Pemetrexed-induced eccrine squamous syringometaplasia manifesting as pseudocellulitis (in a patient with non–small cell lung cancer)

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INTRODUCTION

Pemetrexed (Alimta, Eli Lily and Company, Indianapolis, Indiana) is a multitargeted antifolate drug approved as a single agent or in combination with cisplatin for the treatment of some malignancies including advanced and metastatic nonsquamous non–small cell lung cancer and malignant pleural mesothelioma. Pemetrexed-related cutaneous adverse reactions (CARs) are frequently reported under the nonspecific term, *skin rash*. Nevertheless, specific patterns of CARs have been reported in the literature including alopecia, acute generalized exanthematous pustulosis, urticarial vasculitis, radiation recall dermatitis, toxic epidermal necrolysis, eyelid edema, and pityriasis lichenoides–like dermatitis.[1] To reduce the incidence of CARs, the manufacturer recommends adjunct therapy with dexamethasone the day before, the day of, and the day after administration of pemetrexed.

Cellulitis is defined as a non-necrotizing inflammation of the skin and subcutaneous tissue, usually from acute infection. The examining physician often identifies a distinct clinical picture comprising erythema, swelling, warmth, and tenderness of the affected skin. The term *pseudocellulitis* is used when the clinical picture is compatible with cellulitis but the inflammation is not from an infectious cause. This can sometimes confuse and mislead clinicians. Cases of pseudocellulitis have been well reported with gemcitabine. We present a case of pemetrexed-induced pseudocellulitis that showed eccrine squamous syringometaplasia on skin biopsy.

Abbreviation used:

CAR: cutaneous adverse reaction

CASE REPORT

A 79-year-old Chinese male with metastatic non–small cell lung cancer received treatment with pemetrexed-carboplatin. From December 2014 to May 2015, he received five cycles of chemotherapy, comprising carboplatin and pemetrexed, as well as 2 doses of pemetrexed maintenance, all within 6 months. Before each cycle, the patient received 40 mg of oral prednisolone 1 day before and for 2 days after the chemotherapy.

After his fifth dose, the patient presented with worsening bilateral lower limb swelling and pain that had been present for 2 weeks, which progressed to his abdomen and flanks. He was admitted and treated with intravenous amoxicillin–clavulanic acid, 1.2 g 3 times a day, for a presumptive diagnosis of bacterial cellulitis.

Despite antibiotic therapy for 2 days, there was no improvement; hence, a referral to the dermatology service was made. On examination, the patient was afebrile. There were ill-defined, dull, erythematous, edematous plaques on the bilateral flanks, posterior thighs, and anterior shins (Fig 1). The plaques were warm and tender to touch. Diagnostic tests found a normal total white cell count; blood cultures were free of bacterial growth.

A skin biopsy found squamous metaplasia of eccrine ducts, superficial perivascular infiltrate of

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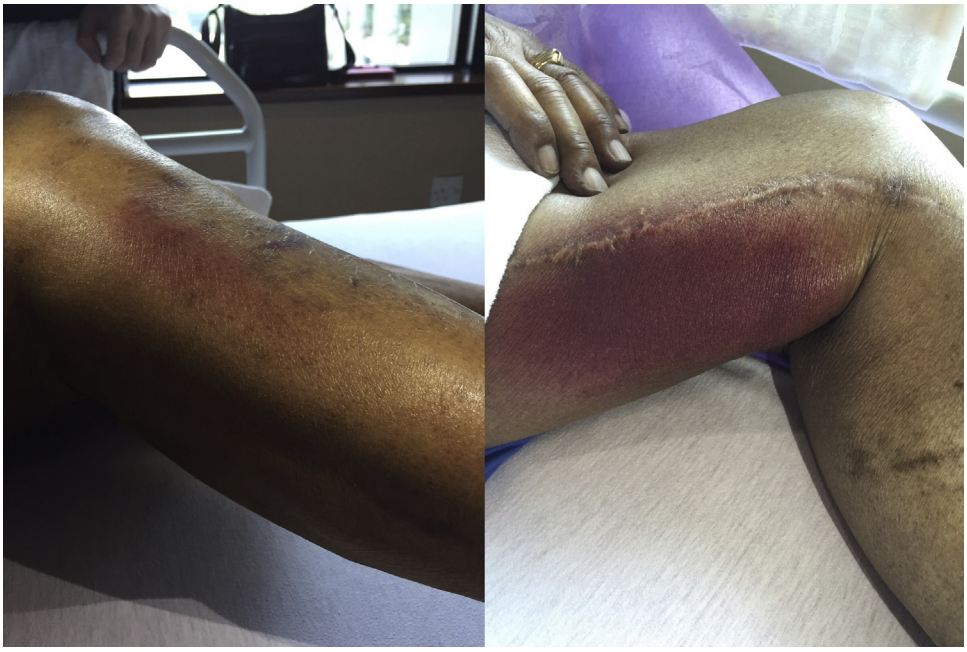

Fig 1. Erythematous, confluent plaques on posterior shins and anterolateral proximal shins that are warm and tender to touch.

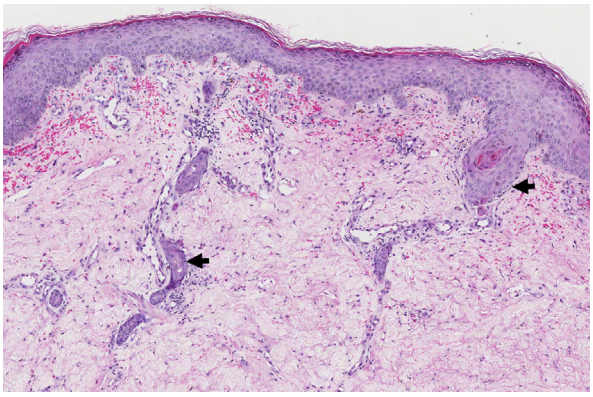

Fig 2. Photomicrograph of the skin biopsy section shows presence of squamous metaplasia of the eccrine ducts (arrows), with background mild chronic inflammatory infiltrate and edema in the dermis. (Hematoxylin-eosin stain; original magnification: ×40.)

lymphocytes, edema, and some extravasated red blood cells (Fig 2). A diagnosis of eccrine squamous syringometaplasia was rendered, a condition known to be an adverse cutaneous reaction to chemotherapy. Grocott's methenamine silver and Ziehl-Neelsen stains showed no identifiable fungal organisms or acid-fast bacilli.

Antibiotic treatment was discontinued after 5 days, as there was no clinical improvement. The diagnosis of pemetrexed-induced pseudocellulitis was made. The patient was then prescribed topical moisturisers, Diprogenta cream (betamethasone dipropionate 0.05% and gentamicin 0.1%) daily, and compression stockings. The other chemotherapy agent used was carboplatin, a DNA alkylating agent, which generally has minimal skin toxicity and deemed not likely to be the cause of the skin eruption.

The patient subsequently underwent skin prick tests, intradermal tests, and patch tests to pemetrexed. These results were all normal, suggesting that the underlying pathophysiology is non−immune mediated.

At a 2-month review in the dermatology clinic, there was significant improvement in the cutaneous eruption, and pemetrexed remained discontinued.

DISCUSSION

Like gemcitabine, pemetrexed inhibits DNA synthesis because of the inhibition of the enzymes that are involved in folate metabolism, purine, and pyrimidine synthesis.[2]

Both gemcitabine and pemetrexed have been associated with several forms of cutaneous toxicities. The pathophysiology of these toxicities has yet to be fully understood. Various hypotheses have been proposed that include vascular damage, drug permeation into interstitial fluid, and drug hypersensitivity. In this case, the distinctive histologic feature of eccrine squamous syringometaplasia suggests that drug-induced eccrine gland reactions[3] could contribute to the clinical manifestation.

Several studies[4,5] suggest a significant reduction in incidence of rash with administration of

dexamethasone, but a fixed recommended dosage is yet to be established. Although our patient did receive corticosteroids as premedication before chemotherapy, it did not prevent him from having this episode of pseudocellulitis. Further research still needs to be conducted to establish the efficacy of prechemotherapy corticosteroid prophylaxis.

Diagnosing pseudocellulitis in an oncologic patient is a challenge, as there are myriad cutaneous eruptions with which the patient can present. A recent case of pemetrexed-induced pseudocellulitis has been reported, albeit with a different histologic finding of eosinophil-rich dermal inflammatory cellular infiltrate.[6]

Eccrine squamous syringometaplasia has been known to be an adverse cutaneous reaction to various chemotherapeutic drugs. It also can occur in the context of wounds, burns, pyoderma gangrenosum, linear scleroderma, squamous cell carcinoma and various skin infections.[7] However, to the best of our knowledge, eccrine squamous syringometaplasia occurring as an adverse reaction to pemetrexed has not been previously reported.

This case study reflects the challenges faced by clinicians managing cutaneous adverse reactions in oncologic patients caused by the multitude of new chemotherapy drugs now being used and the complexity of their underlying diseases. It reiterates the need for awareness of this peculiar adverse reaction, thereby avoiding misdiagnoses and preventing unnecessary antibiotic administration and hospitalization. The overall combination of clinical judgment, laboratory investigations, tissue cultures, and histopathology is still often necessary to distinguish pseudocellulitis from infectious cellulitis. The main treatment of pseudocellulitis thus far is symptomatic and includes nonsteroidal anti-inflammatory drugs, topical steroids, and systemic corticosteroids in addition to discontinuing the offending drug. Further research and observation are needed to know if this particular reaction recurs when there is a rechallenge with pemetrexed. Other pertinent issues to consider include the optimal dose and duration of treatment of pemetrexed and if symptomatic management can be sufficient without needing to discontinue the drug.

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