Gemcitabine-induced pseudocellulitis: a case report and review of the literature

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ABSTRACT

Gemcitabine is a chemotherapeutic agent used in a wide variety of solid tumours. Known side effects include a dose-limiting myelosuppressive toxicity, mild rash, and radiation-dependent dermatitis. Rarely, localized inflammation in the form of pseudocellulitis has also been observed. We present the case of a 77-year-old woman with a history of a Whipple procedure for pancreatic adenocarcinoma who presented to the emergency department after the start of gemcitabine therapy with increased erythema, swelling, and tenderness in her lower legs. Relevant past medical history included peripheral vascular disease, dyslipidemia, and hypertension. A diagnosis of gemcitabine-induced pseudocellulitis aggravated by venous stasis was confirmed after an extensive workup. This case report and the literature review describe this rare reaction, highlighting the need for increased recognition to avoid unnecessary therapeutic intervention.

Key Words Gemcitabine, pseudocellulitis, pancreatic adenocarcinoma

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INTRODUCTION

Gemcitabine (2,2-difluorodeoxycytidine) is a chemotherapeutic agent used in the treatment of various solid tumours, including ovarian, breast, non-small-cell lung, and pancreatic cancers. Although generally well-tolerated, gemcitabine has been shown to have a dose-limiting myelosuppressive toxicity¹. Dermatologic side effects have also been described, including a diffuse mild skin rash and radiation-dependent dermatitis². As the use of gemcitabine increases, formerly rare reactions have been shown to occur with increased frequency, including several cases of localized cutaneous inflammation otherwise known as pseudocellulitis³⁻¹¹.

We report the case of a 77-year-old woman with pancreatic adenocarcinoma who developed bilateral erythematous skin lesions on her lower extremities after initiation of gemcitabine therapy¹². A thorough workup was completed, and the patient was eventually diagnosed with gemcitabine-induced pseudocellulitis. In the Discussion section, we expand on the causes and therapeutic implications of this condition. This case report adds to the understanding of the underlying pathophysiology of pseudocellulitis and aims to further increase awareness of this adverse event.

CASE DESCRIPTION

A 77-year-old woman first presented to her family physician with a 3-week history of fatigue, nausea, acholic stools, and tea-coloured urine. After a series of investigations, including endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography, she was found to have a 2.5×1.5×1.8 cm mass in the pancreatic head. The patient subsequently underwent a Whipple pancreaticoduodenectomy to resect the lesion. The intraoperative pathology report indicated a moderately differentiated adenocarcinoma of the pancreas. The patient's medical history was significant for peripheral vascular disease, bilateral carotid stenosis (95% on the right, 60% on the left), dyslipidemia, hypertension, pancreatitis, diverticulitis, and gastroesophageal reflux disease.

The patient was subsequently initiated on adjuvant gemcitabine therapy at 65% of the ideal dose. She presented to the emergency department 11 days after the start of therapy with reports of a fever and erythema, swelling, and tenderness in her lower legs (Figure 1). The patient was seen by her primary oncologist in the emergency department, and chemotherapy administration was held on suspicion of potential gemcitabine-induced pseudocellulitis, among

other possible causes in the differential diagnosis. At this point, a biopsy was also envisaged, but was deemed to be unnecessarily invasive at the time. She was instead treated

with a course of antibiotics and referred to hematology for further assessment.

Before the patient's assessment in hematology, bilateral lower limb ultrasonography was performed, demonstrating a right great saphenous vein thrombosis with no deep venous thrombosis. The patient's dalteparin (initiated in the emergency department) was discontinued, and the patient was scheduled for follow-up imaging, including ultrasonography of her right leg. At that time, she reported bilateral tingling and burning sensations in her legs. The patient did not report any sharp pain, and no redness in the calf, difficulty breathing, chest pain, or palpitations were observed. There was no history of bleeding.

The patient was further seen by hematology for review 1 week later, with ongoing complaints of left leg swelling and moderate-to-severe pain over the lower third and medial aspect of her leg. The pain was described as "burning," with a severity of 6 out of 10. The patient denied any history of cough or significant breathing difficulty, although she did report tachycardia, which she felt was related to the pain. On examination, the patient's vital signs were stable, and both lower limbs appeared dusky and swollen. Additionally, increased swelling on her left side and erythema on the lower part of her left leg were evident.

Because of the painful edematous lower legs with significant erythema, the patient was then seen urgently in the oncology clinic. She had previously been prescribed amoxicillin-clavulanic acid for presumed cellulitis. At this point, pseudocellulitis secondary to gemcitabine therapy was diagnosed, and chemotherapy was further held to allow for resolution of symptoms with the intention to dose-reduce subsequent cycles to 45% from the initial 65% of the ideal level.

At the patient's follow-up oncology appointment roughly 2 weeks later, she declined further cycles of gemcitabine therapy. Repeat Doppler ultrasonography at that time showed no evidence of deep venous thrombosis, but did indicate a superficial thrombophlebitis deemed to be noncontributory to her lower limb symptoms. The patient was also started on cephalexin in view of potential infection. At that point, it was concluded that the patient's venous stasis and chronic insufficiency likely contributed to a gemcitabine-induced pseudocellulitis, and further chemotherapy was held indefinitely. On follow-up 3 months later, the patient's symptoms had resolved, with her legs showing only signs of venous insufficiency.

The patient's last reported appointment was approximately 1 year after the decision for permanent discontinuation of chemotherapy. Despite an incisional hernia from the Whipple procedure, the woman is back to her daily activities and remains quite happy with the outcome. She is clinically free of disease recurrence.

DISCUSSION

This case highlights the importance of early recognition of pseudocellulitis in patients receiving gemcitabine therapy. Gemcitabine is a pyrimidine antimetabolite that acts to disrupt and inhibit DNA synthesis; it is used in the treatment of a variety of malignancies, and its therapeutic role continues to expand¹³. Notably, gemcitabine has previously

FIGURE 1 Pseudocellulitis in bilateral lower limbs. (A) Anterior view. (B) Lateral view. (C) Posterior view.

been associated with several cutaneous toxicities, including radiation recall dermatitis^{14–18}—a reaction that presents with inflammation in areas previously exposed to radiation. In addition, other common gemcitabine-induced toxicities include flu-like symptoms, fever, fatigue, myelosuppression, dyspnea, and gastrointestinal discomfort.

Pseudocellulitis without prior radiation exposure is a rare, but increasingly recognized, side effect of gemcitabine^{3–5,7,8,10,11,19–21}. As in cellulitis, the patient typically presents with localized inflammation of the dermis and hypodermis, with the reaction typically beginning within 2 days of gemcitabine exposure⁴. Bilateral reactions are more common⁵. Although the reaction is typically self-limiting, it can require withdrawal of gemcitabine and further symptomatic management, often involving non-steroidal anti-inflammatory drugs or topical steroids^{4,11}. In the case presented here, the patient, in consultation with her primary oncologist, eventually chose to discontinue the chemotherapy regimen.

Although the cause of gemcitabine-induced pseudocellulitis is not fully understood, current hypotheses involve impaired lymphatic drainage leading to drug permeation into the interstitial fluid^{9,10}. That mechanism might allow for the relatively lipophilic gemcitabine to accumulate in subcutaneous tissue, altering capillary permeability and, in turn, leading to a localized reaction^{5,7}. In the present case, the patient first had positive ultrasound findings indicative of great saphenous vein thrombosis. Although the exact mechanism remains unclear, the resulting venous stasis, coupled with the patient's known chronic venous insufficiency, might have contributed to the development of pseudocellulitis, offering some insight into the pathophysiology of the reaction.

Diagnosis of gemcitabine-induced pseudocellulitis requires a detailed past medical history, including a comprehensive medication history. Given that cutaneous eruptions in cancer patients have multiple possible causes, differentiating pseudocellulitis from true cellulitis is especially critical, considering that patients receiving chemotherapy are often immunosuppressed¹⁰. Although a specific pathogen is often not isolated in most skin infections, other factors, including biochemical markers such as white blood cell count and timing of gemcitabine exposure, can be helpful in establishing the correct diagnosis^{6,10}. Additionally, atypical presentations, including bilateral lower extremity rash, coinciding with gemcitabine use should raise clinical suspicion for this rare condition³.

Furthermore, radiation recall dermatitis involves a similar inflammatory reaction in an area previously treated with radiotherapy. Because gemcitabine is a radiosensitizer, a delayed cutaneous reaction ranging from a mild rash to severe skin necrosis can occur^{5,9}. Caution must therefore be taken when co-administering gemcitabine with radiation therapy^{14–17}.

Based on a review of the literature, gemcitabine-induced pseudocellulitis is often self-limiting, and minimal interruptions in chemotherapy are required^{5,8,20}. However, in certain cases, including the one described here, gemcitabine therapy is either reduced or discontinued; thus, the severity of the reaction could play a role in therapeutic adherence^{4,10}. Future research might benefit from a further

understanding of the efficacy of agents such as steroids and nonsteroidal anti-inflammatory drugs for symptom management. Additionally, antibiotic use has been reported in this setting—including in the management of the patient in the present report⁸. Additional awareness is therefore required to prevent unnecessary antibiotic exposure, which could in turn increase the risk for *Clostridioides difficile* colitis or antibiotic resistance, which is especially detrimental in this population^{5,7}.

SUMMARY

Gemcitabine is a chemotherapeutic agent widely used in the treatment of solid-tumour malignancies. Although rare, pseudocellulitis represents an adverse event that should be kept in mind when dealing with cutaneous eruptions in patients receiving gemcitabine therapy. The present case highlights the need for increased recognition of this reaction to avoid unnecessary antibiotic exposure and to enhance medication adherence.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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