A rare case of late-onset lichenoid photodermatitis after vandetanib therapy

James Bota, MD,[a] Valerie Harvey, MD, MPH,[a,b] Cynthia Ferguson, PA-C,[a] and Antoinette Hood, MD[a]
Norfolk, Virginia

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INTRODUCTION

Vandetanib (ZD6474, Zactima) is a novel inhibitor of multiple tyrosine kinases that has been used for the treatment of various malignancies including medullary thyroid carcinoma.[1] The drug functions primarily via inhibitory effects on vascular endothelial growth factor receptors, epidermal growth factor receptors, and the RET-tyrosine kinase system.[2] As with other targeted chemotherapy agents, several cutaneous side effects including folliculitis, palmar-plantar hyperkeratosis, desquamation, cutaneous hyperpigmentation, and photosensitization have been reported.[3,4] Photosensitivity, although less commonly reported, was found to make up 37% of cutaneous adverse effects in one case series.[3] Most of these patients were found to exhibit a sunburnlike erythema in sun-exposed regions with subsequent desquamation. However, a small subset of patients exhibited a phenotypically lichenoid photodermatitis and a lymphocytic interface dermatitis with basal vacuolization and keratinocyte apoptosis upon histopathology. Only a handful of cases describing similar lichenoid eruptions after vandetanib use have been reported, most of which developed within a few weeks after exposure.[5-8] We present a patient with a late-onset lichenoid photodermatitis that began 5 months after initiation of vandetanib therapy.

CASE REPORT

A 61-year-old African-American man with Fitzpatrick type IV skin was referred to our dermatology department with a 1-month history of painful and severe sunburn. In 2002, he had medullary thyroid cancer diagnosed and underwent total thyroidectomy with adjuvant radiation. Despite initial treatment, he experienced recurrent metastatic disease involving his lungs, liver, and bones. He subsequently was started on vandetanib therapy at 300 mg daily in December 2012.

Approximately 5 months after initiation of vandetanib, a painful, erythematous eruption developed in sun-exposed regions after gardening outdoors. In the clinic, he had multiple vesicles, erosions, and scaly pink papules over his sun-exposed face, chest, upper back, and dorsal forearms (Fig 1, *A-C*). No additional medications had been added to his regimen since beginning vandetanib therapy, and his only treatment was topical silver sulfadiazine; he denied taking any other known photosensitizing medications. A rheumatoid factor assay and erythrocyte sedimentation rate were both markedly elevated, but a complete blood count, basic metabolic panel, and antinuclear antibody test were all within normal limits. The patient denied any myalgias or muscle weakness. Skin biopsy specimens were taken from representative areas.

HISTOPATHOLOGY

Three specimens had similar histopathologic findings that included orthohyperkeratosis, mild hypergranulosis, mild spongiosis, basal vacuolization, and scattered dyskeratotic cells. A bandlike lymphoplasmacytic infiltrate was present in the papillary dermis. Melanin granules were seen both within macrophages and freely in the papillary dermis (Fig 2).

DISCUSSION

Our patient's clinical and histologic findings are supportive of a lichenoid photo-induced dermatitis.

From the Department of Dermatology, Eastern Virginia Medical School[a] and Hampton University Skin of Color Research Institute.[b]

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Correspondence to: James Bota, MD, Eastern Virginia Medical School, Department of Dermatology, 721 Fairfax Ave, Ste 200, Norfolk, VA 23507.

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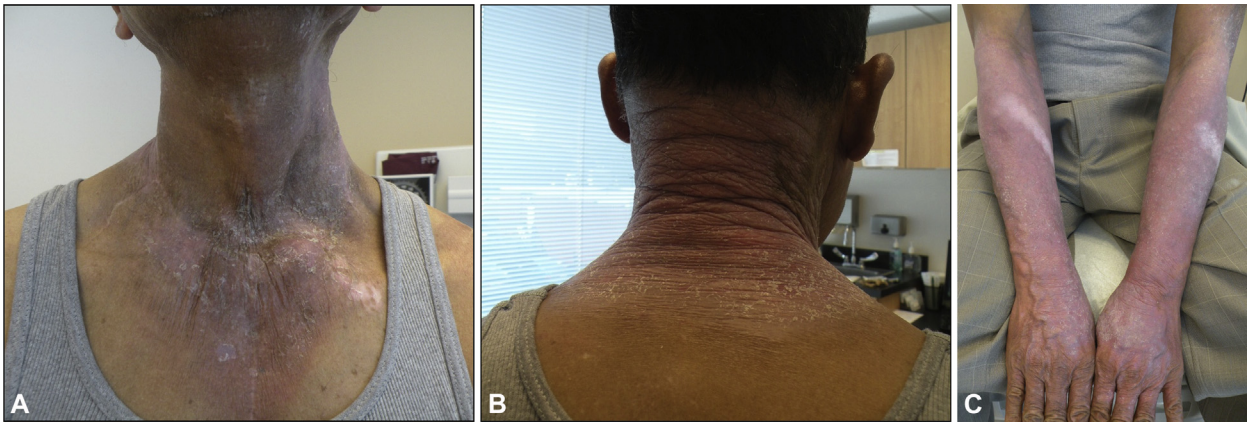

Fig 1. A-C, Pink, lichenified, and faintly hyperpigmented papules and plaques with scale and fine erosions overlying sun-exposed areas.

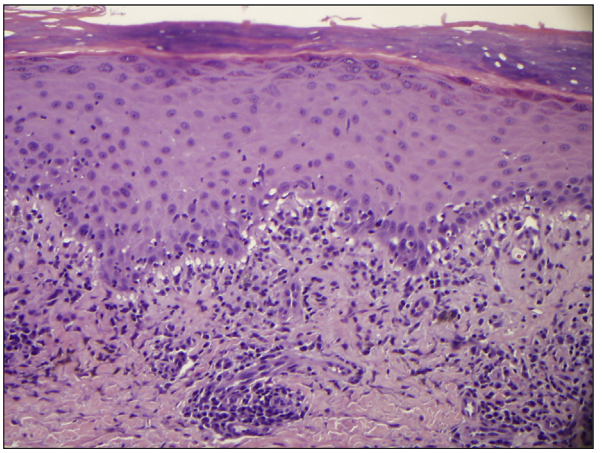

Fig 2. Specimen shows a bandlike lymphoplasmacytic infiltrate with basal vacuolization, dyskeratosis, mild spongiosis, and orthohyperkeratosis. Pigment incontinence is evident in the upper papillary dermis. (Hematoxylin-eosin stain; original magnification: ×10.)

Lichenoid photodermatitis during treatment with vandetanib has been described in a few case reports and a small case series.[3-8] One author hypothesized that photodermatitis was related to deposition of drug or drug metabolites within the dermis.[6] However, the exact mechanism of vandetanib-induced photosensitivity remains unclear. In vitro studies have found that vandetanib has a low molecular weight and polycyclic structure similar to other known photosensitizing agents and that vandetanib may exert its photosensitizing effects through induction of reactive oxygen species, DNA cleavage, and cell apoptosis.[9] It has also been shown that vandetanib inhibits the ABCG2 transporter-associated protein, which suggests a porphyrialike mechanism.[10] Although the cutaneous porphyrias, such as porphyria cutanea tarda, can be associated with a chronic lichenoid photodermatitis, there are no studies to our knowledge evaluating porphyrin levels in patients taking vandetanib.

Given the findings from the aforementioned in vitro studies, it would be reasonable to extrapolate that phototoxicity plays a key role in the pathogenesis of vandetanib-related photosensitivity. However, phototoxicity typically develops within hours to days. With regard to the spectrum of cutaneous side effects of vandetanib, the most commonly reported photosensitive eruptions manifest within a few days to weeks as severe sunburns with erythematous desquamation.[3] The timeline for these eruptions may be consistent with phototoxicity; however, most of the previously described photo-induced lichenoid eruptions exhibit a longer time until onset of symptoms.

One case report by Fava et al[7] describes a similar photosensitive lichenoid eruption that occurred 3 months after initiation of therapy. The authors hypothesized that this delayed case presentation was indicative of photoallergy. In another case series, the median time to development of an eruption was 8 weeks.[3] Our patient did not display symptoms until 26 weeks after initiation, but the patient's clinical and histopathologic findings were remarkably similar to the few previously described cases.

One potential source of confounding is that our patient began vandetanib therapy in the wintertime. The atmospheric ultraviolet light burden may not have been sufficient to trigger photosensitivity at that time; however, his symptoms did not begin until late May—somewhat later than expected for seasonal ultraviolet light variation. The use of silver sulfadiazine to affected areas may have caused additional confounding. Although photosensitivity is not typically seen with silver sulfadiazine, it can be associated with an irritant dermatitis and localized argyria; both of these adverse effects may obfuscate the

clinical picture. Our patient did not commence use of silver sulfadiazine until after the onset of symptoms, and although he achieved no benefit from treatment, he did not report any worsening of his symptoms. Lastly, our patient reports that he had been gardening outdoors near the time of onset; this could have exposed him to additional plant-based photoallergens; however, he reported he had been gardening for years prior without incident. Photo patch testing was offered to help rule out plant-based photoallergy, but the patient declined.

Ultimately, our patient's clinical presentation most strongly implicates vandetanib as the causative etiology. Given the variable latency in presentation between our case and those previously described, there may be a spectrum of action in vandetanib-mediated photosensitivity, including acute-to-subacute phototoxicity and a delayed cell-mediated photoallergy. Accordingly, awareness of this phenomenon must be maintained throughout the duration of treatment with vandetanib, and patients should be counseled appropriately regarding sun-protective behaviors.

Because any type of photosensitivity can be physically debilitating, the question of whether to discontinue vandetanib therapy emerges. In one previously documented case, cessation of vandetanib therapy resulted in clearance of symptoms with residual postinflammatory hyperpigmentation.[6] Another case report describes transient clearance after stopping vandetanib but resensitization with subsequent docetaxel use.[5] These 2 cases illustrate the potential for improvement after discontinuation of therapy; however, the latter case suggests that vandetanib therapy may have permanent implications for future chemotherapy. Moreover, termination of therapy is not an option for many patients on vandetanib, considering the high mortality associated with the underlying disease. Vandetanib may represent a final treatment option. One patient who remained on vandetanib for 3 years after an initial eruption experienced attenuation of symptoms with the use of sunscreen and sun avoidance.[6] For our patient, we opted for topical corticosteroids, oral antihistamines, and sun avoidance for symptomatic relief while making the decision to continue with vandetanib therapy.

The emergence of new kinase receptor inhibitors and their cutaneous side effects presents a challenge for dermatologists and dermatopathologists. Given the increasing number of patients on this medication, the profile of adverse effects associated with vandetanib is still evolving. Associated photosensitive eruptions are well reported in the literature. We propose the need for heightened awareness regarding this late-onset variant that may represent photoallergy. New rashes developing many months into treatment with vandetanib should be thoroughly assessed as a potential side effect. Early discussion of sun protection and sunscreen use at the onset of therapy is quintessential for maximizing patient benefit and prevention. Furthermore, treatment has the potential for complex decision making, which inevitably will benefit from multidisciplinary discussion.

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