Severe EGFR inhibitor-induced acneiform eruption responding to dapsone

Abram Beshay MD, Marta Petersen MD, Jamie LW Rhoads MD MS

Affiliations: Department of Dermatology, University of Utah, Salt Lake City, Utah, USA

Corresponding Author: Abram Beshay MD, Department of Dermatology, University of Utah, 30 North 1900 East 4A330 SOM, Salt Lake City, UT 84132, Tel: 801-581-6465, Fax: 801-581-6484, Email: abram.beshay@hey.com

Abstract

Epidermal growth factor receptor (EFGR) inhibitors are targeted chemotherapeutic agents that are effective in treating various epithelial cancers. Cutaneous adverse effects, most commonly acneiform/papulopustular eruption, can occur with these medications and limit their tolerability. In severe cases, patients may refuse treatment with EGFR inhibitors because of the significant impact on the quality of life and aesthetic discomfort. We present a 72-year-old-man with a history of EGFR+ non-small-cell lung carcinoma who developed a severe acneiform eruption secondary to afatinib that failed to improve with various traditional treatment modalities. The patient was treated with dapsone and his acneiform eruption resolved within two months of initiating therapy. Patient tolerated dapsone with no reported adverse effects and continues on low dose dapsone, as he will remain on afatinib indefinitely. Dapsone can be an effective therapy for refractory or severe cases of EGFR-induced acneiform eruptions. As in this case, dapsone may improve patient adherence to EGFR inhibitors, thereby allowing for effective therapy of underlying malignancy.

Keywords: acneiform eruption, afatinib,dapsone, EGFR tyrosine kinase inhibitor

Introduction

Epidermal growth factor receptor (EGFR) inhibitors are targeted chemotherapeutic agents that have revolutionized the treatment of various malignancies. Epidermal growth factor receptor is a transmembrane glycoprotein with a ligand-binding extracellular domain and an intracellular tyrosine kinase domain. Its activation triggers downstream signaling pathways that promote tumorigenesis via cell proliferation and migration, angiogenesis, and diminished apoptosis. Certain EGFR inhibitors are monoclonal antibodies that disrupt the extracellular EGFR domain, whereas others block the intracellular catalytic domain of the EGFR tyrosine kinase. Their efficacy is the result of overexpression of EGFR in various epithelial cancers, including non-small cell lung carcinoma, breast cancer, colorectal cancer, pancreatic cancer, and squamous cell carcinoma of the head and neck [1].

Cutaneous toxicities frequently occur with these medications and management may require discontinuation. The most common cutaneous side effects include an acneiform/papulopustular eruption, paronychia, and xerosis. In addition, hyperpigmentation, trichomegaly, and telangiectasias may be noted but are less common [2]. In a comparison of EGFR tyrosine kinase inhibitors utilized in lung cancer, afatinib was the most likely to elicit cutaneous adverse effects, most commonly acneiform eruption [3-5]. We report using dapsone for the treatment of a recalcitrant acneiform eruption to the EGFR tyrosine kinase inhibitor, afatinib.

Case Synopsis

A 72-year-old-man with a history of metastatic EGFR+ non-small cell lung carcinoma presented with a one-year history of acneiform eruption. It began two weeks after starting afatinib, which was effective in stabilizing his underlying malignancy. On

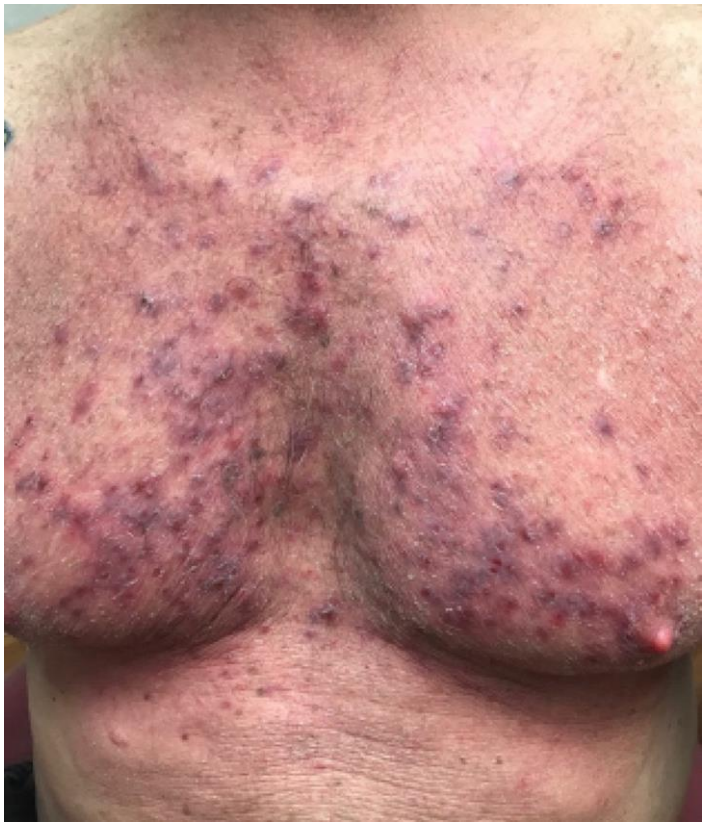

Figure 1. *Folliculocentric violaceous and erythematous nodules and papules scattered on the chest.*

examination, he exhibited pruritic, folliculocentric, violaceous-to-erythematous papules and nodules affecting the face, chest, and abdomen (**Figure 1**). No comedones were appreciated. A skin biopsy submitted for hematoxylin and eosin examination demonstrated a suppurative granulomatous dermatitis secondary to ruptured folliculitis (**Figure 2**) and he was diagnosed with an acneiform eruption secondary to treatment with afatinib. The patient was treated with salicylic acid, topical corticosteroids, topical retinoids, minocycline, and doxycycline without significant improvement despite good compliance. Low dose isotretinoin was initiated, but it had to be discontinued as the patient attempted suicide shortly after its initiation.

Given the recalcitrant nature of the eruption, limited treatment options, and need to continue the afatinib, the patient was started on dapsone 25mg twice daily after baseline laboratory tests (complete blood count, complete metabolic panel, and glucose-6-phosphate dehydrogenase enzyme activity) were within normal limits. The patient noticed improvement within two weeks of initiating dapsone (**Figure 3**). The dose was then escalated to 50mg twice daily and the patient continued to experience significant improvement until all lesions resolved within two months of therapy. The dose was subsequently tapered to 25mg daily with sustained clearance of his eruption. Dapsone was well tolerated by the patient, and he reported no adverse effects.

Case Discussion

Among the EGFR tyrosine kinase inhibitors for the treatment of EGFR+ lung cancer, afatanib has the highest risk of developing cutaneous side effects [3-5]. According to a 2019 meta-analysis, 84.8% of patients treated with afatanib developed a rash [3]. The presentation of the associated acneiform eruption is similar to acne vulgaris except that it lacks comedones and can be markedly pruritic. The severity and incidence of this eruption parallels both

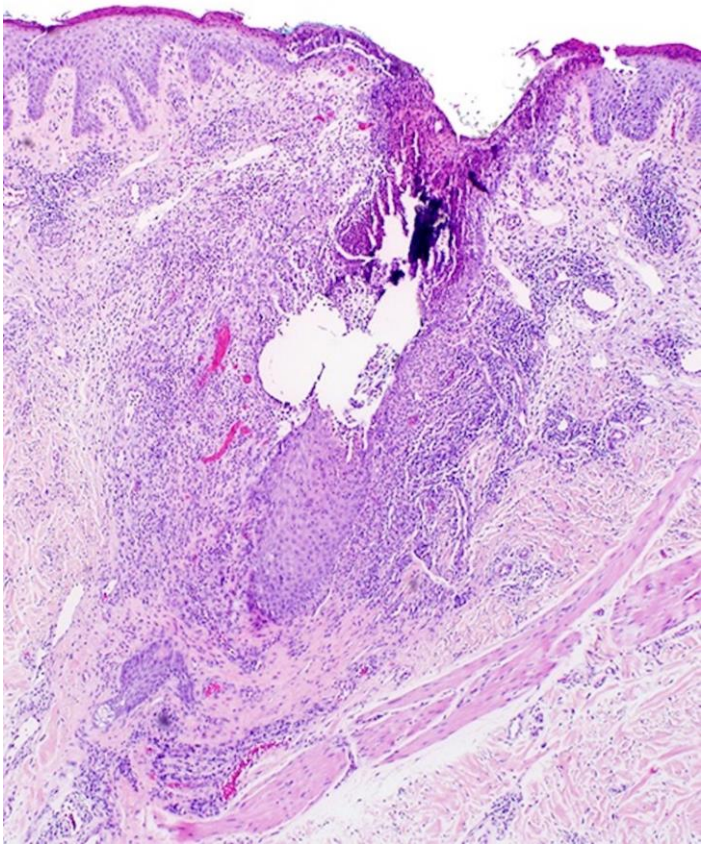

Figure 2. *Remnants of a disrupted hair follicle surrounded by a mixed granulomatous and suppurative inflammatory infiltrate. H&E, 40×.*

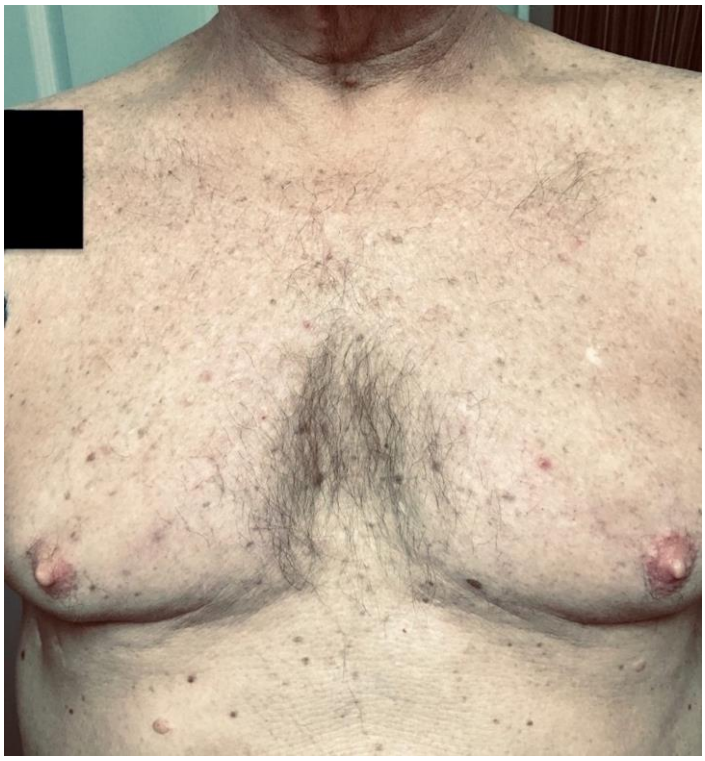

Figure 3. *The acneiform eruption resolved and remained clear after the initiation with dapsone.*

the EGFR inhibitor dose and treatment duration [2]. Although it may cause significant discomfort, studies have shown that a rash of moderate severity or greater is associated with afatanib efficacy and increased survival [2,6,7]. The treatment for an acneiform eruption induced by EGFR inhibitors is similar to that of acne vulgaris. Unfortunately, therapy options are limited in severe cases and patients may refuse treatment with EGFR inhibitors owing to the significant impact on the quality of life and aesthetic discomfort [2].

Because of its bacteriostatic and anti-inflammatory properties, the use of dapsone is well-established in treating a wide variety of infectious and inflammatory skin conditions [8]. Oral dapsone has been effective in treating variants of acne, including several cases of acne conglobata, nodulocystic acne [9], and more recently, isotretinoin-induced acne fulminans [10].

As our patient developed a recalcitrant acneiform eruption that failed traditional therapy and attempted suicide while taking isotretinoin, we pursued treatment with dapsone. After two months of treatment, dapsone led to a dramatic improvement in symptoms. To our knowledge, this is the first report of an EGFR inhibitor-induced acneiform eruption treated effectively with dapsone. Since the patient will be on afatinib indefinitely, we plan to keep him on low dose dapsone to maintain control of his eruption.

Conclusion

Dapsone can be an effective therapy for refractory or severe cases of EGFR inhibitor-induced acneiform eruption. Not only can this medication improve the quality of life of patients with these eruptions, but it can also aid oncologists by improving patients' adherence to taking EGFR inhibitors and thereby allowing for the most effective therapy for the underlying malignancy.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Yewale C, Baradia D, Vhora I, Patil S, Misra A. Epidermal growth factor receptor targeting in cancer: a review of trends and strategies. *Biomaterials* 2013;34:8690-707. [PMID: 23953842].
2. Hu JC, Sadeghi P, Pinter-Brown LC, Yashar S, Chiu MW. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. *J Am Acad Dermatol* 2007;56:317-26. [PMID: 17141360].
3. Ding PN, Lord SJ, Gebski V, et al. Risk of treatment-related toxicities from EGFR tyrosine kinase inhibitors: A meta-analysis of clinical trials of gefitinib, erlotinib, and afatinib in advanced EGFR-mutated non-small cell lung cancer. *J Thorac Oncol* 2017;12:633-43. [PMID: 28007626].
4. Annunziata MC, Ferrillo M, Cinelli E, et al. Retrospective analysis of skin toxicity in patients under anti-EGFR tyrosine kinase inhibitors: our experience in lung cancer. *Open Access Maced J Med Sci* 2019;7:973-7. [PMID: 30976343].
5. Osborn LP, Cohen PR. Afatinib-associated cutaneous toxicity: a correlation of severe skin reaction with dramatic tumor response in a woman with exon 19 deletion positive non-small-cell lung cancer. *Cureus*. 2016;8:e763. [PMID: 27725919].
6. Nasu S, Suzuki H, Shiroyama T, et al. Skin rash can be a useful marker for afatinib efficacy. *Anticancer Res*. 2018;38:1783-8. [PMID: 29491117].
7. Kudo K, Hotta K, Bessho A, et al. Development of a skin rash within the first week and the therapeutic effect in afatinib monotherapy for EGFR-mutant non-small cell lung cancer (NSCLC): Okayama

lung cancer study group experience. *Cancer Chemother Pharmacol*. 2016;77:1005-9. [PMID: 27029623].

8. Ghaoui N, Hanna E, Abbas O, Kibbi AG, Kurban M. Update on the use of dapsone in dermatology. *Int J Dermatol*. 2020;59:787-95. [PMID: 31909480].
9. Wakabayashi M, Fujii N, Fujimoto N, Tanaka T. Usefulness of dapsone for the treatment of asian severe acne. *J Dermatol*. 2013;40:502-4. [PMID: 23621696].
10. Legal K, Misery L. Isotretinoin-induced acne fulminans without systemic symptoms treated successfully with oral dapsone. *Acta Derm Venereol*. 2020;100:adv00036. [PMID: 31626323].