with history of peripheral T-cell lymphoma presented to the emergency department at our institution with acute-onset redness, tenderness, and swelling of the legs that was concerning for cellulitis. The patient's history was notable for receiving gemcitabine 1000 mg/m^2 for treatment of refractory lymphoma (12 and 4 days prior to presentation) as well as lymphedema of the legs. Her complete treatment course included multiple rounds of chemotherapy and matched unrelated donor nonmyeloablative allogeneic stem cell transplantation with a single dose of TBI at 200 cGy at our institution. Her transplant was complicated only by mild cutaneous graft-versus-host disease, which resolved with prednisone and tacrolimus.

On physical examination, the patient was afebrile with symmetric erythema and induration extending from the bilateral knees to the dorsal feet. A complete blood cell count was notable for a white blood cell count of 5400/µL (reference range, 4500–11,000/µL) and a platelet count of 96,000/µL (reference range, 150,000–400,000/µL). Plain film radiographs of the bilateral ankles were remarkable only for moderate subcutaneous edema. She received vancomycin in the emergency department and was admitted to the oncology service. Blood cultures drawn on admission were negative. Dermatology was consulted on admission, and a diagnosis of pseudocellulitis was made in conjunction with oncology (Figure). Antibiotics were held, and the patient was treated symptomatically with ibuprofen and was discharged 1 day after admission. The reaction resolved after 1 week with the use of diphenhydramine, nonsteroidal anti-inflammatory drugs, and compression. The patient was not rechallenged with gemcitabine.

Gemcitabine-induced pseudocellulitis is a rare cutaneous side effect of gemcitabine therapy. Reported cases have suggested key characteristics of pseudocellulitis (Table). The reaction is characterized by localized



Poorly defined erythema and edema of the bilateral lower legs and dorsal feet 5 days after gemcitabine infusion.

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Gemcitabine-Induced Pseudocellulitis in Cases Without Localized Radiation Therapy

Reference (Year)	Patient Age, y/ Sex	Primary Malignancy	Gemcitabine Dose	Time to Reaction From Last Dose	Antibiotics Given Prior to Diagnosis of Pseudocellulitis?	Other Workup Results	Reaction in Area of Prior Lymphadema?	Treatment	Reaction Reproducible?
Brandes et al[1] (2000)	50s/F	Metastatic endometrial cancer	1000/m^2 on days 1, 8, 15 preceded by tropisetron	40 h	NR[a]	C-reactive protein, <0.1 mg/dL (reference range, <0.5 mg/dL); white blood cell count, 2500/μL (reference range, 4000–9500/μL)	Yes	Gemcitabine dose reduction	Yes
	60s/F	Metastatic NSCLC	1000/m^2 on days 1, 8, 15 preceded by tropisetron	48 h	NR[a]	C-reactive protein, 1.46 mg/dL (reference range, <0.5 mg/dL); white blood cell count, 7920/μL (reference range, 4000–9500/μL)	Yes	Gemcitabine dose reduction	Yes
	60s/F	Metastatic NSCLC and breast cancer	1000/m^2 on days 1, 8, 15 preceded by tropisetron	48 h	NR[a]	C-reactive protein, 0.49 mg/dL (reference range, <0.5 mg/dL); white blood cell count, 4570/μL (reference range, 4000–9500/μL)	Yes	Gemcitabine dose reduction	Yes
Kuku et al[2] (2002)	50s/M	Malignant mesothelioma	1000 mg/m^2 in 4-wk cycles	48 h	NR	NR	No	Withdrawal of gemcitabine	Yes
Zustovich et al[3] (2006)	60s/M	Metastatic renal cancer	900 mg/m^2 on days 1, 8, 15, then every 28 d with dexamethasone-metoclopramide	6 d	Yes	Ultrasound of the right lower extremity (where the inflammatory reaction was predominant) negative for DVT	No	Withdrawal of gemcitabine	Yes
Korniyenko et al[4] (2012)	50s/M	SCC of the lung	NR	12–24 h	Yes	Normal C-reactive protein and white blood cell count; ultrasound of the legs negative for DVT	Yes	NR	Yes

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Reference (Year)	Patient Age, y/ Sex	Primary Malignancy	Gemcitabine Dose	Time to Reaction From Last Dose	Antibiotics Given Prior to Diagnosis of Pseudocellulitis?	Other Workup Results	Reaction in Area of Prior Lymphadema?	Treatment	Reaction Reproducible?
Singh and Hampole[5] (2012)	Elderly/M	Metastatic pancreatic adenocarcinoma	NR	7 d	Yes	White blood cell count, 5000/μL (reference range, 4500–11,000/μL); ultrasound negative for DVT	No	Withdrawal of gemcitabine	NR
Curtis et al[6] (2016)	30s/M	Metastatic perivascular sarcoma of the pelvis	NR	5 d	Yes	White blood cell count, 5000/μL (reference range, 4500–11,000/μL); lower extremity ultrasound negative for DVT; negative blood cultures	Yes	Withdrawal of gemcitabine	Not rechallenged
Current case[b]	60s/F	PTCL	1000 mg/m^2 with 10-mg dexamethasone injection	48 h	Yes	White blood cell count, 5400/μL (reference range, 4500–11,000/μL); radiography of the bilateral ankles revealed subcutaneous edema	Yes	Withdrawal of gemcitabine; treatment with NSAIDs, diphenhydramine, and compression	Not rechallenged

Abbreviations: F, female; NR, not recorded; NSCLC, non–small cell lung carcinoma; M, male; DVT, deep vein thrombosis; SCC, squamous cell carcinoma; PTCL, peripheral T-cell lymphoma; NSAID, nonsteroidal anti-inflammatory drug.

[a]One of 3 patients reported by Brandes et al[1] received antibiotics, but the authors did not specify which patient.

[b]Patient was treated with a single dose of total body irradiation (200 cGy) 8 months prior to presentation.

erythema, edema, and tenderness of the skin, with onset generally 48 hours to 1 week after receiving gemcitabine.[1-6] Lymphedema appears to be a risk factor.[1,3-5] Six cases (including the current case) demonstrated confinement of these findings to areas of prior lymphedema.[1,4,6] Infectious workup is negative, and rechallenging with gemcitabine likely will reproduce the reaction. Unlike radiation recall dermatitis, there is no prior localized radiation exposure.

Our patient had a history of hematologic malignancy and a one-time low-dose TBI of 200 cGy, unlike the other reported cases described in the Table. It is difficult to attribute our patient's localized eruption to radiation recall given the history of TBI. The clinical examination, laboratory findings, and time frame of the reaction were consistent with gemcitabine-induced pseudocellulitis.

It is important to be aware of pseudocellulitis as a possible complication of gemcitabine therapy in patients without history of localized radiation. Early recognition of pseudocellulitis may prevent unnecessary exposure to broad-spectrum antibiotics. Patients' temperature, white blood cell count, clinical examination, and potentially ancillary studies (eg, vascular studies, inflammatory markers) should be reviewed carefully to determine whether there is an infectious or alternate etiology. In patients with known prior lymphedema, it may be beneficial to educate clinicians and patients alike about this potential adverse effect of gemcitabine and the high likelihood of recurrence on re-exposure.

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