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Gemcitabine-Induced Pseudocellulitis in Metastatic Pancreatic Cancer

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Abstract

Gemcitabine-induced pseudocellulitis is a noninfectious inflammatory reaction that closely mimics bacterial cellulitis and can result in substantial diagnostic uncertainty and interruptions in cancer care. We report the case of a woman in her mid-seventies with metastatic pancreatic adenocarcinoma who developed recurrent bilateral lower extremity erythema and edema following gemcitabine therapy. The condition resulted in three unplanned hospitalizations, multiple chemotherapy delays, and five courses of broad-spectrum antibiotics, ultimately leading to antibiotic-associated *Clostridioides difficile* colitis. The diagnosis of gemcitabine-induced pseudocellulitis was established only during the third hospitalization after recognition of the bilateral symmetric distribution, normal inflammatory markers, negative microbiologic cultures, and a reproducible temporal relationship with gemcitabine administration. Gemcitabine was discontinued, supportive measures were initiated, and the patient's symptoms resolved completely. This case highlights the considerable oncologic and healthcare burden associated with delayed recognition of gemcitabine-induced pseudocellulitis and underscores the importance of early diagnosis by the hematology-oncology team to avoid unnecessary hospitalizations, inappropriate antibiotic exposure, and interruptions in cancer-directed therapy.

A patient in her mid-seventies with stage IV pancreatic adenocarcinoma and peritoneal metastases was receiving palliative gemcitabine (1000 mg/m², days 1, 8, and 15 of a 28-day cycle). Relevant comorbidities included bilateral lower extremity deep vein thromboses on anticoagulation, chronic venous insufficiency with baseline edema, and a prior history of *Clostridioides difficile* infection. Approximately three months into treatment, the patient presented with two months of progressive bilateral leg swelling and erythema.

Her vital signs were temperature 36.5° C, blood pressure 115/76, respiratory rate of 17 breaths per minute, heart rate 91 beats per minute, and oxygen saturation of 95% on room air. Physical examination revealed warmth on palpation, and confluent erythema from the ankles to mid-calves bilaterally. There was 2+ pitting edema, and mild tenderness without fever, skin breakdown, purulence, or bullae. WBC was 7,200/μL (normal: 4,500-11,000/μL) with normal differential, CRP 8.2 mg/L (normal: less than 10 mg/L), and ESR 22 mm/hr (normal: less than 30 mm/hr in women). Bilateral venous duplex ultrasonography showed chronic but no acute thrombosis. She was admitted for presumed bilateral cellulitis. The patient received intravenous vancomycin (3

days), then oral cephalexin (10 days); blood cultures were negative. Erythema responded minimally, but the edema persisted. After a six-day admission during which gemcitabine was held and one treatment cycle missed, the patient was discharged on doxycycline for six additional days with only marginal improvement.

One week after completing doxycycline, the patient was rehospitalized with worsening bilateral erythema and edema (WBC 6,800/μL, CRP 7.1 mg/L). Intravenous cefepime and vancomycin were initiated, later transitioned to linezolid. The admission was complicated by *C. difficile* colitis confirmed by toxin assay, requiring oral vancomycin and five additional inpatient days. Two further gemcitabine cycles were missed. The skin findings again failed to respond to antibiotics.

Two months later, the patient returned on outpatient intravenous vancomycin that had been initiated at an outside facility for presumed recurrent cellulitis in the interval period; her bilateral erythema had acutely worsened three days after the most recent gemcitabine infusion. A careful temporal review revealed a consistent pattern across all prior episodes: symptoms reliably emerged within 2-5 days of each infusion. Examination showed symmetric confluent blanching erythema with well-de-



Figure 1. Bilateral lower extremity erythema and edema consistent with gemcitabine-induced pseudocellulitis. Note the symmetric confluent blanching erythema with well-demarcated superior borders extending to the mid-calves. The absence of skin breakdown, bullae, or purulence combined with bilateral symmetry distinguishes this noninfectious chemotherapy adverse effect from bacterial cellulitis.

marked superior borders, 2+ pitting edema, and tenderness without fluctuance or breakdown ([Figure 1](#)).

The triad of bilateral symmetry, consistent infusion-linked timing, and failure of five successive antibiotic courses in the absence of any systemic infection markers established gemcitabine-induced pseudocellulitis. Gemcitabine was held, antibiotics stopped, and supportive care begun with leg elevation, graduated compression stockings, and topical emollients. Symptoms improved within three weeks. A milder recurrence emerged six weeks after gemcitabine discontinuation, which was managed conservatively with full resolution. Gemcitabine was ultimately stopped given cumulative toxicity and disease progression, and the patient transitioned to supportive care.

Gemcitabine-induced pseudocellulitis is a noninfectious inflammatory skin reaction presenting with erythema, warmth, edema, and tenderness that is clinically indistinguishable from bacterial cellulitis.^{1,2} Estimated incidence ranges from 0.3% to 2.7%, though systematic misdiagnosis likely renders this an underestimate.^{1,3} The condition preferentially involves the lower extremities of patients with pre-existing venous insufficiency, lymphedema, or deep vein thrombosis, comorbidities disproportionately common in oncology populations.^{3,4} When misidentified as infection, the consequences cascade: unnecessary hospitalizations averaging \$195 million to \$515 million, prolonged antibiotic courses with attendant toxicity including *C. difficile* colitis, nosocomial risks, and most consequentially interruption of cancer therapy.⁵⁻⁷

Bacterial cellulitis and gemcitabine-induced pseudocellulitis share an almost identical clinical appearance, but differ in several diagnostically important ways.^{1,2,8} Bacterial cellulitis is typically unilateral, associated with fever and leukocytosis, and responds to antibiotics. Gemcitabine-induced pseudocellulitis is characteristically bilateral and symmetric, occurs without systemic inflammatory response, fails antibiotics entirely, and most usefully follows a reproducible temporal pattern tied to infusion, with onset within 2-7 days of dosing and improvement between cycles. The pathophysiology of pseudocellulitis likely involves accumulation of gemcitabine or its metabolites in tissues with impaired venous or lymphatic drainage, producing direct endothelial injury and a localized inflammatory response.⁹ This explains the predilection for lower extremities in patients with venous insufficiency, lymphedema, or prior thrombosis. Histopathology shows perivascular lymphocytic infiltration and dermal edema without organisms.¹⁰ Recurrence after gemcitabine discontinuation, as occurred in our patient, is reported in the literature and likely reflects persistent drug accumulation in damaged tissue. Recurrence on rechallenge approaches 70%, making the decision to resume gemcitabine one that requires careful oncologic judgment.^{9,11}

The differential diagnosis of bilateral symmetric lower extremity erythema and edema is broad and includes, in addition to gemcitabine-induced pseudocellulitis: bilateral bacterial cellulitis (uncommon but reported, particularly in immunocompromised patients), stasis dermatitis, lipodermatosclerosis, contact or allergic dermatitis, bilateral deep vein thrombosis, congestive heart failure with dependent edema, and lymphedema. Among these, stasis dermatitis and lipodermatosclerosis are particularly important mimics, as both produce chronic erythema and induration of the lower extremities in patients with underlying venous insufficiency, and neither respond to antibiotics. The key distinguishing feature of gemcitabine-induced pseudocellulitis is its reproducible temporal relationship to chemotherapy infusion, with symptom onset within 2-7 days of dosing and spontaneous improvement between cycles. Recognition of this temporal pattern within the broader differential is essential to avoid misdiagnosis.

While gemcitabine is among the most commonly implicated agents, pseudocellulitis-like reactions have been reported with other anticancer therapies.¹² Within the antimetabolite class, cytarabine and capecitabine have been associated with similar cutaneous inflammatory presentations.^{1,7,10} Beyond antimetabolites, EGFR inhibitors and select immunotherapy agents have been associated with inflammatory cutaneous toxicities that may complicate the distinction between drug toxicity and infection.^{7,10,11,13} Taxanes, including docetaxel and paclitaxel, have also been associated with dermatologic reactions resembling pseudocellulitis.¹⁴ Clinicians should

therefore consider pseudocellulitis in any patient receiving oncologic therapy who presents with bilateral symmetric lower extremity erythema and edema with a temporal relationship to drug administration, regardless of whether the agent is an antimetabolite.

Multidisciplinary consultation was not formally pursued during the first two admissions in this case, which likely contributed to the diagnostic delay. Infectious diseases was not consulted, despite the complexity of recurrent antibiotic-refractory skin findings; such consultation might have prompted earlier reconsideration of the cellulitis diagnosis and avoidance of escalating antibiotic regimens. Dermatology was similarly not involved, despite bilateral symmetric presentation that falls outside the typical pattern of bacterial cellulitis. In atypical or treatment-refractory cellulitis-like presentations, particularly in patients receiving chemotherapy, early subspecialty involvement from infectious diseases and dermatology can facilitate more timely diagnosis and prevent unnecessary antibiotic escalation. The eventual diagnosis in this case was made by the hematology-oncology team through systematic temporal analysis, underscoring the value of a collaborative, multidisciplinary approach in complex oncology patients with unusual or refractory dermatologic presentations.

Once the diagnosis is established, management is relatively straightforward and includes discontinuing gemcitabine, stopping unnecessary antibiotics, and initiating supportive measures such as compression therapy and limb elevation. Systemic corticosteroids may be considered for severe or refractory cases, though evidence remains anecdotal. If diagnostic uncertainty about superimposed infection exists, a time-limited antibiotic trial with clear re-evaluation criteria and prompt clinical as-

essment is reasonable. Antibiotics should be discontinued if objective evidence of bacterial infection does not emerge.¹⁵ The decision to rechallenge, dose-reduce, or transition to an alternative regimen should be made by the oncology team in the context of remaining therapeutic options and the patient's goals of care.

Gemcitabine has long been a foundational therapy for advanced pancreatic cancer.^{16,17} Gemcitabine-induced pseudocellulitis is an underrecognized chemotherapy adverse effect whose consequences extend far beyond the skin. In this case, delayed recognition produced three hospitalizations, five antibiotic courses, *C. difficile* colitis, and multiple missed chemotherapy cycles, all preventable. The diagnosis requires no specialized testing; it requires awareness. Multidisciplinary teams who recognize the bilateral symmetric presentation and infusion-linked temporal pattern can intervene early, spare patients unnecessary harm, and preserve the continuity of cancer treatment.

Disclosures/Conflicts of Interest

None

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