

BRIEF ARTICLES

Unilateral Pemetrexed-induced Pseudocellulitis Mimicking Bacterial Cellulitis

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ABSTRACT

Pseudocellulitis, manifesting as erythema, warmth, and tenderness of the lower extremities, is a recently recognized cutaneous adverse reaction (CAR) associated with the use of pemetrexed, a multi-targeted folate antagonist. This reaction typically manifests bilaterally, helping to distinguish pemetrexed-induced pseudocellulitis from a bacterial cellulitis. We present a case of unilateral pemetrexed-induced pseudocellulitis. The patient was initially treated for cellulitis but failed to respond adequately to antibiotics, prompting a biopsy that showed the characteristic findings of pemetrexed-induced pseudocellulitis. Pemetrexed-induced pseudocellulitis is important to recognize as it may be dose-limiting or necessitate treatment modification. Furthermore, increased awareness of this CAR can help clinicians avoid unnecessary antibiotic use.

INTRODUCTION

Pemetrexed is a multi-targeted anti-folate chemotherapeutic agent approved for the treatment of malignant pleural mesothelioma and locally advanced or metastatic non-small cell lung cancer (NSCLC).¹ It interferes with DNA synthesis by inhibiting thymidylate synthetase and other enzymes involved in folate metabolism.² It is used as either a single agent or in combination with cisplatin or carboplatin.²

A variety of cutaneous adverse reactions (CARs) have been reported with usage of pemetrexed and combinations of pemetrexed and cisplatin/carboplatin. The most common CARs, including periorbital edema with conjunctivitis and limb edema with severe

fluid retention, have been observed in approximately one-third of patients, but have not significantly influenced treatment.³ Cases of more severe CARs have also been reported including toxic epidermal necrolysis, asteatotic eczema, radiation recall dermatitis, pityriasis lichenoides, acute generalized exanthematous pustulosis and pseudocellulitis, which typically manifests bilaterally.^{2, 4-9} Here we present a case of unilateral pemetrexed-induced pseudocellulitis.

CASE REPORT

A 67-year-old obese man with a history of peripheral vascular disease and stage IV moderately differentiated adenocarcinoma of the right lung with presumed bone

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metastases received four cycles of combination carboplatin and pemetrexed and two maintenance doses of pemetrexed. Eight days into his first dose of maintenance pemetrexed, he was admitted to the hospital with fever, pancytopenia and presumed pneumonia. He was initially treated with cefepime and then transitioned to amoxicillin-clavulanate, completing a seven-day course of antibiotics. During this admission, he developed erythema of the right lower extremity. Ultrasound was negative for deep vein thrombosis (DVT). The erythema slowly improved during admission, though it did not completely resolve.

Shortly after discharge, the erythema of his right ankle worsened and was associated with new pain and swelling. His primary care physician prescribed trimethoprim-sulfamethoxazole out of concern that persistence of the painful erythema was due to a MRSA infection. At a follow-up appointment one week later, he reported minimal improvement. The following week, he received a second dose of maintenance pemetrexed as scheduled by his oncologist. Following the treatment, he noticed progression of the erythema and increased tenderness and edema. He was again admitted to the hospital for cellulitis and treated with broad spectrum antibiotics.

The erythema failed to improve despite adequate treatment with broad spectrum antibiotics and the dermatology team was consulted. Exam was notable for bright red blanching erythema of the right lower extremity extending from the dorsal foot to the distal knee (Figure 1). The entire area was warm and tender to light touch. There was also 2+ edema of the lower extremities bilaterally. However, his overall clinical presentation was inconsistent with a poorly-controlled, antibiotic-resistant infection as he was generally well-appearing, afebrile and



Figure 1: The patient was initially diagnosed with cellulitis but, after inadequate response to broad spectrum antibiotics, a biopsy was performed consistent with pemetrexed induced pseudocellulitis.

without leukocytosis. Doppler ultrasound was negative for DVT. A 4-mm punch biopsy of the right upper thigh was performed to evaluate for cellulitis vs pemetrexed-induced pseudocellulitis. Biopsy revealed mild acanthosis of the epidermis and superficial lymphocytic infiltrate with numerous eosinophils, characteristic of pemetrexed-induced pseudocellulitis (Figure 2). There was no evidence of cutaneous infection. Antibiotics and pemetrexed were discontinued and the patient was started on triamcinolone 0.1% cream applied twice daily.

At his initial follow up appointment, there was significant improvement in the redness, swelling and pain. On the right lower extremity, extending from the lower thigh

distally to the toes, was a blanching, light pink patch that was no longer warm or tender. There was superficial desquamation on the right thigh and shin. Twice daily application of triamcinolone 0.1% cream for an additional month was recommended, as well as urea 40% cream as needed. Pemetrexed was discontinued by oncology and the rash has since resolved and not reappeared over the last six months.

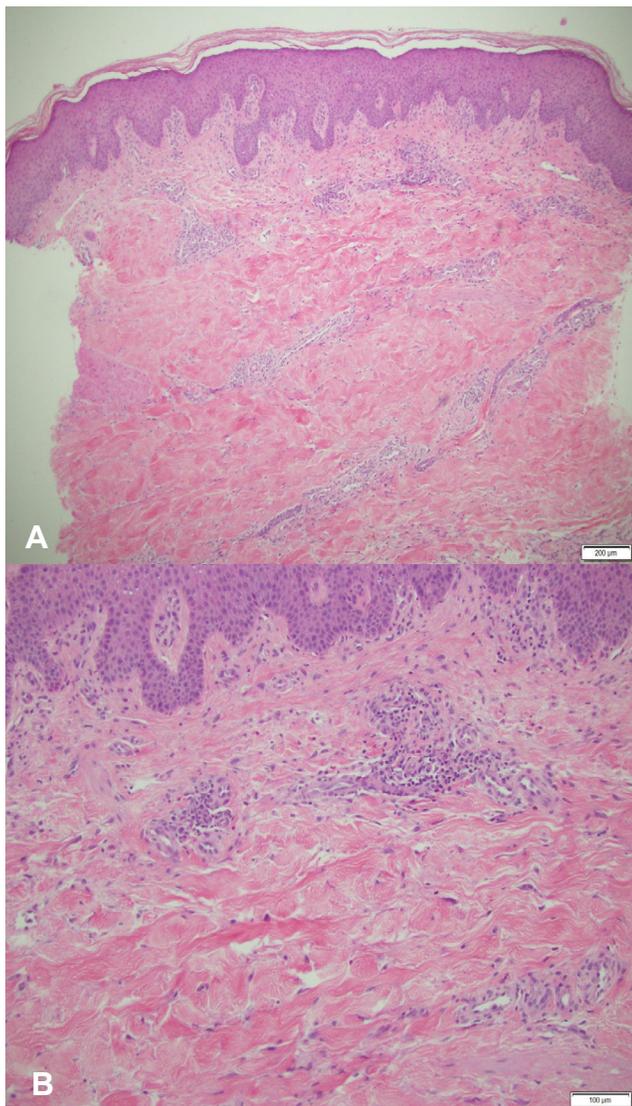


Figure 2: Pathology was consistent with pemetrexed-induced pseudocellulitis, showing mild acanthosis of the epidermis and a superficial lymphocytic infiltrate (A) with numerous eosinophils (B).

DISCUSSION

In this case, the patient's presentation of unilateral lower extremity erythema, edema, warmth, and tenderness was consistent with cellulitis and was treated as such after the evaluation by multiple specialists, including hematology and oncology, emergency medicine and infectious disease. However, the patient not only failed to respond adequately to antibiotics, but failed to develop any other signs or symptoms of uncontrolled bacterial cellulitis, clues pointing to an alternate diagnosis. In these situations, histologic evaluation can be particularly helpful.

While other adverse events of pemetrexed are often attributed to its cytotoxicity, the eosinophilic infiltrate in pseudocellulitis suggests a hypersensitivity reaction. Interestingly, pseudocellulitis has also been reported in patients treated with gemcitabine, another chemotherapeutic agent that interferes with DNA synthesis.^{10,11} Recognizing the potential for pemetrexed-induced pseudocellulitis or other drug hypersensitivity reactions to present unilaterally could limit unnecessary use of broad-spectrum antibiotics, and in some cases, including this one, may require adjusting a patient's cancer treatment regimen.

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