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Inflamed actinic keratoses associated with pemetrexed and carboplatin therapy

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Abstract

Eruptive actinic keratosis (AK) consequent to systemic chemotherapy can be confused with drug allergies. We present the first case of inflamed AKs in one patient after receiving combination therapy with pemetrexed and carboplatin.

A 68-year-old woman with non-small cell lung adenocarcinoma (NSCLC) presented with numerous pruritic ill-defined, gritty, erythematous papules consistent with AKs on her upper chest, upper back, and arms two weeks after completing the first cycle of combination therapy with carboplatin and pemetrexed. The care team managed her with topical steroids and the lesions resolved within one month. The patient resumed the second cycle of chemotherapy and reported the occurrence of a similar but milder eruption.

This case illustrates that eruptive AKs should be considered in the differential diagnosis of drug-related rashes, especially if the physical exam is suggestive. The mainstay of treatment should be directed at symptomatic improvement, and chemotherapy may be continued.

Keywords: actinic keratosis, carboplatin, drug rash, pemetrexed

Introduction

Herein we report a case of inflamed actinic keratoses (AKs) in a patient with NSCLC after receiving combination therapy with pemetrexed and carboplatin.

Case Synopsis

A 68-year-old woman with a two-month history of biopsy-confirmed stage IIIA NSCLC, pT3N1, status-post bilobectomy, presented with a rash on her upper chest, upper back, and arms bilaterally (**Figure 1**) on day 13 after completing the first cycle of combination chemotherapy with carboplatin (474mg) and pemetrexed (950mg). She denied any other new medications, supplements, or environmental exposures. The rash was described as having a red, pruritic, and mild "burning/stinging" quality and worsened with exposure to sunlight. In addition to a standard three-day prophylactic course of dexamethasone from days 1-3, the patient was taking 25mg of diphenhydramine and applying over

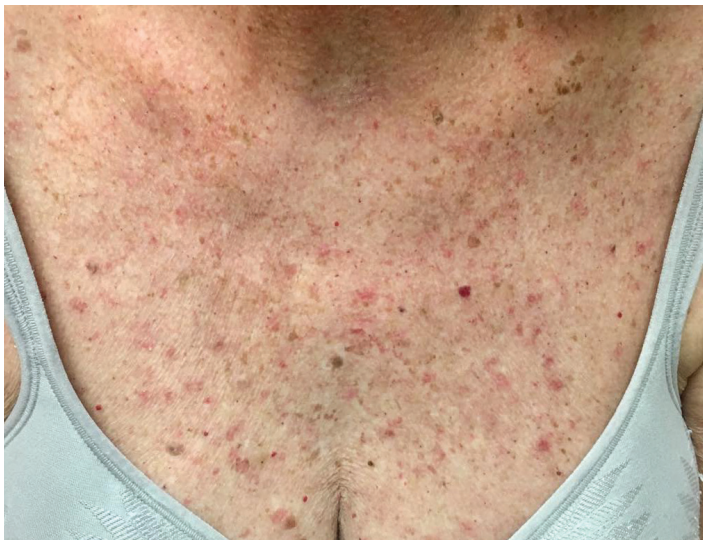

Figure 1. *Broad view of upper chest.*

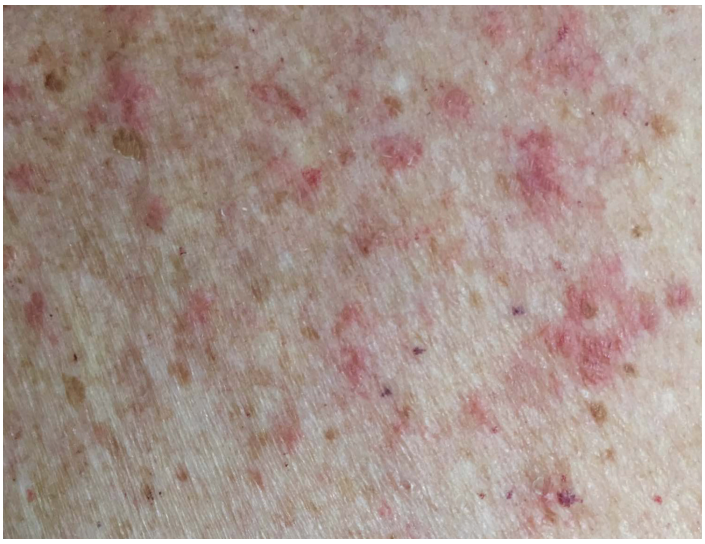

Figure 2. *Close-up view of primary lesions on a background of actinic damage located on upper chest.*

the counter diphenhydramine-hydrocortisone cream as needed on days 13-14 with no improvement. Her oncologist saw her on day 20 and prescribed dexamethasone 4mg twice per day for the eruption. The oncologist also decided to delay initiation of cycle 2 of the patient's chemotherapy (typically given every three weeks) until further evaluation was made by the dermatology department. When the patient was seen at the dermatology clinic on day 24, the patient reported that while the rash was still present, it was not as red or symptomatic as it was initially. She denied any fever, facial or acral swelling, mucosal involvement (eyes, mouth, genital), bleeding, malaise, or difficulty breathing or swallowing. On physical exam, numerous ill-defined, gritty, thin, distinct, erythematous, blanchable papules were present on the upper chest, upper back, dorsal arms, and distal lower extremities over background changes of chronic photodamage (**Figure 2**).

Based on the distribution of the eruption in sun-exposed areas and the characteristic physical exam findings, the diagnosis of inflammatory, eruptive AKs was made. We postulated that the lesions resulted from a reactive inflammatory response to systemic chemotherapy from pemetrexed and carboplatin. The patient was started on triamcinolone 0.1% ointment twice per day to the lesions. Flaring of the rash, to a much lesser degree, was reported with the second cycle of chemotherapy.

Case Discussion

AKs represent dysplastic growths of keratinocytes from cumulative UV-induced DNA damage. Underlying nuclear atypia provides a permissive environment for the action of antineoplastic agents. Reactive AKs secondary to systemic chemotherapy is not unusual and there exists numerous case records that implicate the following agents: carboplatin, erlotinib, doxorubicin, docetaxel, capecitibine, vincristine, and fluorouracil [1]. The earliest incidental finding of this phenomenon was with systemic fluorouracil (5-FU) therapy [2] and formed the basis for modern topical 5-FU therapy for multiple AKs. Pemetrexed (trade name, Alimta®) is a folate antimetabolite that inhibits multiple folate-requiring enzymes involved in purine and pyrimidine synthesis; it primarily targets thymidylate synthetase [3], thereby blocking the conversion of uridine monophosphate to thymidine monophosphate. Coincidentally, pemetrexed is functionally similar to 5-FU, as both agents target thymidylate synthetase [2, 3]. Although the exact mechanism of pemetrexed-associated inflammation of AKs is unknown, it is possibly similar to 5-FU. It is not clear how the carboplatin may have additionally contributed to the patient's response.

One potential adverse reaction to pemetrexed is the development of a rash. The most commonly reported cutaneous adverse reactions to pemetrexed are radiation recall dermatitis, alopecia, urticarial vasculitis, acute generalized exanthematous pustulosis, and pityriasis lichenoides [4]. Rashes were reported in 2% of patients taking pemetrexed as a single agent for NSCLC, stage IIIb and IV, in a phase III double-blind randomized control trial (RCT), [5]. Medication related eruptions are even more common with combination therapy. Indeed, 7.5% of patients developed a rash in a similar phase III RCT involving pemetrexed and carboplatin [6]. In both studies, patients were given prophylactic therapy with oral dexamethasone 4mg twice daily the day before, the day of, and the day after initiation of pemetrexed, as instructed by manufacturers, to prevent pemetrexed-associated rashes [7].

It is important for clinicians to be able to distinguish inflamed AKs from more serious drug eruptions to avoid delay or cessation of life-saving medication administration. Accordingly, it is prudent to note that the reported cases of chemotherapy-induced

inflammatory AKs thus far exhibit a characteristic AK appearance in a photodistribution. Moreover, inflamed AKs consequent to chemotherapeutic agents typically originate in pre-existing AKs. However, subclinical AKs may not be visually evident prior to the onset of chemotherapy-induced flaring, as in our patient.

Management of inflamed AKs involves topical corticosteroids and anti-histamines for symptomatic relief. Biopsy is not necessary unless ruling out allergic or toxic reaction. The general consensus is that chemotherapy may be continued [8]. For pemetrexed-associated rashes, drug manufacturers recommend prophylactic therapy with dexamethasone during the initiation of therapy to reduce the incidence and severity [7]. Onset and resolution of medication eruptions vary widely with the individual, lasting from weeks to months [9]. In this particular case, onset occurred approximately two weeks after initiation of chemotherapy and was almost completely resolved in one month, prior to flaring with the subsequent chemotherapy cycle.

To our knowledge, there is one case report of pemetrexed-associated inflamed AKs and there are other reports of inflamed AKs from combination therapy involving carboplatin [10, 11, 12]. However, to our knowledge, there are no reports of inflamed AKs specifically associated with pemetrexed and carboplatin combination therapy.

Conclusion

It is difficult to determine whether pemetrexed, carboplatin, or both may have induced the inflamed AKs. Pemetrexed and carboplatin may work synergistically in mounting this inflammatory response. It is generally accepted that patients should continue chemotherapy despite reactive AKs and treatment of reactive AKs should be aimed at symptomatic improvement.

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