Gemcitabine-induced pseudocellulitis in a patient with non–small cell lung carcinoma

Eseosa Asemota, MD, MPH,[a] Erika Reid, MD,[a] and Carrie Kovarik, MD[b]
Philadelphia, Pennsylvania

Key words: gemcitabine chemotherapy; noninfectious; pseudocellulitis.

INTRODUCTION

Gemcitabine (2,2-difluorodeoxycytidine) is a nucleoside analogue used as a chemotherapeutic agent to treat various malignancies. The common side effects of gemcitabine include myelosuppression, gastrointestinal disturbances, influenzalike symptoms, and elevation of liver enzyme levels. Gemcitabine is also associated with cutaneous adverse effects such as rash, alopecia, pruritus, radiation recall dermatitis, hypersensitivity reactions, hyperpigmentation, and erysipeloid reactions.[1-3] There are also a few isolated cases of livedo reticularis, sclerodermalike changes, Sweet's syndrome, and toxic epidermal necrolysis.[3]

Rarely, gemcitabine is associated with pseudocellulitis, a nonnecrotizing inflammation of the dermis and subcutis from a noninfectious etiology, which could be confused clinically for cellulitis.[1,4] We report a case of recurrent gemcitabine-induced pseudocellulitis after the use of gemcitabine and carboplatin combination therapy.

CASE PRESENTATION

A 77-year-old man was receiving gemcitabine and carboplatin for stage IV non–small cell carcinoma of the lung and metastases to the brain. He previously received gamma knife and radiotherapy to his chest and carboplatin/pemetrexed chemotherapy.

The patient originally presented as an outpatient with an acute onset of bilateral lower extremity erythema 2 days after receiving his third cycle of gemcitabine chemotherapy. Cephalexin was initiated for a presumptive diagnosis of bacterial cellulitis, and when he did not improve after 3 days, he switched to clindamycin. After still not improving, he presented to the emergency department. Intravenous vancomycin was initiated; however, chills and rigors developed abruptly, and vancomycin was discontinued. The dermatology team was then consulted.

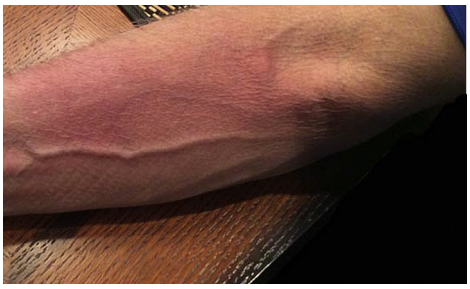

Fig 1. Prior episode of pseudocellulitis on right forearm arm after gemcitabine chemotherapy.

On assessment, he denied recent trauma to his legs. He reported 2 similar previous episodes of erythema of the extremities a few days after the gemcitabine treatment, which had both resolved spontaneously within 1 week after the onset. The first episode involved his right forearm (Fig 1), and the second episode was described as red patches on his lower extremities. Each subsequent episode seemed to be more exuberant and last longer than the prior episode.

On examination, the patient was found to be afebrile. There was well-demarcated, confluent erythema of bilateral lower extremities (left greater than right), extending from the dorsal surface of his feet to the upper shin (Fig 2). He also had 2+ pitting pedal edema extending up to his upper shins. There

From the Department of Dermatology,[a] and Departments of Dermatology, Dermatopathology, and Infectious Diseases,[b] University of Pennsylvania.

Funding sources: None.
Conflicts of interest: None declared.

Correspondence to: Carrie Kovarik, MD, Associate Professor, Dermatology, Dermatopathology, and Infectious Diseases, University of Pennsylvania, Philadelphia, PA. E-mail: carrie.kovarik@uphs.upenn.edu.

JAAD Case Reports 2015;1:178-81.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2015.04.007

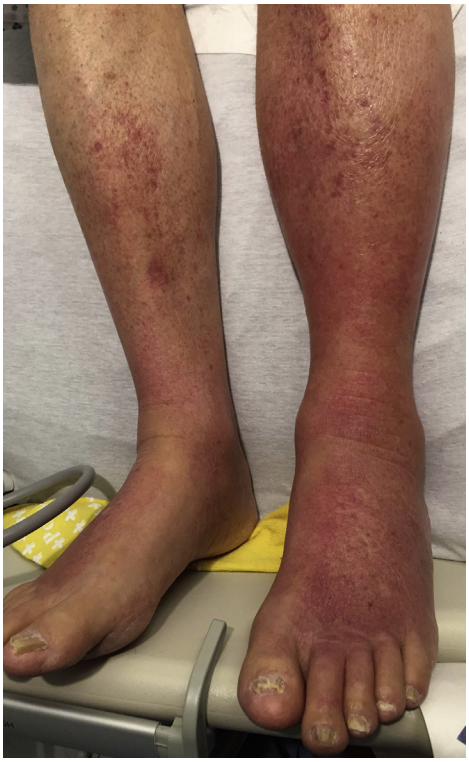

Fig 2. Current case of pseudocellulitis on both lower extremities.

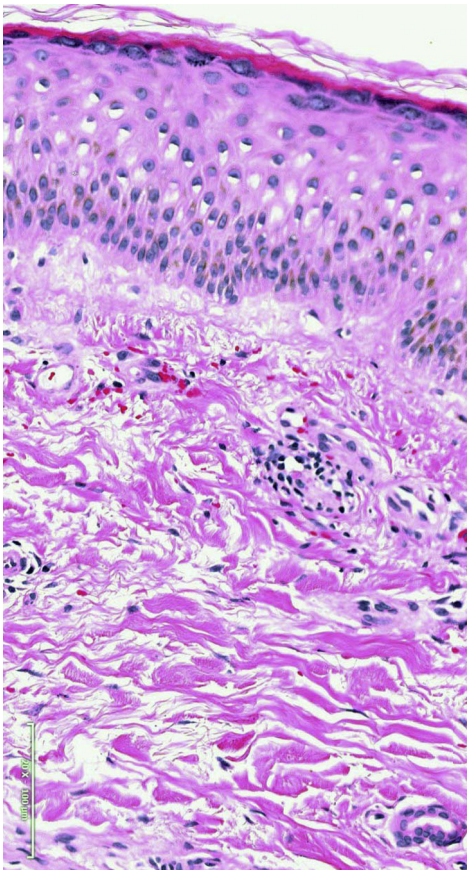

Fig 3. Histology was consistent with hypersensitivity reaction, with edema and sparse mixed inflammation. (Hematoxylin-eosin staining; original magnification: ×200.)

was mild local tenderness, and dorsalis pedis pulses were felt bilaterally. The rest of his physical examination findings were essentially normal.

Diagnostic tests were done, and pending results, the primary medical team started treatment with nafcillin to cover for possible cellulitis. The laboratory panel results showed a normal white blood cells count of 4.4×10^9 cells/L, and the patient remained afebrile. A biopsy specimen taken for histology was consistent with hypersensitivity reaction, with edema and sparse mixed inflammation with lymphocytes, occasional neutrophils, and rare eosinophils (Fig 3). Tissue culture showed no growth.

Based on the absence of fever, normal white cell count, tissue cultures and biopsy result, recurrent nature of the disease, and temporal relation between of the appearance of the lesions and the administration of gemcitabine, a diagnosis of gemcitabine-induced pseudocellulitis was made, and antibiotics were discontinued. The patient was treated with 0.1% triamcinolone acetonide cream under occlusion and compression stockings to manage lymphedema. The erythema regressed over the next 3 days, and he was discharged from the hospital in a stable condition. Recommendations were made not to withdraw gemcitabine chemotherapy, as the patient was responding remarkably to this treatment. We recommended similar treatment, if any erythema was detected during future gemcitabine cycles. After discharge, the patient was seen in the outpatient clinic with no further complaints.

DISCUSSION

Gemcitabine is a pyrimidine antimetabolite, which is incorporated as an active nucleotide metabolite into DNA, resulting in chain termination and inhibition of DNA synthesis. Gemcitabine is used as treatment for a variety of malignancies. The American Society of Clinical Oncology guidelines recommend combination of platinum-based doublets with drugs such as gemcitabine as the preferred chemotherapy for advanced non–small cell carcinoma of the lung.[5] As the therapeutic use of gemcitabine expands, awareness of its potential toxicities is increasingly important.

Gemcitabine has been associated with several cutaneous toxicities, notably, radiation recall reactions.[6] Because gemcitabine is a radiosensitizer, radiation recall may occur when the agent is given

Table I. Review of previous published cases of gemcitabine-induced pseudocellulitis in absence of previous radiation exposure

Study	Tumor type	Location of pseudocellulitis	Associated lymphedema with pseudocellulitis	Time from last dose of gemcitabine to reaction	Treatment of gemcitabine-induced pseudocellulitis
Brandes et al 2000[10]	Metastatic NSCLC and breast cancer, metastatic endometrial cancer, metastatic endometrial cancer	Bilateral legs, abdomen and thighs, thigh	Pre-existing lymphedema of both lower extremities, lymphatic edema of lower abdomen and thighs, thigh edema postosteosynthesis	All 3 presented within 2 days	Resolved within 14 days without specific treatment
Curtis et al 2014[2]	Metastatic perivascular sarcoma of the pelvis	Bilateral lower legs	Lower extremity edema caused by lymphatic obstruction	Within 5 days	Spontaneous resolution and discontinuation of gemcitabine therapy
Dasanu and Bockorny 2014[1]	Adenocarcinoma of the pancreas	Bilateral lower legs	Moderate bilateral pedal edema	Within a few weeks of therapy	Reassurance, spontaneous resolution
Korniyenko et al 2012[4]	Squamous cell lung carcinoma	Bilateral lower legs	Bilateral lower extremity edema	Less than 1 day	Diphenhydramine with NSAIDs for symptomatic management.
Kuku et al 2002[11]	Mesothelioma	Left elbow and knee	None	2 days	Spontaneous resolution
Obeid and Venugopal 2013[9]	Metastatic liver disease	Bilateral lower legs	Bilateral lower extremity edema	2 days	Self-resolution after initial antibiotic therapy
Singh and Hampole 2012[3]	Metastatic pancreatic adenocarcinoma	Bilateral lower legs	Bilateral lower extremity edema	7 days	Withdrawal of gemcitabine and symptomatic management with NSAIDs
Zustovich et al 2006[12]	Metastatic renal cancer	Bilateral lower legs (R > L)	Mild bilateral lower extremity edema	6 days	

NSAIDs, Nonsteroidal anti-inflammatory drugs; *NSCLC*, Non−small cell lung carcinoma.

within a few months of radiotherapy or years after radiation treatment. The pathophysiology of radiation recall is hypothesized to be caused by vascular damage and increased localized permeability of the skin capillaries in areas previously treated with radiotherapy. Another hypothesis proposes a drug hypersensitivity mechanism.[7]

However, recently, a new phenomenon known as *gemcitabine-related pseudocellulitis*, occurring in the absence of prior radiotherapy, has been described (Table I). Gemcitabine-related pseudocellulitis may occur in an area of lymphedema, as one of the episodes of this case. The etiology of the lymphedema in this case is unknown and may be a side effect of gemcitabine, as seen in some other case reports. The pathophysiology of this reaction is still unknown, although it is theorized that areas of impaired lymphatic drainage lead to drug permeation into interstitial fluid, drug accumulating in the subcutaneous tissue, and inadequate drug inactivation in subcutaneous tissue.[2,4]

The evaluation of gemcitabine-induced pseudocellulitis poses a challenge because many possible etiologies exist for cutaneous eruptions in cancer patients. Clinical judgment, laboratory analysis, tissue cultures, and histopathology can help distinguish pseudocellulitis from infective cellulitis. Wells syndrome (eosinophilic cellulitis) could also be considered clinically; however, it is distinguished histologically because of the marked infiltrate of eosinophils in the dermis. Also, because gemcitabine is often used in combination with other chemotherapeutic agents, it is important to ensure a reaction observed is not caused by the other agent. In this case report, the other agent used was carboplatin, a DNA alkylating agent, which generally has minimal skin toxicity.[8]

The duration of gemcitabine-induced pseudocellulitis is proposed to be related to the drug's pharmacokinetics and may exist until the drug is displaced from the subcutaneous tissue of the affected area.[2] Nonsteroidal anti-inflammatory drugs, diphenhydramine, and topical steroids may be given for symptomatic therapy.[1,4,9]

This case reiterates the need for awareness of this adverse reaction by the medical team. Awareness is vital to help avoid misdiagnosis as infectious cellulitis, unnecessary hospitalization, and exposure to antibiotics and enable gemcitabine chemotherapy to be continued with proper precautions.

REFERENCES

1. Dasanu CA, Bockorny B. Recurrent pseudocellulitis due to gemcitabine: Underrecognized and underreported? *J Oncol Pharm Pract*. http://dx.doi.org/10.1177/1078155214531610. Published online April 24, 2014.
2. Curtis S, Hong S, Gucalp R, Calvo M. Gemcitabine-induced pseudocellulitis in a patient with recurrent lymphedema: a case report and review of the current literature. *Am J Ther*. http://dx.doi.org/10.1097/MJT.0000000000000024. Published online January 21, 2014.
3. Singh A, Hampole H. Gemcitabine associated pseudocellulitis. *J Gen Intern Med*. 2012;27(12):1721.
4. Korniyenko A, Lozada J, Ranade A, Sandhu G. Recurrent lower extremity pseudocellulitis. *Am J Ther*. 2012;19(4):e141-e142.
5. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol*. 2004;22(2):330-353.
6. Zhang L, Patel R, Mehdi S. Gemcitabine-Induced Radiation Recall Phenomenon in Two Distinctive Sites on the Same Patient. *J Community Support Oncol*. 2014;12(5):188-190.
7. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. *Radiother Oncol*. 2001;59(3):237-245.
8. McKeage MJ. Comparative adverse effect profiles of platinum drugs. *Drug Saf*. 1995;13(4):228-244.
9. Obeid KM, Venugopal AA. Gemcitabine-associated "pseudocellulitis" and "pseudosepsis": a case report and review of the literature. *Am J Ther*. 2013;20(1):118-120.
10. Brandes A, Reichmann U, Plasswilm L, et al. Time- and dose-limiting erysipeloid rash confined to areas of lymphedema following treatment with gemcitabine- a report of three cases. *Anticancer Drugs*. 2000;11:15-17.
11. Kuku I, Kaya E, Sevinc A, et al. Gemcitabine-induced erysipeloid skin lesions in a patient with malignant mesothelioma. *J Eur Acad Dermatol Venereol*. 2002;16:271-272.
12. Zustovich F, Pavei P, Cartei G. Erysipeloid skin toxicity induced by gemcitabine. *J Eur Acad Dermatol Venereol*. 2006;20:757-758.