Peripheral Skin Edema as Unusual Toxicity in Three Patients with Advanced Non-small Cell Lung Cancer Treated with Pemetrexed Alone or in Combination with Cisplatin

To the Editor:

Pemetrexed (P) represents one of the most widely used drugs in the treatment of patients with nonsquamous non-small cell lung cancer with a favorable toxicity profile. Rash, desquamation, and pruritus are the most frequent cutaneous toxicities.[1] Recently, a series of 14 patients with peripheral skin edema related to P administration has been reported.[2] The most relevant aspects of this clinical picture were fluid retention or cellulites, mainly localized to the distal lower extremities ranging from ankle swelling to pitting edema with overlying skin erythema.

CASE REPORTS

Retrospectively, we identified three cases showing similar signs and symptoms to those described by D'Angelo et al.[2] of the 120 patients with advanced non-small cell lung cancer treated with P in the last 5 years at our institution. Two patients (A and B) received P in combination with cisplatin as first-line treatment and one patient (C) was given P as second-line treatment.

Patient A, a 59-year-old man developed skin edema to bilateral lower extremities after the fourth cycle of therapy, which initially was treated with topical steroids. There was significant worsening of the condition after the fifth cycle. Dermatologist diagnosed erysipelas and started antibiotic therapy with macrolides, in combination with systemic steroids, obtaining a slight improvement. The sixth cycle, administered with a 25% dose reduction of P, was associated with a flare of the edema (Figure 1). P was discontinued with a complete disappearance of the edema within 30 days.

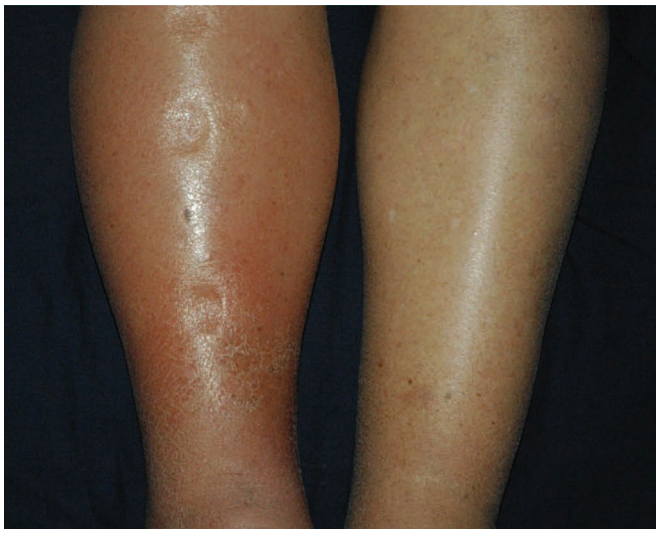

FIGURE 1. Clinical presentation of the patient's lower extremity edema after sixth cycle of pemetrexed.

Patient B, a 65-year-old woman showed intense unilateral dermatologic toxicity of the lower extremity after the second cycle of chemotherapy. Systemic steroid therapy led to improvement of local signs and symptoms. The patient progressed after the fourth cycle, and she then received second-line therapy with complete resolution of P-related toxicity within 20 days.

Patient C, a 66-year-old man developed bilateral lower leg edema and erythema after the third cycle of P. Treatment with diuretics was ineffective, and a 25% dose reduction of P with the fourth cycle was not associated with improvement. Subsequently, systemic steroid therapy was started with a further dose reduction of P, leading to disappearance of skin findings. In all patients, the vascular echodoppler study was negative for phlebitis; no patient underwent biopsy.

DISCUSSION

During the clinical development of P, skin rash was described, although little is published about its mechanism. Lopes et al.[3] performed cutaneous biopsies and described an urticarial vasculitis (UV); findings similar to those were observed in rheumatologic diseases or with drugs such as diltiazem and procarbazine. The authors considered UV as one of the possible manifestations of P-related rash. Indeed, this UV is in contrast to common urticaria, which resolves in minutes to hours and may migrate. As described herein, the lesions may be painful or pruritic and resolve with purpura or hyperpigmentation. Treatment of choice seems to be dose reduction of P, combined with systemic steroids. Treatment discontinuation should be considered only in nonresponsive patients.

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Disclosure: The authors declare no conflicts of interest.
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