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Erlotinib-induced Acneiform Rash Not Affecting Previously Irradiated Skin

Erupción Acneiforme Onducida por Erlotinib que Respeta el Área de Piel Previamente Irradiada

To the Editor:

Erlotinib is a tyrosine kinase inhibitor that acts by blocking the activity of the epidermal growth factor receptor (EGFR). This receptor is frequently overexpressed and mutated in many solid tumors, and is also abundant in the basal cells of the epidermis and in follicular keratinocytes, where it contributes to the differentiation and development of the hair follicle.[1] Currently, erlotinib is indicated for the treatment of non-small cell lung cancer and pancreatic cancer, and is being investigated as a treatment option in cancers of the head and neck, ovary and kidney. Adverse skin reactions are the most frequent adverse effect of erlotinib. Among these reactions, acneiform rash is a dose-dependent response that has been observed in most of the patients treated with erlotinib.[2] The pathogenesis of acneiform rash is unknown, although it may be related to follicular hyperkeratosis, plugging and obstruction of the follicular ostium, and an altered hair growth cycle, accompanied by an intense inflammatory response.[1] We describe the case of a patient with laryngeal cancer receiving treatment with erlotinib, who developed an acneiform rash that spared previously irradiated skin.

The patient was a 46-year-old man with moderately differentiated squamous cell carcinoma of the glottic larynx, with supraglottic extension (pT3N1M0), who underwent total laryngectomy and cervical lymphadenectomy. Three months after surgery he received radiation therapy to the resection bed and cervical chains at a dose of 50 Gy over 6 weeks. Two months after the final radiation therapy session the patient began treatment with erlotinib (150 mg/d orally). Ten days after beginning drug therapy, numerous papules and confluent pustules appeared that were distributed on the face, trunk, and arms. Surprisingly, the rash spared 2 rectangular areas located on the anterior and posterior area of the neck and upper trunk, which had been included within the fields of radiation therapy (Figure 1). Biopsy of the skin affected by the rash demonstrated acute superficial folliculitis (Figure 2), whereas biopsy of the irradiated area only demonstrated some discrete perivascular infiltrates formed predominantly of lymphocytes. The patient was treated with oral doxycycline (100 mg/d). After 2 months, the oncologists decided to suspend the treatment with erlotinib due to inefficacy. The skin lesions gradually improved and had completely disappeared by 3 months.

In the case described, the type of lesions and the time of onset were similar to those found in most patients who suffer this adverse skin reaction caused by treatment with erlotinib.[1] The main interest of the case presented is that the lesions spared previously irradiated skin. To date, very few cases have been reported of EGFR-inhibitor-associated acneiform reactions that have spared irradiated skin,[3-8] and erlotinib was involved only in 3 of those cases.[6-8]

The pathogenesis of this event is unknown. One theory suggests that radiation therapy causes atrophy of the sebaceous glands, which would explain the lack of lesions in the irradiated area.[5] Our case does not support this hypothesis, because pilosebaceous units were observed in the irradiated area.

The effects of radiation therapy vary according to the time since the treatment. During the first 3 weeks, radiation therapy leads to increases in basal layer proliferation and in the mitotic index. Several weeks after irradiation there is a local reduction in the drug effect, due to either a progressive loss of endothelial cells and the drug not reaching the irradiated area, or to a modification of epidermal sensitivity to EGFR inhibitors.[3] There are reports of cases in which following the concomitant administration of an EGFR inhibitor during the course of radiation therapy

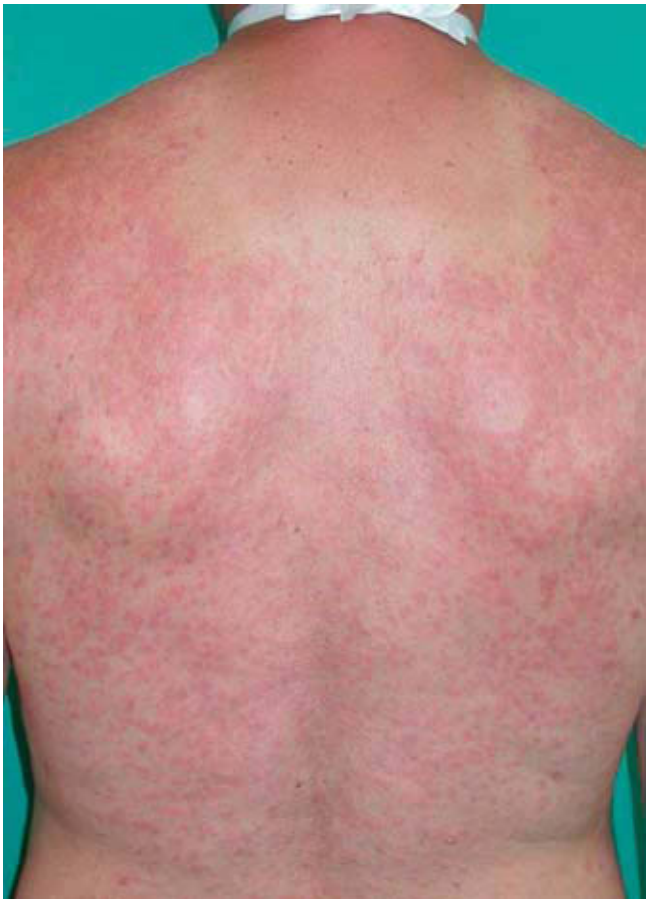

Figure 1 Papulopustular rash on the posterior trunk, showing a rectangular area on the upper back devoid of lesions.

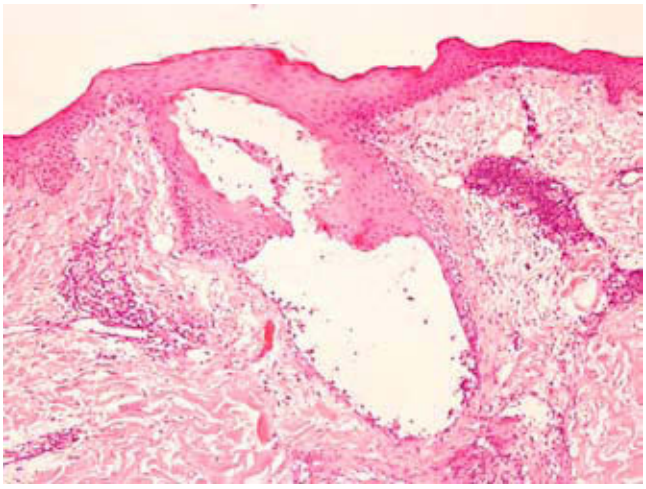

Figure 2 Skin sample from the nonirradiated area showing a neutrophilic infiltrate surrounding the hair follicle. Hematoxylin-eosin, ×40.

or immediately afterwards, the acneiform rash was limited to or more severe in the previously irradiated skin when an EGFR inhibitor was administered during the course of radiation therapy or immediately afterwards.[9,10] Variations in the interval between irradiation and the administration of EGFR inhibitors probably explain the absence or increased severity of the acneiform rash in the irradiated skin.[11]

Conflict of Interests

The authors declare no conflict of interests.

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