Nevoid melanoma and eruptive nevi from erlotinib

Jason S Seidman[1] PhD, Dawn Z Eichenfield[2] MD PhD, Charisse M Orme[2] MD PhD

Affiliations: [1]School of Medicine, University of California San Diego, San Diego, California, USA, [2]Department of Dermatology, University of California San Diego, San Diego, California, USA

Corresponding Author: Charisse M Orme, 8899 University Center Lane, Suite 350, San Diego, CA 92122, Tel: 858-657-8322, Email: chorme@ucsd.edu

Abstract

Cutaneous side effects such as acneiform eruption, xerosis, and paronychia are frequently observed in patients undergoing treatment with epidermal growth factor receptor (EGFR) inhibitors for non-small cell lung cancer and other solid tumors. Interestingly, these side effects appear to positively correlate with length of remission, indicating that disruption of homeostatic EGFR signaling in the skin may serve as a marker of therapeutic EGFR inhibition in tumors. We report the case of a woman with metastatic lung cancer in remission being treated with the EGFR inhibitor, erlotinib, who experienced numerous commonly occurring adverse cutaneous reactions early in her treatment, and after two years of treatment developed eruptive nevi as well as a nevoid melanoma. Changes in pigmented lesions and the development of melanoma have been described during treatment with the BRAF inhibitor, vemurafenib, and are believed to relate to paradoxical activation of BRAF and the MAPK pathway. We speculate that a similar mechanism may occur during treatment with EGFR inhibitors. Therefore, thorough skin examinations are essential for patients undergoing long term treatment with erlotinib.

Keywords: erlotinib, eruptive nevi, melanoma, EGFR inhibitor

Introduction

Erlotinib is a small molecule epidermal growth factor receptor (EGFR) inhibitor used to treat non-small cell lung cancer and other solid tumors. In clinical trials, erlotinib has been associated with a variety of adverse cutaneous reactions, most commonly acneiform rash, xeroderma, pruritus, and paronychia [1]. Herein, we present a woman who developed a nevoid melanoma and eruptive nevi while on erlotinib for metastatic lung cancer.

Case Synopsis

A 73-year-old Fitzpatrick type II woman was initially evaluated for a painful non-blanching papulopustular eruption on her lower extremities and chest. She had a history of breast cancer in remission and metastatic non-small cell lung cancer, treated with erlotinib for 6 months. Her treatment course was complicated by numerous cutaneous adverse effects including a persistent acneiform

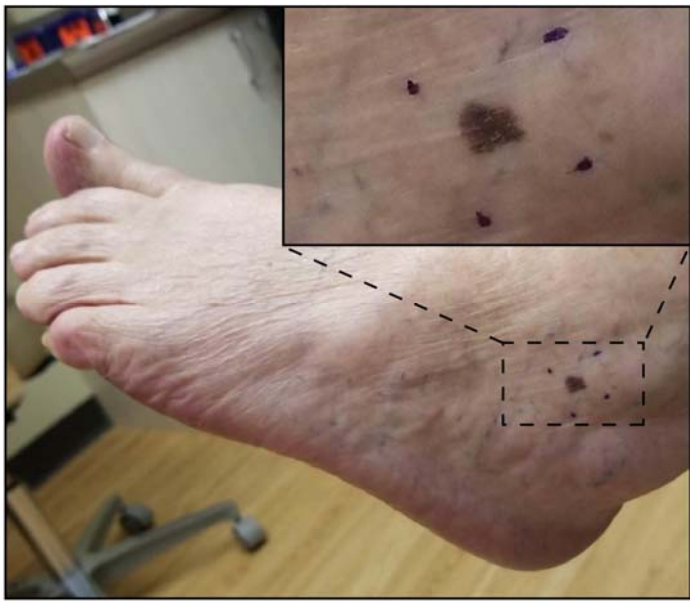

Figure 1. *Left ankle nevoid melanoma.*

eruption (treated with doxycycline, followed by minocycline owing to gastrointestinal intolerance of doxycycline), wiry hair, xerosis and pruritus (treated with loratadine), paronychia (treated with clobetasol and vinegar soaks), and an intermittent small vessel leukocytoclastic vasculitis (LCV, which resolved with erlotinib dose reduction).

After two years on erlotinib, the patient returned for evaluation of a 4mm irregularly-bordered darkly-pigmented macule on the left lateral ankle (**Figure 1**). A skin biopsy was performed, which demonstrated variably sized, randomly scattered, haphazard melanocytic nests with a component of pseudo-maturation on sun-damaged skin. The nuclear features were focally aberrant and melanocytes did not appear to be uniformly mature in the same zones. Dual immunohistochemistry with Melan-A and Ki67 showed an up-tick in the proliferative index between 5-10%. Although p16 expression was preserved, phosphohistone-H3 was performed, which showed the presence of focal mitotic activity. In an attempt to better position this melanocytic lesion on the continuum of benign → partially transformed → malignant, array-based comparative genomic hybridization was performed, which revealed gain of chromosomal 7, loss of chromosome 17, and loss of the X chromosome. Given the clinical findings, histopathology, immunohistochemistry, and molecular data, a diagnosis of micro-nested nevoid melanoma, stage pT1a (Breslow thickness of 0.4mm) was rendered. This melanoma was subsequently treated by wide local excision.

In the following months, the patient developed multiple new clinically-benign dark brown 2-4mm nevi on her trunk and extremities (**Figure 2**). She elected for clinical monitoring given the lack of change and banal dermoscopic features of these numerous lesions.

Case Discussion

The EGFR signaling pathway regulates homeostatic functions in the skin, including keratinocyte differentiation and development, epidermal growth, inflammation, and wound healing. Disruption of these pathways can lead to the dermatologic side effects seen with administration of EGFR inhibitors [2]. Multiple studies have identified a positive correlation between cutaneous side effects of EGFR inhibitors and length of remission, indicating that

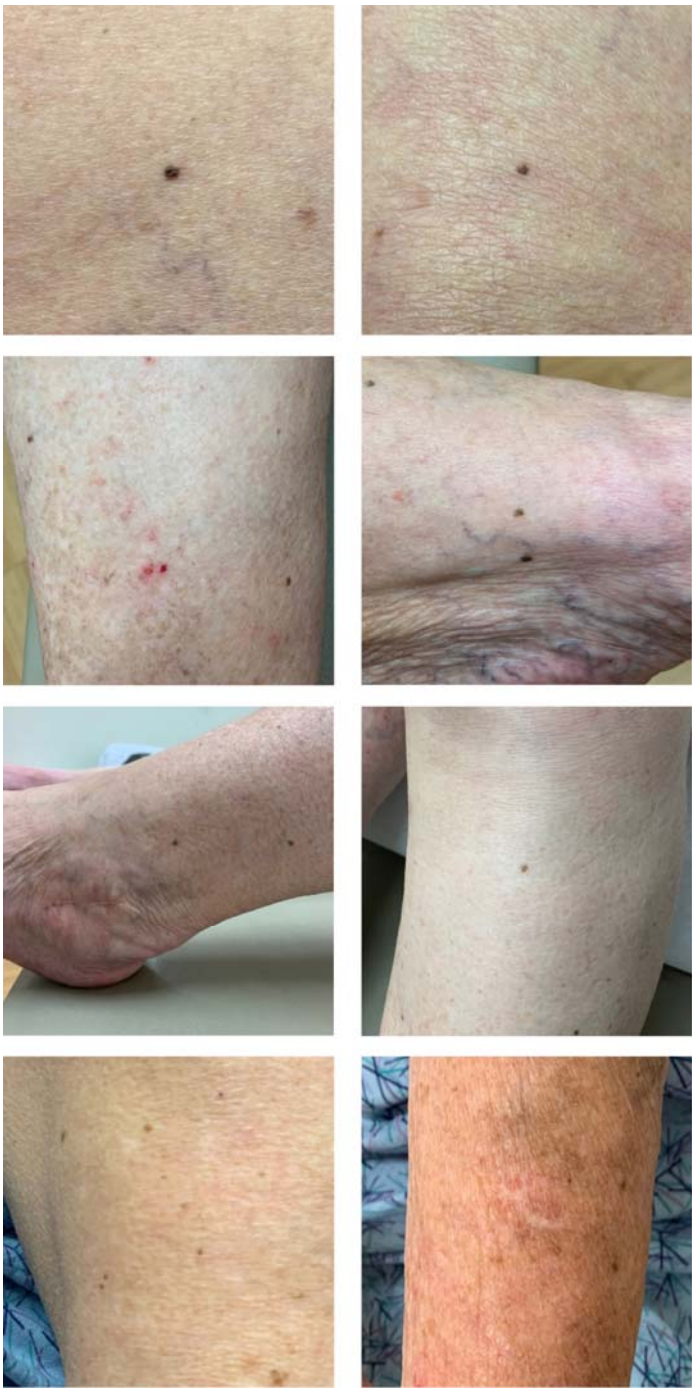

Figure 2. *Eruptive Nevi. From left to right, top to bottom: right thigh, right knee, right calf, left medial ankle, left lateral ankle, left leg, right upper arm, left forearm.*

these side effects may predict a beneficial therapeutic response [3].

To date, multiple targeted cancer therapeutic medications have been associated with eruptive melanocytic nevi, including the multi-kinase inhibitors, sorafenib, regorafenib, and nilotinib [4]. Changes in pigmented lesions, including the development of melanocytic lesions such as melanoma, have been predominantly described with the BRAF inhibitor, vemurafenib [4, 5]. The changes induced by vemurafenib are believed to be a paradoxical activation of BRAF and the MAPK pathway during treatment [6]. Blockade of EGFR by erlotinib may have similar effects, suggesting that paradoxical activation of the MAPK pathway during treatment with kinase inhibitor drugs may be a critical step in the mechanism for nevi induction.

To our knowledge, there has been one prior report of eruptive nevi related to erlotinib [7], which was part of a case series covering a range of cutaneous reactions observed in 14 patients treated with cetuximab and erlotinib for lung or colorectal cancer. This patient first developed papulopustular lesions and later developed pyogenic granuloma and paronychia, with eruptive nevi appearing after over 180 days of treatment (**Table 1**). Herein, we present a similar patient who first developed acneiform rash, paronychia, and LCV, then developed multiple benign eruptive nevi over two years after starting therapy with erlotinib.

Conclusion

This case is unique in that it suggests erlotinib, by predisposing patients to multiple eruptive nevi, may unmask melanoma in a predisposed patient population. Therefore, thorough skin examinations are essential in patients with prolonged treatment with erlotinib.

Potential conflicts of interest

The authors declare no conflicts of interests.

Table 1. *Comparison of key features in the currently reported case and a prior case report by Santiago et al. [7].*

	Age/ gender	Treatment interval	Adverse cutaneous reaction	Location	Treatment
Patient 1 Santiago et al 2011, *An Bras Dermatol,* [7]	60/M	10 d	PPE	Face Trunk Abdomen Forearm Thighs	Erlotinib dose reduction Minocycline Metronidazole /Topical corticosteroid Emollient
		> 6 mo	Eruptive nevi PG Paronychia	Trunk Hallux	Under monitoring TC and fusidic acid
Current report	73/F	1 mo	Acneiform rash	Face/trunk	Doxycycline /minocycline
		4-6 mo	Wiry hair Xerosis Pruritis Paronychia	Scalp eyebrows /eyelashes Chest /Lower extremities Fingernails	Loratadine Clobetasol/vinegar soaks
		6 mo	LCV	Lower extremities	Erlotinib dose reduction Prednisone taper
		2.5 yr	Nevoid melanoma	Ankle	Wide local excision
		3 yr	Eruptive nevi	Face/trunk	Under monitoring

Abbreviations: PPE, papulopustular lesion; PG, Pyogenic granuloma; LCV, leukocytoclastic vasculitis.

References

1. Kiyohara Y, Yamazaki N, Kishi A. Erlotinib-related skin toxicities: treatment strategies in patients with metastatic non-small cell lung cancer. *J Am Acad Dermatol*. 2013;69:463-72. [PMID: 23602600].
2. Mitchell EP, Perez-Soler R, Van Cutsem E, Lacouture ME. Clinical presentation and pathophysiology of EGFRI dermatologic toxicities. *Oncology (Williston Park)*. 2007;21:4-9. [PMID: 18154212].
3. Liu HB, Wu Y, Lv TF, et al. Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: a systematic review and meta-analysis. *PLoS One*. 2013;8:e55128. [PMID: 23383079].
4. Vena GA, Fargnoli MC, Cassano N, Argenziano G. Drug-induced eruptive melanocytic nevi. *Expert Opin Drug Metab Toxicol*. 2017;13:293-300. [PMID: 27759434].
5. Cohen PR, Bedikian AY, Kim KB. Appearance of New Vemurafenib-associated Melanocytic Nevi on Normal-appearing Skin: Case Series and a Review of Changing or New Pigmented Lesions in Patients with Metastatic Malignant Melanoma After Initiating Treatment with Vemurafenib. *J Clin Aesthet Dermatol*. 2013;6:27-37. [PMID: 23710269].
6. Holderfield M, Nagel TE, Stuart DD. Mechanism and consequences of RAF kinase activation by small-molecule inhibitors. *Br J Cancer*. 2014;111:640-5. [PMID: 24642617].
7. Santiago F, Goncalo M, Reis JP, Figueiredo A. Adverse cutaneous reactions to epidermal growth factor receptor inhibitors: a study of 14 patients. *An Bras Dermatol*. 2011;86:483-90. [PMID: 21738965].