EGFR Inhibitors-related Panniculitis: A New Side Effect

Abstract

Epidermal growth factor receptor (EGFR) inhibitors are widely used in the treatment of advanced malignancies, and their skin toxicity is frequent and well recognized in the literature. We report the case of a 69-year-old patient with a history of adenocarcinoma of the lung treated with several EGFR inhibitors and the development of skin lesions compatible with panniculitis. The reproducibility of the lesions with different inhibitors reinforces the causal relationship with the drug, representing the first report in the literature of this side effect.

Keywords: *Drug toxicity, EGFR inhibitors, oncology, panniculitis, ulcer*

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Introduction

Epidermal growth factor receptor (EGFR) inhibitors have been groundbreaking in the treatment of advanced malignancies.[1-3] Despite their benefit, skin toxicity is common.[1,3-6] Previous studies suggest that the presence and severity of the rash correlates significantly with tumor response to therapy and overall survival, while it is still not proven for other cutaneous manifestations.[1,2,4]

Case History

A 69-year-old female was observed in our dermatology department owing to leg ulcers evolving for the past six months. Her medical history was remarkable for stage IIIa adenocarcinoma of the lung under erlotinib, an EGFR inhibitor, for the past 7 months, with good response. She had been previously medicated with gefitinib, withdrawn because of exuberant paronychia. Clinically, we observed multiple deep ulcers with well-defined borders and a necrotic center, exclusively located on the back of both legs, along with perilesional erythema [Figure 1]. Under the suspicion of EGFR inhibitor toxicity, erlotinib was suspended. Skin biopsy revealed ulceration that extended to subcutaneous fat, where a septal panniculitis with predominance of polymorphonuclear neutrophils was present along with fibrinoid necrosis in the vessel walls [Figure 2a and b]. Microbiologic and immunologic studies were normal. Chest x-ray showed stability of the tumor and no signs of tuberculosis. She initiated 0.5 mg/kg/day prednisolone and local treatment with maltodextrin, with significant improvement. Two months later, the lesions healed [Figure 3]. Meanwhile, afatinib was initiated. After 8 months of therapy, the patient developed new ulcers, similar to the former, located in the submammary and intergluteal folds [Figure 4]. Because of a decline on patient's general condition, we decided not to biopsy these new lesions as they were clinically similar to the previously reported. She was started on topical betamethasone with significant improvement. At this point, the disease evolved to stage IV and a new mutation, T790M, was identified, forcing the replacement of afatinib for osimertinib, a third generation EGFR inhibitor. After 5 months of treatment with this drug, there are no sign of skin adverse effects.

Discussion

Skin toxicity among patients under treatment with EGFR inhibitors has protean manifestations because its receptor is highly expressed in keratinocytes, sebocytes, and outer root sheath of hair follicle.[1,6,7] Rash is the most frequent cutaneous side effect, usually manifesting as an acneiform eruption.[2-6] Pruritus, xerosis, nail, hair, and mucosal changes are also reported.[3,4] Less common

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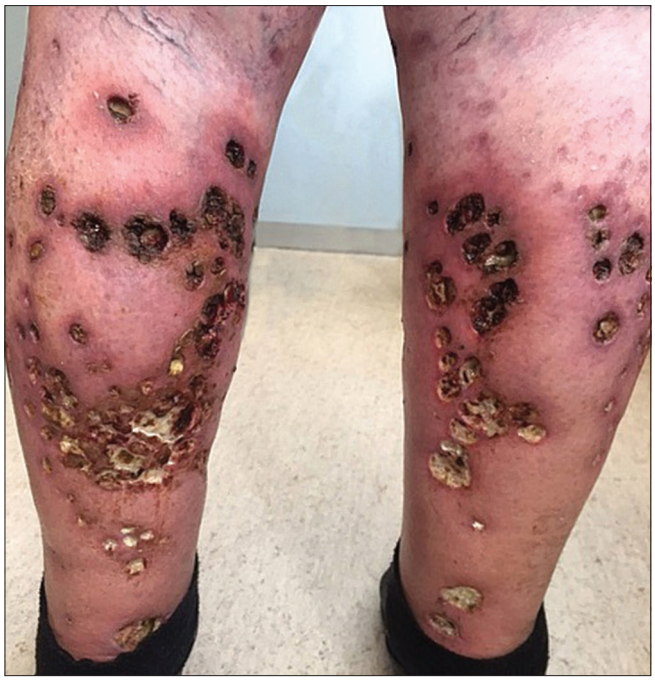

Figure 1: Deep ulcerated lesions with a necrotic center of the posterior aspects of both legs

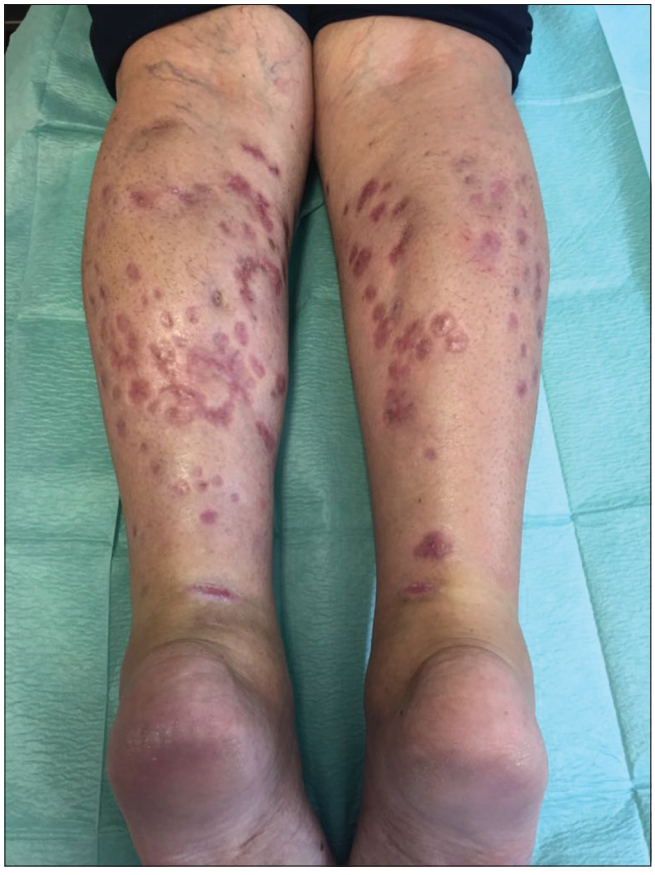

Figure 3: Posterior aspects of both legs after healing of the ulcers

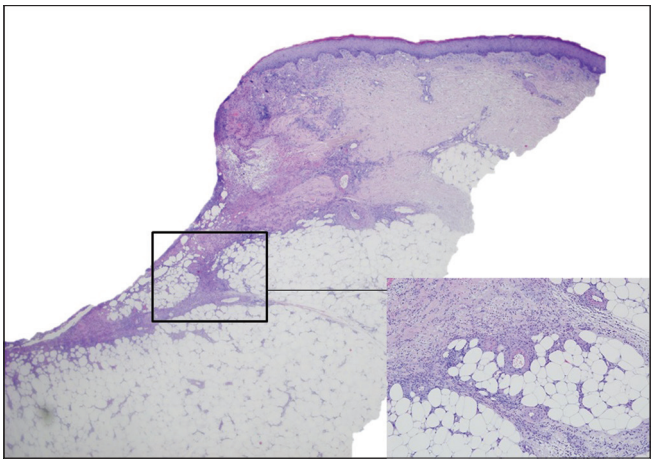

Figure 2: On low power, there is an ulcer that extends deep into the subcutaneous fat (H and E, 10×). On high power, note the septal "panniculitis-like" lesion with an inflammatory infiltrate with neutrophils along with fibrinoid necrosis in the vessel walls (H and E, 200×)

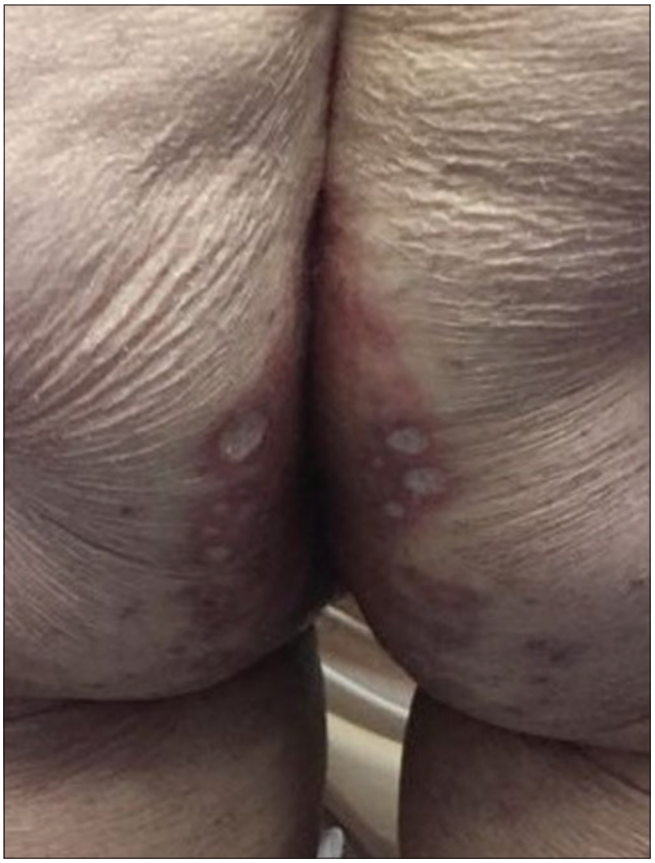

Figure 4: Ulcers on the intergluteal fold after 8 months of treatment with afatinib

manifestations include leukocytoclastic vasculitis and nonscarring alopecia.[6,7] These adverse events are transversal to the entire pharmacological group and therefore considered class-specific.[1,4] The inhibition of EGFR in basal keratinocytes and hair follicles seems to explain the cutaneous side effects of these drugs, but still remains unclear why only some patients are affected.[8] Although usually mild to moderate, these manifestations interfere with patient's quality of life and can lead to delay in treatment, dose adjustment, or ultimately drug

discontinuation, threatening clinical outcome.[1,3] Previous studies show comparable incidence of cutaneous toxicity between erlotinib and afatinib, with fewer side effects and better tolerability with gefitinib, probably because of the differences in their molecular structures.[1,5] Osimertinib is used in patients with T790M-positive advanced lung malignancies, and according to previous trials has similar adverse effects to other agents of the class, but less studies are available.[9]

Panniculitis represents an inflammatory infiltrate of the subcutaneous fat that may show concomitant septal thickening and vasculitis.[10] Rarely, neutrophilic panniculitis has been described as a drug side effect of chemotherapies and targeted molecular therapies.[10] To our knowledge, this is the first report of panniculitis related to EGFR inhibitors. We attributed the panniculitis to a side effect of EGFR inhibitors because there were no confounding elements explaining the cutaneous findings. The higher incidence of erlotinib and afatinib cutaneous effects in comparison with gefinitib, could justify why the panniculitis did not occur in the first place under treatment with gefitinib. Considering that skin lesions have reproduced simultaneously with cancer progression, it is likely that this side effect may not be considered a marker of efficacy as opposed to previously recognized cutaneous effects.

Given the potential severity of the cutaneous lesions, there may be implications in the maintenance of long-term tumor-targeted therapy. The increasing use of these drugs in oncology and future occurrence of similar cases will clarify the importance of this side effect in the progression of oncologic disease.

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Conflicts of interest

There are no conflicts of interest.

References

1. Chanprapaph K, Pongcharoen P, Vachiramon V. Cutaneous adverse events of epidermal growth factor receptor inhibitors: A retrospective review of 99 cases. Indian J DermatolVenereolLeprol 2015;81:547.
2. Owczarczyk-Saczonek A, Witmanowski H, Placek W. Acneiform rash during lung cancer therapy with erlotinib (Tarceva((R))). PostepyDermatolAlergol 2013;30:195-8.
3. Zhu H, Zhu Z, Huang W, Cheng X, He J, Xiong C, *et al.* Common and uncommon adverse cutaneous reactions to erlotinib: A study of 20 Chinese patients with cancer. CutanOculToxicol 2018;37:96-9.
4. Agero AL, Dusza SW, Benvenuto-Andrade C, Busam KJ, Myskowski P, Halpern AC. Dermatologic side effects associated with the epidermal growth factor receptor inhibitors. J Am AcadDermatol 2006;55:657-70.
5. Bachet JB, Peuvrel L, Bachmeyer C, Reguiai Z, Gourraud PA, Bouche O, *et al.* Folliculitis induced by EGFR inhibitors, preventive and curative efficacy of tetracyclines in the management and incidence rates according to the type of EGFR inhibitor administered: A systematic literature review. Oncologist 2012;17:555-68.
6. Pongpudpunth M, Demierre MF, Goldberg LJ. A case report of inflammatory nonscarring alopecia associated with the epidermal growth factor receptor inhibitor erlotinib. J CutanPathol 2009;36:1303-7.
7. Brandi G, Venturi M, Dika E, Maibach H, Patrizi A, Biasco G. Cutaneous leukocytoclasticvasculitis due to erlotinib: Just an adverse event or also a putative marker of drug efficacy? CutanOculToxicol 2013;32:336-8.
8. Holcmann M, Sibilia M. Mechanisms underlying skin disorders induced by EGFR inhibitors. Mol Cell Oncol 2015;2:e1004969.
9. Lamb YN, Scott LJ. Osimertinib: A Review in T790M-Positive advanced non-small cell lung cancer. Target Oncol 2017;12:555-62.
10. Stewart J, Bayers S, Vandergriff T. Self-limiting ibrutinib-induced neutrophilicpanniculitis. Am J Dermatopathol 2018;40:e28-9.