Edema of the face and extremities secondary to pemetrexed

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Key words: blanching erythema; dermatologic adverse reactions; facial edema; pembrolizumab; pemetrexed; periorbital edema; pitting edema; pseudocellulitis; skin toxicity.

INTRODUCTION

Pemetrexed is an anti-folate chemotherapy first approved in 2004 by the Food and Drug Administration (FDA) for malignant pleural mesothelioma and more recently for metastatic nonsquamous, nonsmall cell lung cancers. As cancer patients may be treated with multiple concomitant therapies, understanding specific dermatologic adverse events (dAEs) associated with a particular agent or class can help identify and modify the appropriate culprit. Pemetrexed, like most anticancer agents, has been reported to cause diverse dAEs, including alopecia, edema, erythema, urticarial vasculitis, acute generalized exanthematous pustulosis, radiation recall dermatitis, toxic epidermal necrolysis, pityriasis lichenoides-like dermatitis, and pseudocellulitis.[1,2] Here, we present a patient with pemetrexed-induced localized edema of the face, upper extremities, and lower extremities.

Abbreviations used:

dAEs:	dermatologic adverse events
FDA:	Food and Drug Administration
MRI:	magnetic resonance imaging
SRS:	stereotactic radiosurgery

CASE

A 54-year-old Dominican male with metastatic adenocarcinoma of the lung was initially treated with stereotactic radiosurgery (SRS) to brain metastases and 6 cycles of carboplatin, pemetrexed, and pembrolizumab. He responded well without significant toxicity and began maintenance therapy with pemetrexed and pembrolizumab. Four months later, a new brain metastasis was found, and he received a second treatment of SRS and 6 months of bevacizumab. Pembrolizumab and pemetrexed were continued during and after these additional treatments. Of note, the patient was given dexamethasone with all pemetrexed infusions.

Thirty-seven months after initiating pemetrexed and pembrolizumab, the patient presented to his oncologist with 1 week of non-tender edema and erythema of his right upper extremity. Ultrasound was negative for deep vein thrombosis, and the patient was prescribed a 5-day course of cephalexin for suspected cellulitis. No improvement was noted after the antibiotics, and mild edema was appreciated in his left upper extremity and bilateral lower extremities. His malignancy was stable, and brain magnetic resonance imaging (MRI) 1 month after first reporting symptoms showed no evidence of new metastatic disease.

Two months after edema onset, the patient was referred to the Skin Toxicities Program. He reported new pain in the upper extremities. On exam, there was significant bilateral periorbital edema, central forehead pitting edema with blanching erythema, pitting and doughy edema of the bilateral hands, forearms, and distal upper arms, peau d'orange changes on the proximal forearms, and edema with blanching erythema of bilateral feet and lower legs (Figs 1 to 3).

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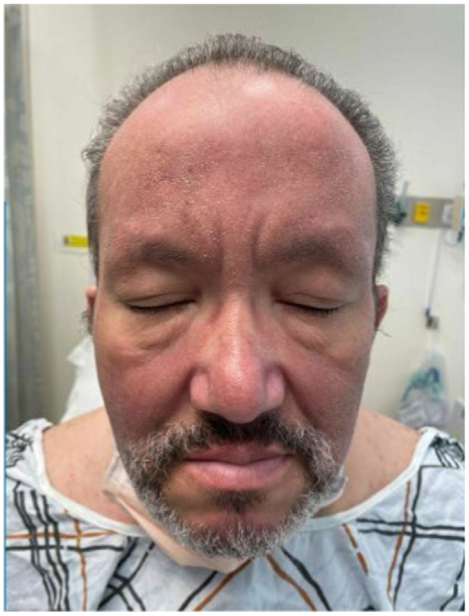

Fig 1. Bilateral periorbital edema with erythema and pitting edema of central forehead.

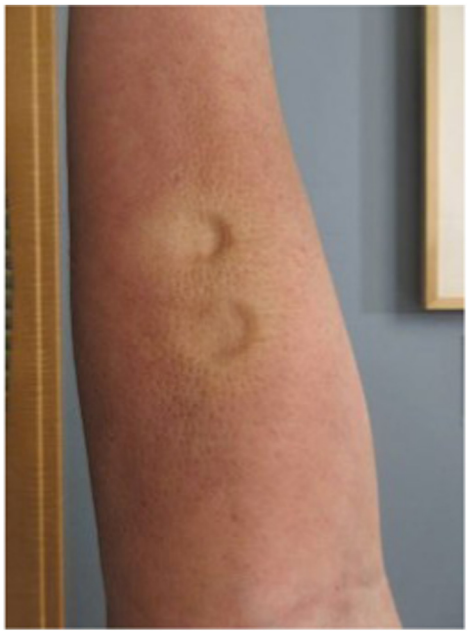

Fig 2. Blanching erythema, peau d'orange changes, and doughy pitting edema of the forearm.

The patient was also noted to have ill-defined, bound down, firm, sclerotic changes of the bilateral feet and thighs with a hyperpigmented sclerotic plaque on the central lower back. He reported lower extremity changes had been present for many months. Laboratory results revealed positive antinuclear antibody HEP-2 (1:320) and borderline low albumin (3.4 g/dL). Folate was not measured, but the

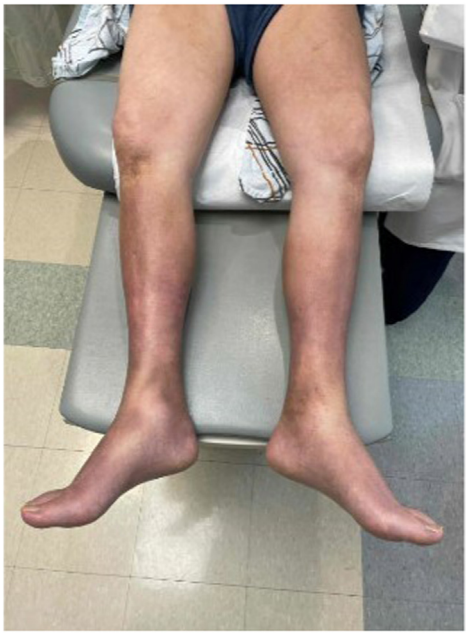

Fig 3. Feet and lower extremities with pitting edema and blanching erythema with prominent sclerosis of the ankles and pigmentary change.

patient was on a folate supplement of 400 mcg daily. The patient was normotensive, did not experience significant weight gain, and did not show signs of acute kidney injury.

Based on the locations affected by edema, specifically periorbital and of upper extremities, the patient's presentation was most consistent with pemetrexed-induced localized edema with pseudocellulitis and sclerosis of the lower extremities. He was prescribed betamethasone dipropionate 0.05% ointment twice daily to active areas along with compression, elevation, massage, and physical therapy to reduce edema and improve range of motion. Systemic immunosuppression was deferred given active malignancy. Pemetrexed was discontinued while pembrolizumab was continued. The patient self-reported "70%" improvement in his swelling and symptoms 2 months later. On exam, he had near resolution of forehead and periorbital swelling, and upper and lower extremity edema was improved. He had stable sclerosis with no further loss of range of motion in his extremities. He had used betamethasone dipropionate for 1 week only; this was resumed on the lower extremities, and compression, elevation, massage, and physical therapy were again encouraged.

DISCUSSION

Pemetrexed-induced edema, pseudocellulitis, and sclerosis can be challenging to diagnose in complex patients on combination therapy. This patient initially

presented with lower extremity edema, a common clinical finding in the oncology setting. He also had marked sclerosis, including morphea-like plaques on the thighs and lower back. Periorbital edema became more noticeable throughout his course, which in the oncology setting is a specific dAE most often associated with drugs that target BCR-ABL or CSFR1 or pemetrexed.[3-5] Edema preceding sclerosis is associated with cytotoxic therapies most commonly including gemcitabine and taxanes but can be seen with bleomycin and pemetrexed, as in this case.[6] The differential diagnosis included rare presentations of sclerosis or eosinophilic fasciitis induced by checkpoint blockade, though periorbital edema would not be an expected feature with either of these presentations and therefore pemetrexed was favored. Improvement with continued pembrolizumab confirmed this to be less likely. Additionally, the patient did not experience signs of capillary leak syndrome. The patient's long standing vitamin supplementation made vitamin deficiency an unlikely etiology as well, though folate deficiency may be associated with this finding in pemetrexed treated patients.[7]

This case reflects the difficulty of identifying rare dAEs, the necessity of total body skin examination in these patients, and the importance of periorbital edema in helping identify the drug culprit. This change can happen slowly and early on, and may not be readily apparent to anyone other than the patient. Identifying the drug trigger is paramount, such that the offending agent can be adjusted and detriments to quality of life limited and ideally reversed. Additionally, this case highlights the challenge of appreciating erythema and edema in patients of color, leading to delayed diagnosis and treatment. While corticosteroid therapy may be effective prophylactic treatment against some pemetrexed-induced adverse events, skin toxicity still occurs in some cases despite premedication, as in our patient.[8] Edema progressing to sclerosis is an inflammatory process and is most often treated with additional systemic steroids and immunosuppressive agents, such as methotrexate. In the setting of active malignancy, we opted to manage conservatively with topicals, supportive care, and discontinuation of the offending agent. Proposed mechanisms of this toxicity include diffusion of drug into interstitial fluid leading to vascular damage and hypersensitivity.[9,10] The addition of bevacizumab in this case may have disrupted vascular repair mechanisms. More research is needed to better understand mechanisms and approaches to prevention and treatment in the active malignancy patient.

Conflicts of interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article. Nicole R. LeBoeuf is a consultant and has received honoraria from Bayer, Seattle Genetics, Sanofi, Silverback, Fortress Biotech, and Synox Therapeutics outside the submitted work.

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