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Painful generalized erythematous patches: A severe and unusual cutaneous reaction to pemetrexed

To the Editor: Pemetrexed gained approval by the US Food and Drug Administration as first-line treatment for malignant pleural mesothelioma combined with cis-diamminedichloroplatinum (cisplatin), and alone as second-line treatment in resistant or relapsing non–small cell lung cancer (NSCLC) after an open-label, phase III trial that compared pemetrexed with docetaxel. There was no significant difference in overall response or survival rates; however, toxicities were greater for patients treated with docetaxel. Pemetrexed is usually tolerated well, but cutaneous toxicity has been reported, principally as a rash in 17% to 22% of patients and described in many forms, such as asymptomatic diffuse hyperpigmentation with desquamation, urticarial vasculitis, acute generalized exanthematous pustulosis, and toxic epidermal necrosis, but this appears to be rare.

The mechanism for the development of skin toxicity is still unclear, but some studies report that its severity is associated with the patient’s nutritional folate status and its incidence was reduced with daily folate supplementation and prophylactic steroids; thus, not affecting the chemotherapeutic efficacy of the drug.

In other clinical trials, skin changes were minor and completely resolved merely by the cessation of therapy. We report a patient who developed painful generalized erythematous patches on the lower extremities 2 days after receiving pemetrexed for the treatment of a NSCLC. We believe this was an unusual reaction which, to our knowledge, has not been linked with the use of this agent.

A 36-year-old woman with stage IIIB NSCLC, in her second cycle of pemetrexed treatment, presented with a 3-week history of bilateral lower extremity swelling, redness, pruritus, and pain. The physical examination revealed that both lower extremities had more than three pitting, edematous, large and bright red, warm and tender indurated patches (Fig 1). The patient was afebrile, with mild leukocytosis (white blood cell count, 12.3 K/mcL; normal, 3.6-11.0 K/mcL). After an extensive laboratory work-up, including negative blood cultures and a Doppler ultrasound that was negative for deep vein thrombosis, the diagnosis of bilateral cellulitis of the lower extremities was made. Vancomycin was started; however, it was suspended after the first dose because of a marked increase in the patient’s creatinine level from baseline of 0.5 to 2.6. Piperacillin/tazobactam and cefazolin subsequently were started, without improvement after 15 days of continuous treatment. A biopsy was performed with results that were consistent with interface dermatitis (Fig 2). The patient was started on triamcinolone acetonide ointment 0.1% and hydroxyzine 25 mg three times daily with a marked decrease in the size of the lesions after just 2 days of treatment.

Fig 1. Left lower extremity with large bright red patches.

Fig 2. Close-up view of the epidermis. Note the focal point of interface dermatitis—vacuolar degeneration of the basal keratinocytes with mild lymphocytic exocytosis. (Hematoxylin–eosin stain; original magnification: ×40.)
The association of the skin lesions with pemetrexed treatment was made after other etiologies were ruled out. They were morphologically similar to those of a fixed drug reaction but without any history of same site or time-related appearance of lesions after the offending drug administration; no classic histopathologic features of fixed drug reaction were identified. On the other hand, the unusual bilateral involvement of the lower extremities resembling cellulitis, the poor response to broad spectrum antibiotics, and the marked improvement evident with the use of the combination of topical steroids and an antihistamine pointed toward a new severe manifestation of pemetrexed-related cutaneous toxicity.

The histologic findings were nonspecific but suggestive of drug hypersensitivity (Fig 2). Dermatologists should become familiar with this type of reaction because the more widespread use of this agent may lead to more reports of this condition.

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Cutaneous Churg–Strauss syndrome:
Response to dapsone therapy

To the Editor: A 60-year-old man presented with a 2-month history of pruritic papules and plaques on the forehead, scalp, and legs. His medical history included asthma, chronic sinusitis, seizures, deep venous thrombosis, and lupus anticoagulant treated with coumadin. The physical examination revealed multiple erythematous, indurated papules, some with dusky crust, on the vertex of the scalp, nuchal area, forehead, and right medial malleolus (Fig 1, A). The left shin had a nonblanching, erythematous, edematous plaque with central eschar (Fig 1, B).

A biopsy specimen from the left shin lesion revealed epidermal necrosis, a dense superficial and deep, perivascular and interstitial inflammatory infiltrate rich in eosinophils (Fig 2, A). Small and medium blood vessels exhibited fibrin thrombi.

Fig 1. A, Multiple red, nonblanching papules on the forehead and scalp. B, Red indurated plaque with central ulceration and eschar on the left shin. C, Healing of the shin ulceration on low-dose prednisone and dapsone.