



Gemcitabine-associated acute lipodermatosclerosislike eruption: An underrecognized phenomenon

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Key words: acute lipodermatosclerosis; gemcitabine; pseudocellulitis.

INTRODUCTION

Gemcitabine is a commonly used chemotherapy for the treatment of various solid tumors as well as sarcomas and hematologic malignancies. Although side effects such as bone marrow suppression are well described, cutaneous side effects are less recognized. Certain gemcitabine-associated cutaneous reactions have been categorized under the umbrella terminology *pseudocellulitis*, including lipodermatosclerosislike and erysipeloid reactions, sclerodermalike changes, and radiation recall events.^{1,2} Additionally, these reactions are often confused with other diagnoses, in particular, infectious cellulitis, which may subject patients to unnecessary treatment with antibiotics, hospitalizations, and interruption of chemotherapy. Given the widespread use of gemcitabine and the relatively few reported cases of associated acute lipodermatosclerosis (ALDS), we believe that the condition is underrecognized and underreported. We propose using a more specific diagnosis for cutaneous reactions to gemcitabine that will guide appropriate management. In this series, we report 4 cases of gemcitabine-associated ALDS-like eruptions and a literature review of 16 similar cases. To the best of our knowledge, this is the largest case series review reported for gemcitabine-associated ALDS-like eruptions.

CASE SERIES

Patient 1

A 73-year-old man with a history of metastatic pancreatic adenocarcinoma was started on gemcitabine and Abraxane (protein-bound paclitaxel, Celgene Corp, Summit, NJ) and presented 5 days after his first dose with a new-onset lower extremity

Abbreviation used:

ALDS: acute lipodermatosclerosis

eruption. Pertinent medical history was notable for atrial fibrillation on warfarin, venous hypertension with lower extremity edema, and no history of radiation therapy. Physical examination found exquisitely tender red plaques of the bilateral shins (predominantly above the medial malleoli) with overlying petechiae (Fig 1, A). In addition, there was 2+ pitting edema of the feet extending up to the knees. The patient was afebrile and complete blood count found thrombocytopenia (platelets, 60) but normal white blood cell count. Gemcitabine-associated ALDS-like eruption was diagnosed and treated with leg elevation, compression socks, and clobetasol 0.05% ointment under saran wrap occlusion. At 2-week follow-up, his cutaneous eruption was markedly improved with decreased edema, resolution of the tender plaques, and residual hemosiderin deposition (Fig 1, B). The patient remained on treatment without dose reduction.

Patient 2

A 79-year-old woman with a history of adenocarcinoma of the pancreatic head with liver metastases presented with bilateral lower extremity edema and pain. Her initial treatment regimen included nivolumab, gemcitabine, and abraxane; however, nivolumab was discontinued secondary to severe infusion hypersensitivity reaction. Two weeks after receiving her second dose of gemcitabine and Abraxane, she had 2+ edema, tenderness,

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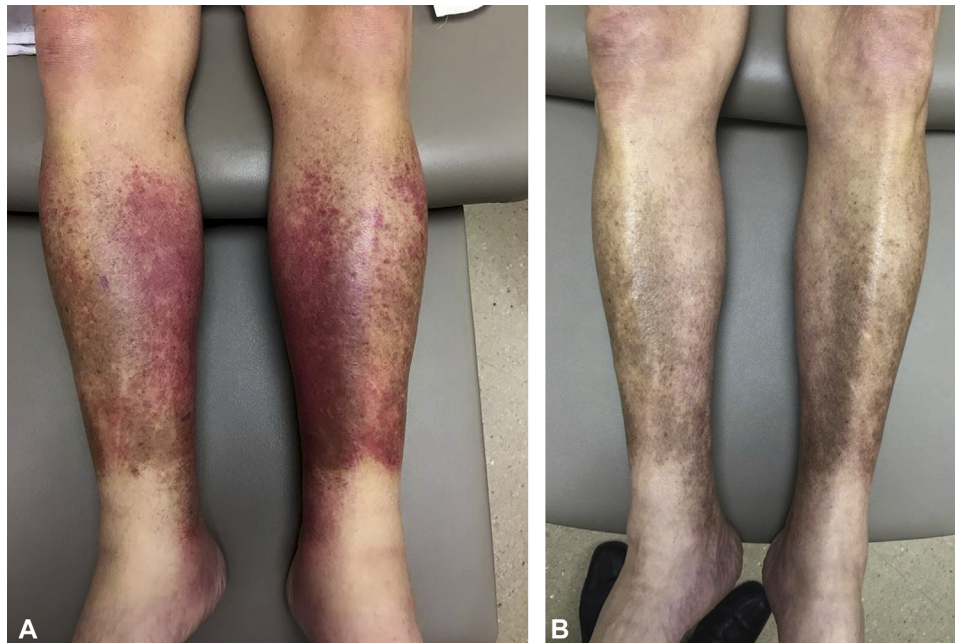


Fig 1. **A**, Tender, erythematous plaques on the bilateral lower extremities with overlying petechiae (patient 1). **B**, Resolution of the intense erythema and tenderness with hemosiderin deposition 2 weeks after compression therapy and high-potency topical steroids under occlusion (patient 1).



Fig 2. Significant edema and erythema in another patient with gemcitabine-associated ALDS-like eruption (patient 2).

and mild erythema of the bilateral lower extremities (Fig 2). The patient was admitted for presumed cellulitis, and, after no improvement with empiric

sulfamethoxazole/trimethoprim, she was referred to the Yale Onco-Dermatology Clinic. The leading diagnosis was changed to gemcitabine-associated ALDS-like eruption, and the patient was treated with compression therapy, high-potency topical steroids twice daily, discontinuation of antibiotics, and resumption of gemcitabine. Follow-up 1 week later found resolution of the erythema and tenderness, with mild residual edema. She was encouraged to use compression socks daily for maintenance therapy and leg elevation as often as possible.

Patient 3

A 76-year-old man with a history of pancreatic adenocarcinoma after Whipple procedure was started on adjuvant chemotherapy with gemcitabine. The dermatology service was consulted after the fifth dose of gemcitabine for new-onset swelling and painful shins. The patient had no history of lower extremity edema. Physical examination found tender, erythematous plaques on the bilateral lower extremities with slight induration and 1+ edema from the ankles to the upper shins (Fig 3). The patient was afebrile without leukocytosis. After diagnosis of ALDS-like eruption, he was started on clobetasol 0.05% ointment twice daily for 2 weeks and compression therapy. He remained on treatment with gemcitabine, and the eruption improved over 2 weeks. At 2-month follow-up, the patient was seen at the onco-dermatology clinic for recurrence of the



Fig 3. Confluent light pink patches and tenderness over the shins in a third patient with gemcitabine-associated ALDS-like eruption (patient 3).

eruption 2 days after gemcitabine infusion, in the setting of discontinuation of leg compression and topical steroids. Compression socks and clobetasol ointment were reinitiated. The patient subsequently had leukopenia, thrombocytopenia, and bilateral pleural effusions. His performance status and pulmonary function deteriorated, and his gemcitabine treatment was discontinued. At follow-up visit several weeks later, he had hemosiderin deposition and asymptomatic mild induration of the bilateral shins.

Patient 4

A 73-year-old man with a history of recurrent invasive transitional cell carcinoma of the bladder presented with painful lower legs that he first noted 4 days after his second dose of gemcitabine. Physical examination found red tender plaques of the bilateral shins and dorsal feet with 1+ edema (Fig 4). The patient was afebrile with no leukocytosis. ALDS-like eruption secondary to gemcitabine was diagnosed. His eruption responded to treatment with twice-daily topical clobetasol 0.05% ointment and leg elevation alone, without compression therapy.

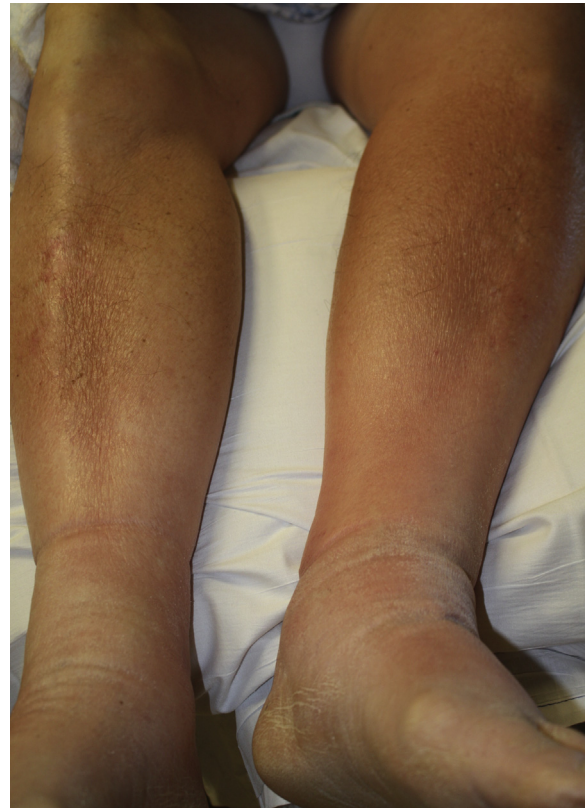


Fig 4. Tender erythematous plaques on the bilateral shins and dorsal feet in a fourth patient with gemcitabine-associated ALDS-like eruption (patient 4).

DISCUSSION

Gemcitabine is a pyrimidine analogue that blocks progression of cells through the G1/S phase.³ It is active against many solid organ malignancies including breast, ovarian, non-small cell lung, transitional cell bladder, pancreatic, and biliary tract cancers, as well as various sarcomas and hematologic malignancies. Like other chemotherapeutics, it may be associated with alopecia, mucositis, and cutaneous hypersensitivity reactions. It is also important to be familiar with the less common cutaneous adverse effects.

Gemcitabine-associated ALDS-like eruption is likely an underrecognized condition that is often mistakenly treated as cellulitis. The differential diagnosis includes infectious cellulitis, drug hypersensitivity, toxic erythema of chemotherapy, and other panniculitides such as erythema nodosum. It commonly presents with a sudden onset of erythematous and tender plaques of the lower extremities (often bilateral). In addition, patients usually have lower extremity edema and slight induration of the involved sites. Unlike cellulitis, fever and leukocytosis are usually absent; however, gemcitabine may cause a drug-induced fever and myelosuppression,

Table I. Summary of acute lipodermatosclerosislike eruptions in the setting of gemcitabine therapy

Patient No.	Study	Age/Sex	Cancer	Preexisting edema	Reaction site	Latency, d	Dose	Drug discontinued	Radiation therapy	Resolution
1	Current report	73/M	Metastatic pancreatic adenocarcinoma	Yes	Bilateral lower extremities	5	1st dose, 1000 mg/m ²	No	No	7 d
2	Current report	79/F	Metastatic pancreatic adenocarcinoma	No	Bilateral lower extremities	13	2nd dose, 1000 mg/m ²	No	No	14 d
3	Current report	76/M	Adenocarcinoma of pancreas	No	Bilateral lower extremities	6	5th dose, 1000 mg/m ²	No	No	14 d
4	Current report	73/M	Metastatic transitional cell carcinoma of bladder	No	Bilateral lower extremities	4	2nd dose, 1000 mg/m ²	No	No	Improved, 2 d Resolved, 8 wk
5	Strouse et al, 2016 ¹⁵	62/F	Metastatic pancreatic adenocarcinoma	Yes	Bilateral lower extremities	7	2nd dose, 1200 mg/m ²	No	No	7 d
6	Curtis et al, 2016 ⁵	39/M	Metastatic perivascular sarcoma of pelvis	Yes	Right lower extremity	4	3rd dose	Yes	No	Improved, 1 d Resolved, 2 d
7	Asemota et al, 2015 ⁶	77/M	Non–small cell carcinoma of lung	Yes	Bilateral lower extremities, right forearm	2	1st dose	No	Chest	7 d
8	Ruiz-casado et al, 2015 ⁷	42/F	Adenocarcinoma of pancreas	Yes	Bilateral lower extremities	2	10th dose	Yes	Pancreas	Not reported
9	Dasanu et al, 2015 ⁸	72/M	Metastatic pancreatic adenocarcinoma	Yes	Bilateral lower extremities	Not reported	8th dose, 1000 mg/m ²	No	No	14 d
10	Singh et al, 2012 ⁹	Not Reported / M	Metastatic pancreatic adenocarcinoma	No	Bilateral lower extremities	7	2nd dose	Yes	No	“Promptly” when drug discontinued
11	Obeid et al, 2011 ¹⁰	74/F	Metastatic pancreatic carcinoma	No	Bilateral lower extremities	2	3rd dose	Yes (encephalopathy after 4th dose)	Pancreas	5 d
12	Korniyenko et al, 2010 ¹¹	59/M	Squamous cell carcinoma of lung	No	Bilateral lower extremities	<1	1st dose	No	No	2 d
13	Tan et al, 2007 ¹	57/M	Malignant pleural mesothelioma	Yes	Abdomen, genitalia, medial thighs	2	1st dose	Not Reported	Left chest	14 d
14	Zustovich et al, 2006 ¹²	65/M	Renal sarcomatoid carcinoma	No	Bilateral lower extremities, feet	6	1st dose, 900 mg/m ²	Yes	No	7 d
15	Bessis et al, 2004 ¹³	50/M	Metastatic transitional cell carcinoma of bladder	No	Bilateral lower extremities	2 d	2nd dose, 1200 mg/m ²	Yes	No	Improved, 14 d Progressed to cutaneous sclerosis

Continued

Table I. Cont'd

Patient No.	Study	Age/Sex	Cancer	Preexisting edema	Reaction site	Latency, d	Dose	Drug discontinued	Radiation therapy	Resolution
16	Kuku et al, 2002 ¹⁴	50/M	Malignant mesothelioma	No	Left elbow, right knee	2	1st dose, 1000 mg/m ²	No	No	Improved, 1 d
17	Chu et al, 2001 ⁴	70/M	Squamous cell carcinoma of lung	No	Bilateral lower extremities	3	4th dose, up to 1000 mg/m ²	No	No	Resolved, 5 d
18	Brandes et al, 2000 ²	61/F	Metastatic non-small cell carcinoma of lung	Yes	Thigh	2	1st dose, 1000 mg/m ²	No	No	Improved, several days
19	Brandes et al, 2000 ²	57/F	Metastatic endometrial carcinoma	Yes	Pelvis, thighs	1-2	1st dose, 1000 mg/m ²	No	No	14 d
20	Brandes et al, 2000 ²	65/F	Metastatic breast and non-small cell lung carcinoma	Yes	Bilateral lower extremities	2	1st dose, 1000 mg/m ²	No	No	14 d

which can complicate the diagnosis. Historically, the term *pseudocellulitis* has been used to describe reactions to gemcitabine that presented as radiation recall, erysipeloid eruptions, sclerodermalike changes, and ALDS¹; however, for cases such as ours, we encourage the diagnosis *ALDS-like eruption* to more accurately depict the etiology and clinical findings, while guiding the appropriate management. In addition, unlike cutaneous sclerosis, which may warrant discontinuation of therapy, patients with ALDS-like eruption can generally continue treatment without dose adjustment.

Classically, lipodermatosclerosis, or sclerosing panniculitis, occurs in the setting of venous insufficiency.⁴ The pathogenesis likely involves reduced fibrinolytic activity from venous hypertension and increased vascular permeability.⁴ In the acute phase, painful, erythematous plaques develop above the medial malleoli or other dependent sites, whereas the chronic phase manifests with sharply demarcated induration and hyperpigmentation caused by hemosiderin deposition. Lipodermatosclerosis may be distinguished from a pigmented purpuric dermatosis such as Schamberg disease, which presents with discrete, yellow-brown petechial patches, without tender plaques or sclerosis of the dermis and subcutis. Lipodermatosclerosis is diagnosed clinically, and biopsy is not routinely performed. Histologically, stasis changes with both septal and lobular panniculitis may be seen, and lipomembranous changes are found in advanced lesions.⁴

We reviewed the literature for gemcitabine-related “pseudocellulitis,” “erysipeloid,” “lipodermatosclerosis,” and “scleroderma,” and created a table that includes the clinical features, demographics, risk factors, and treatment response of what we believe to be all previously described cases (Table I).^{1,2,4-15} Radiation recall events were excluded, as we believe they represent a separate category of cutaneous reactions and can be distinguished based on clinical history and physical findings.

Skin reactions involved the lower extremities in all 20 patients (100%). Seventeen (85%) of 20 patients had bilateral lower extremity involvement. Preexisting edema was reported in 10 (50%) of 20 patients. In a patient with malignant ascites but no peripheral edema, the eruption occurred on dependent areas of the abdomen, genitalia, and medial thighs.¹ Another patient with endometrial carcinoma and iliac lymph node dissection was noted to have skin changes in the pelvis.² Preexisting lymphedema is hypothesized to interfere with the pharmacokinetics of gemcitabine, with accumulation of the drug and its metabolites in the interstitial fluid.³

The cutaneous reactions typically developed rapidly within 2 to 5 days after gemcitabine infusion. In 10 of 19 patients (52%), skin changes appeared within 48 hours of the infusion (average number of days was 4). The initial skin eruption appeared anywhere between the first and 10th dose of gemcitabine. Ten patients (50%) were treated with antibiotics for presumed infectious cellulitis, and approximately half of these cases were treated with intravenous antibiotics.^{1,2,4,6,7,9-12} Most (13 patients) continued gemcitabine despite the cutaneous adverse event, whereas treatment was discontinued in 6 patients with resolution of symptoms. When reported, improvement in skin lesions began within 24 to 48 hours in 4 patients, and significant improvement was noted within 1 week in 10 patients and within 2 weeks in 18 patients.

The mechanism of gemcitabine-associated ALDS-like eruption is unclear; increased vascular permeability, either from direct venous endothelial damage or by the release of vasoactive cytokines, may accelerate a local coagulation response.^{3,4} Although peripheral edema may occur in 15% to 20% of patients on gemcitabine,³ those predisposed to chronic venous stasis changes may be more likely to develop this cutaneous reaction.

Treatment for patients with gemcitabine-associated ALDS-like eruption involves conservative measures such as high-potency topical steroids, compression therapy, leg elevation, and anti-inflammatory drugs for symptomatic relief. Furthermore, before initiation of therapy with gemcitabine, patients should be evaluated and treated for preexisting lymphedema, which may increase their risk for the development of the cutaneous reaction. It is important to recognize this treatment-related adverse event to avoid interruption of therapy and unnecessary antibiotics and hospitalizations. Furthermore, the term *pseudocellulitis* is vague and can create confusion about the etiology of these

reactions. Instead, we propose use of the term *ALDS-like eruption* when an appropriate clinical diagnosis can be made.

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