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Cutaneous Manifestations of EGFR-Inhibitors in African Americans and Treatment Considerations

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ABSTRACT

Epidermal growth factor (EGFR)-inhibitors have emerged as the primary therapy in advanced solid tumor malignancies because of improvement in survival with overall favorable side effect profile. However, 50–90% of patients treated with EGFR-inhibitors develop a follicular or acneiform rash, which can be symptomatic and source of psychosocial distress, negatively impacting quality of life. As this acneiform rash is a well-recognized cutaneous toxicity of EGFR-inhibitors, a treatment algorithm has been proposed for management based on severity. However, treatment options for EGFR-inhibitor induced rash may not be generalizable to African Americans whose differences in skin biology and sensitivity present pathophysiologic challenges. Herein, we present a case of an African American patient who developed this acneiform rash while on cetuximab. We also review the few cases that have been reported in the literature of EGFR-inhibitor rash in African Americans, highlighting important management considerations in this patient population.

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INTRODUCTION

Targeted therapies in particular epidermal growth factor (EGFR)-inhibitors have emerged as the primary therapy in advanced solid tumor malignancies including colorectal, pancreas, head and neck cancers, and non-small cell lung carcinoma because of improvement in survival with overall favorable side effect profile.[1,2] EGFR-inhibitors include small molecule tyrosine kinase inhibitors (TKIs) such as gefitinib, erlotinib, and lapatinib, as well as monoclonal antibodies such as cetuximab and panitumumab.[3,4,5] However, 50–90% of patients treated with EGFR-inhibitors develop a follicular or acneiform rash, which can be symptomatic and source of psychosocial distress, negatively impacting quality of life.[1,2,3] The pathogenesis of this rash is thought to be due to EGFR inhibition preventing keratinocyte migration, inducing keratinocyte apoptosis, and modulating cytokine release, which leads to the influx of inflammatory cells in the epidermis and dermis.[2,6] The epidermis becomes thin leading to skin atrophy and xerosis, and extensive follicular involvement can lead to scarring alopecia.[4] Areas with the highest follicle and sebaceous gland density, including the head and neck, chest, and back, are most frequently involved.[1,4]

As this acneiform rash is a well-recognized cutaneous toxicity of EGFR-inhibitors, a treatment algorithm has been proposed for management based on severity. However, this algorithm does not account for biologic differences in skin in patients of different races and ethnicities. Herein, we provide a case of an African American patient who developed this acneiform rash while on cetuximab.

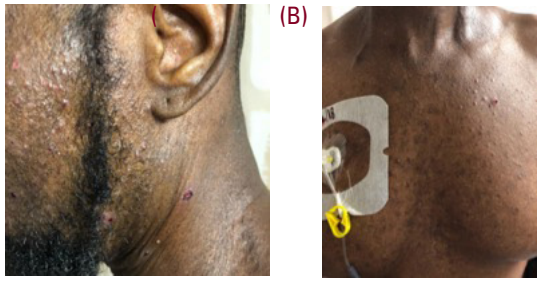
CASE

A 52-year-old African American male with a history of recurrent, metastatic oropharynx squamous cell carcinoma involving the lymph nodes, lungs, liver, and bone, on cetuximab weekly and a VEGFR inhibitor daily for the past four months, presented to dermatology with pruritic acneiform papules and pustules diffusely over the face, neck, upper chest, and back (Figure 1A–B). He had not previously tried any topical or oral medications to treat the rash. He was otherwise afebrile, well-appearing, with normal labs. Diagnosis of EGFR-inhibitor acneiform rash grade 2 was made and patient was started on oral antibiotics, doxycycline 100 mg twice a day in addition to topical clindamycin and alclometasone. The acneiform rash improved while on this regimen, but he had areas that became hyperpigmented.

DISCUSSION

The typical algorithm for EGFR-inhibitor induced rash includes use of an emollient,[3] a non-alcohol based sunscreen with titanium dioxide and zinc oxide,[2,4,7,8,9] topical steroids with or without topical antibiotics, and oral tetracyclines.[2,3,4,6] Treatment is guided by extent of rash using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE),[3,4,6] although studies have suggested better efficacy with prophylactic use of tetracyclines.[3] Treatment of acneiform eruption, rather than EGFR-inhibitor dose reduction or discontinuation, is preferred as there has been a positive correlation described between rash severity and cancer survival.[1,2,4] However, treatment options for EGFR-inhibitor induced rash may not be generalizable to African Americans, who not only differ in

FIGURE 1. Acneiform rash to cetuximab (A) neck and (B) upper chest showing papulopustules and dyspigmentation.



their skin biology but are also underrepresented in therapeutic clinical trials, preventing complete understanding of side effects.[4,9,10,11,12]

EGFR-inhibitor rash in African American patients has only been reported a few times previously. One case was of a 61-year-old male with oropharyngeal cancer also treated with cetuximab who developed a mild facial acneiform rash after the second cycle of treatment, that progressed in severity with continued treatment. He was similarly treated with doxycycline with improvement.[2] The second case was of a 41-year-old African American female who developed a milder presentation after six cycles of lapatinib and was treated only with low potency topical steroids. In both cases, treatment was continued, although in the first case, dose was held for one week.[6] Although one case eluded to the challenges in treating this rash in patients of skin of color or darker skin types, both cases were treated similarly according to known rash algorithm.

One of the main challenges in treating this rash in different patient populations is inherent biologic differences in skin of African Americans and Caucasians.[9,13] Although the acneiform rash from EGFR-inhibitors has a different pathogenesis from typical acne with inflammation beginning in the pilosebaceous unit, we know that African Americans have a higher baseline density of P. acnes, and larger sebaceous glands with increased sebum secretion.[8,9,12,13] Consequently, skin of color displays substantial histological inflammation even around comedones that are not clinically inflamed.[8,9,12] This heightened inflammatory response may be why African Americans with even mild to moderate acne develop post-inflammatory hyperpigmentation (PIH).[9,12,13] African Americans also have an increased number of fibroblasts, as well as larger fibroblasts, resulting in an increased prevalence of keloids.[13,15]

These inflammatory mediators can also stimulate tyrosinase activity and subsequent melanin synthesis.[11] It is known that the differences in skin color are not due to the number of melanocytes, but rather the activity of tyrosinase in melanosomes, the number, size, and aggregation of melanosomes within melanocytes, and the efficiency of melanosome transfer from melanocyte to keratinocyte.[9,11,13] In African Americans, the number of melanosomes transferred to keratinocytes is significantly higher, melanosomes are more active in producing melanin, and they are larger and present in all layers of the epidermis.[9,13] PIH is more prevalent in African Americans due to these increased melanosomes which exhibit labile responses to irritation and injury.[11,13] Other factors that may contribute to worsening PIH include increased skin sensitivity in African Americans thought to be due to impaired barrier function/increased transepidermal water loss, which may increase irritation after topical acne products such as retinoids.[8,12,13] Furthermore, skin care practices including use of hair emollients and heavy oils leading to "pomade acne" and the increased incidence of other follicular skin and hair disorders in the African American population such as acne keloidalis may also contribute to worsening acneiform rash in patients receiving EGFR inhibitors.[8,9,12,13,14]

CONCLUSION

Treatment of EGFR-inhibitor induced rash in patients with skin of color can present both cultural challenges, due to skin care product use, and pathophysiologic challenges, due to differences in skin biology and sensitivity.[2,4,8] Delays in treatment and misdiagnoses may lead to sequelae such as PIH and keloids which is more prevalent in this population.[9] Reducing skin irritation and xerosis, which may adversely affect darker skin, is a key goal in treating rash in skin of color.[8] Further studies are needed to evaluate EGFR-inhibitor rash presentation and treatment outcomes with standard algorithm in African Americans to determine if the typical management approach needs to be modified in this patient population.[7]

DISCLOSURES

ANG does not have any relevant conflicts of interest to disclose. SJN served as a consultant/speaking role for Kyowa Kirin and Array Biopharma.

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