Pemetrexed-induced scleroderma-like lesions in a lung cancer patient

Javier Sánchez[1], Ignacio Rivera[2], Beatriz Aldea[2], Isabel Abadías[2], Mariano Ara[2]

[1]Servicio de dermatología del Hospital General San Jorge, Huesca, España
[2]Servicio de dermatología del Hospital Clínico Universitario Lozano Blesa, Zaragoza, España

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Correspondent author:
Javier Sánchez Bernal
Email:
javisanchez_5@hotmail.com

Resumen

El pemetrexed es un antifolato empleado en el tratamiento del carcinoma de pulmón de células no pequeñas avanzado y metastásico y del mesotelioma pleural maligno, que induce reacciones adversas cutáneas en aproximadamente el 20% de los pacientes. Presentamos el caso de una reacción adversa poco frecuente inducida por pemetrexed en forma de lesiones esclerodermiformes en extremidades inferiores. Este efecto adverso cutáneo puede no ser identificado, provocando un retraso en el diagnóstico, que a menudo conduce a un empeoramiento de las lesiones y aumenta el riesgo tratamientos innecesarios y de secuelas.

Palabras claves: Efectos adversos del pemetrexed; Esclerodermia localizada inducida químicamente; Efectos adversos de agentes antineoplásicos; Terapia del Carcinoma de Pulmón no microcítico

Abstract

Pemetrexed is a multi-targeted folate antagonist drug approved for the treatment of advanced and metastatic non-small cell lung carcinoma (NSCLC), and malignant pleural mesothelioma, and is known to induce cutaneous adverse reactions in approximately 20% of patients. We report a case of an uncommon toxicity induced by pemetrexed: scleroderma-like condition of the lower extremities. This cutaneous adverse effect is often unrecognized, resulting in delayed diagnosis, which often leads to a worsening in the condition and increasing the risk of further fibrosing sequelae.

Key words: Adverse effects of Pemetrexed; Chemically induced localized Scleroderma; Adverse effects of antineoplastic Agents; Non-Small-Cell Lung Carcinoma therapy

Pemetrexed is a multi-targeted folate antagonist drug approved as a single agent or in combination with cisplatin for the treatment of advanced and metastatic non-small cell lung carcinoma (NSCLC), and malignant pleural mesothelioma[1]. It is known to induce cutaneous adverse reactions in approximately 20% of patients[2].

We report here a case of scleroderma-like side-effects of pemetrexed.

Case report

A 59-year-old woman with history of metastatic pulmonary adenocarcinoma (stage IV), currently receiving treatment with pemetrexed cycles every three weeks for the last three years, with good control of her condition. She was referred to our Dermatology clinic for evaluation of a skin lesion placed in her right lower leg which had appeared 3 days earlier, two days after the last cycle of chemotherapy. She denied fever or any other systemic symptoms.

On physical examination, she presented a painful erythematous plaque with oedema in the distal part of the right leg. This lesion seemed to continue as a linear hyperpigmented infiltrated plaque on the outer side of the thigh (Figure 1). In addition, several hyperpigmented lesions were found on the right buttock and left thigh.

Laboratory test did not show any relevant findings (including complete blood count, chemistry blood test, immunoglobulins, complement and autoantibodies), except for an increase in the C-reactive protein level. Patient reported that she had noticed before similar lesions to the one in her lower right

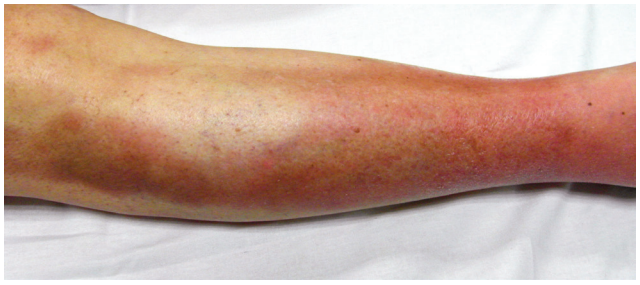

Figure 1
Erythematous pigmented red-brownish plaque in lower right leg that is continued by a linear hyperpigmented plaque.

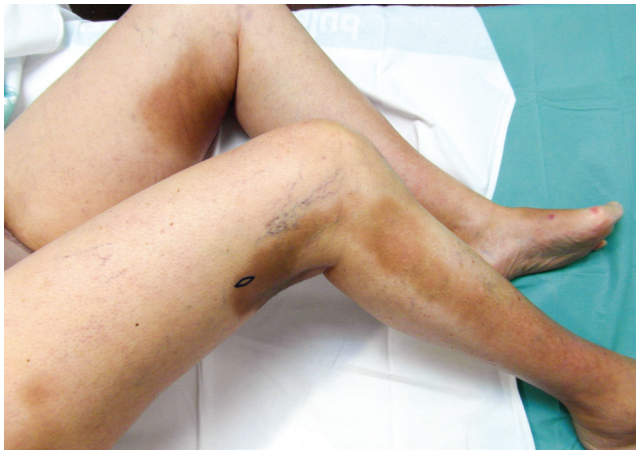

Figure 2
Multiple hyperpigmented lesions on both legs

leg, which appeared few days after each chemotherapy cycle from cycle 40. These plaques self-resolved, leaving residual hyperpigmentated and infiltrated plaques (Figure 2).

The histopathological examination of a punch biopsy revealed a thickening in the collagen bundles in the dermis, as well as a perivascular dermal infiltrate composed mostly by lymphocytes and some eosinophils. These findings were consistent with a scleroderma-like condition. Due to the temporal relationship between permetrexed cycles and the appereance of skin lesions, these were attributed to the drug. Permetexed was replaced by crizotinib, and the patient has not developed any new lesions since then. Residual plaques partially improved after 2 months of topical corticosteroid treatment.

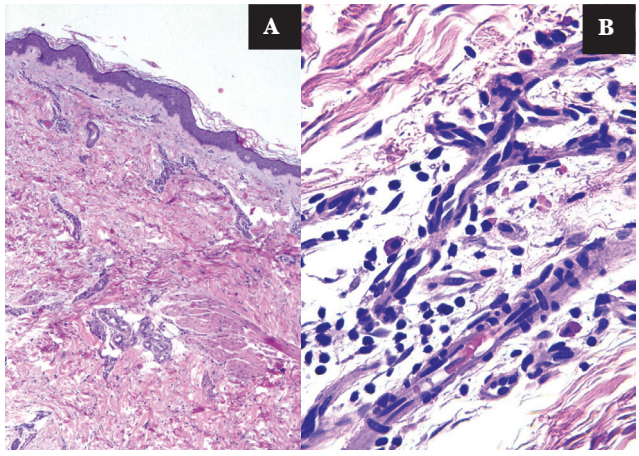

Figure 3
Skin biopsy.
A. The most remarkable finding is a thickened dermis filled with collagen (Hematoxylin and eosin, x10).
B. A perivascular inflammatory infiltrate is also seen, composed mostly by lymphocites and few eosinophils (Hematoxylin and eosin, x100).

Discussion

It is known to induce cutaneous adverse reactions in 17% of patients receiving pemetrexed alone and 22% of patients receiving the pemetrexed-cisplain combination[1,2]. Most of them are reported as skin rashes, but cases of urticarial vasculitis, pseudocellulitis, hyperpigmentation, acute generalized exanthematous pustulosis, toxic epidermal necrolysis, eyelid edema dermatitis recall, or fibrosing disorders have been reported[1,2,3]. Furthermore, as several chemotherapeutic agents, such as taxanes, gemcitabine and bleomycin, pemetrexed can also induce scleroderma-like changes[2,3]. Few cases have been reported in the literature[1-5]. These lesions are usually initially mistaken for cutaneous infections (such as cellulitis or erysipela) and treated with antibiotics, despite the absence of fever. Therefore, there is a delay in their diagnosis, which often leads to a worsening in the condition and increasing the risk of further fibrosing sequelae.

Differential diagnosis is broad, and it includes many different entities such as soft tissue infection, pseudocellulitis, and lipodermatosclerosis secondary to pemetrexed.

The bilateral distribution of skin lesions, the absence of systemic symptoms or laboratory abnormalities, the poor response to antibiotherapy, the antecedent of a previous chemotherapy cycle, the skin induration with hyperpigmentation, and the histopathological findings, are clues that can help in this differential diagnosis[1,3].

Conclusion

In conclusion, when we encounter patients undergoing chemotherapy, we should keep fibrosing conditions in our differential diagnosis. A higher level of suspicion may help avoiding diagnostic delays and unnecessary treatments and guiding the physician to suspend, change or continue chemotherapy treatment.

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