

Darkening and Eruptive Nevi During Treatment With Erlotinib

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PRACTICE POINTS

- Cutaneous side effects of erlotinib include acneform eruption, xerosis, paronychia, and pruritus.
- Clinicians should monitor patients for darkening and/or eruptive nevi as well as melanoma during treatment with erlotinib.

To the Editor:

Erlotinib is a small-molecule selective tyrosine kinase inhibitor that functions by blocking the intracellular portion of the epidermal growth factor receptor (EGFR)^{1,2}; EGFR normally is expressed in the basal layer of the epidermis, sweat glands, and hair follicles, and is overexpressed in some cancers.^{1,3} Normal activation of EGFR leads to signal transduction through the mitogen-activated protein kinase (MAPK) signaling pathway, which stimulates cell survival and proliferation.^{4,5} Erlotinib-induced inhibition of EGFR prevents tyrosine kinase phosphorylation and aims to decrease cell proliferation in these tumors.

Erlotinib is indicated as once-daily oral monotherapy for the treatment of advanced-stage non-small cell lung cancer (NSCLCA) and in combination with gemcitabine for treatment of advanced-stage pancreatic cancer.¹ A number of cutaneous side effects have been reported, including acneform eruption, xerosis, paronychia, and pruritus.⁶ Other tyrosine kinase inhibitors, which also decrease signal transduction through the MAPK pathway, have some overlapping side effects; among these are vemurafenib, a selective BRAF inhibitor, and sorafenib, a multikinase inhibitor.^{7,8}

A 70-year-old man with NSCLCA presented with eruptive nevi and darkening of existing nevi 3 months after starting monotherapy with erlotinib. Physical examination demonstrated the simultaneous appearance of scattered acneform papules and pustules; diffuse xerosis; and numerous dark brown to black nevi on the trunk, arms, and legs. Compared to prior clinical photographs taken in our office, darkening of existing medium brown nevi was noted, and new nevi developed in areas where no prior nevi had been visible (Figure 1).

The patient's medical history included 3 invasive melanomas, all of which were diagnosed at least 7 years prior to the initiation of erlotinib and were treated by surgical excision alone. Prior treatment of NSCLCA consisted of a left lower lobectomy followed by docetaxel, carboplatin, pegfilgrastim, dexamethasone, and pemetrexed. A thorough review of all of the patient's medications revealed no associations with changes in nevi.

A review of the patient's treatment timeline revealed that all other chemotherapeutic medications had been discontinued a minimum of 5 weeks before starting erlotinib. A complete cutaneous examination performed in our office after completion of these chemotherapeutic agents and prior to initiation of erlotinib was unremarkable for abnormally dark or eruptive nevi.

Since starting erlotinib treatment, the patient underwent 10 biopsies of clinically suspicious dark nevi performed by a dermatologist in our office. Two of these were diagnosed as melanoma in situ and one as an atypical nevus. A temporal association of the darkening and eruptive nevi with erlotinib treatment was established; however, because erlotinib was essential to his NSCLCA treatment, he continued erlotinib with frequent complete cutaneous examinations.

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A number of cutaneous side effects have been described during treatment with erlotinib, the most common being acneform eruption.⁶ The incidence and severity of acneform eruptions have been positively correlated to survival in patients with NSCLCA.^{3,5,6} Other common side effects include xerosis, paronychia, and pruritus.^{1,5,6} Less common side effects include periungual pyogenic granulomas and hair growth abnormalities.¹

Eruptive nevi previously were reported in a patient who was treated with erlotinib.¹ Other tyrosine kinase inhibitors that also decrease signal transduction through the MAPK pathway, including sorafenib and vemurafenib, have been reported to cause eruptive nevi. There are 7 reports of eruptive nevi with sorafenib and 5 reports with vemurafenib.⁷⁻⁹ Development of nevi were noted within a few months of initiating treatment with these medications.⁷

A PubMed search of articles indexed for MEDLINE using the terms *erlotinib and melanoma* and *erlotinib and nevi* yielded no prior reports of darkening of existing nevi or the development of melanoma during treatment with erlotinib. However, vemurafenib has been reported to cause dysplastic nevi, melanomas, and darkening of existing nevi, in addition to eruptive nevi.⁸⁻¹⁰ The side effects of vemurafenib have been ascribed to a paradoxical upregulation of MAPK in BRAF wild-type cells. This effect has been well documented and demonstrated in vivo.^{8,10} Perhaps erlotinib has a similar potential to paradoxically upregulate the MAPK pathway, thus stimulating cellular proliferation and survival.

Another tyrosine kinase receptor, c-KIT, is found on the cell membrane of melanocytes along with EGFR.^{11,12} The c-KIT receptor also activates the MAPK pathway and

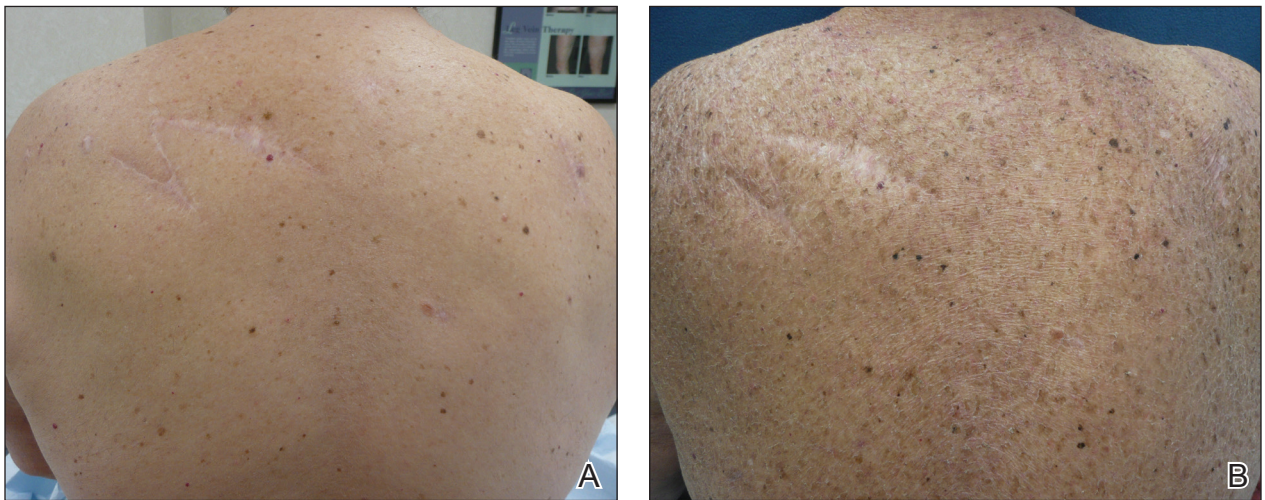


FIGURE 1. A, Clinical photograph of the patient's back before starting treatment with erlotinib. B, After 4 months of treatment, eruptive nevi and darkening of existing nevi were noted in the same area.

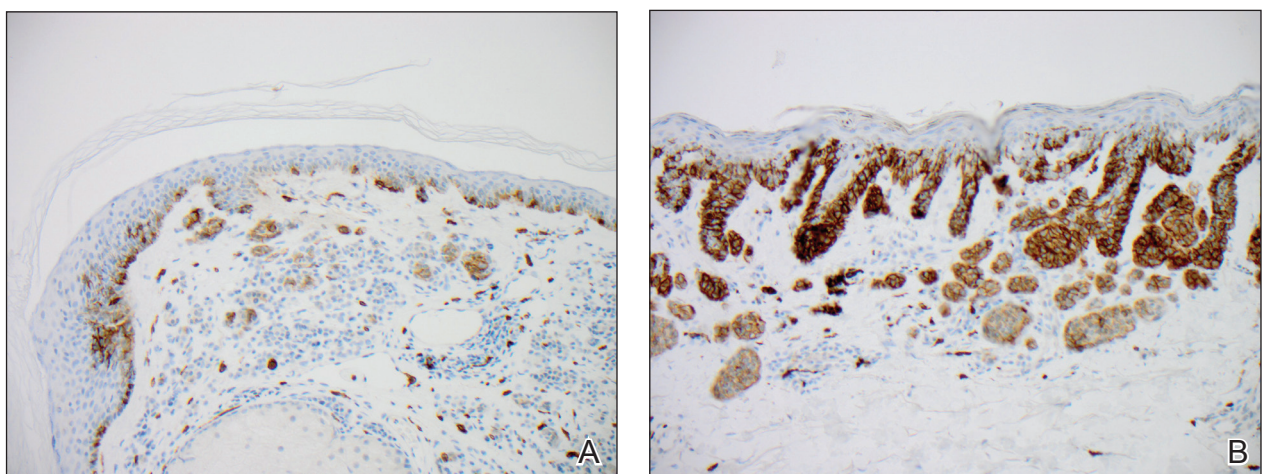


FIGURE 2. A, Melanocytic nevus before treatment with erlotinib demonstrating weak c-KIT immunostaining of the dermal melanocytes (original magnification $\times 200$). B, In a nevus biopsied after 4 months of treatment with erlotinib, c-KIT immunostaining was stronger and most appreciated in the dermal melanocytes (original magnification $\times 200$).

is critical to the development, migration, and survival of melanocytes.^{11,13} Stimulation of the c-KIT tyrosine kinase receptor also can induce melanocyte proliferation and melanogenesis.¹¹ The c-KIT receptor is encoded by the *KIT* gene (KIT proto-oncogene receptor tyrosine kinase). Mutations in this gene are associated with melanocytic disorders. Inherited *KIT* mutation leading to c-KIT receptor deficiency is associated with piebaldism. Acquired activating *KIT* mutations increasing c-KIT expression are associated with acral and mucosal melanomas as well as melanomas in chronically sun-damaged skin.¹³

We hypothesized that erlotinib-induced inhibition of the MAPK pathway could lead to a reactive increase in expression of c-KIT and thus stimulate melanocyte proliferation and pigment production. Similar feedback upregulation of an MAPK pathway stimulating receptor during downstream MAPK inhibition has been demonstrated in colon adenocarcinoma; in this setting, BRAF inhibitors blocking the MAPK pathway leads to upregulation of EGFR.¹⁴ In our patient, c-KIT immunostaining revealed a mild to moderate increase in intensity (ie, the darkness of the staining) in nevi and melanomas during treatment with erlotinib compared to nevi biopsied before erlotinib treatment (Figure 2). The increased intensity of c-KIT immunostaining was further confirmed via semiquantitative digital image analysis. Using this method, a darkened nevus biopsied during treatment with erlotinib demonstrated 43.16% of cells (N=31,451) had very strong c-KIT staining, while a nevus biopsied before treatment with erlotinib demonstrated only 3.32% of cells (N=7507) with very strong c-KIT staining. Increased expression of c-KIT, possibly reactive to downstream inhibition the MAPK pathway from erlotinib, could be implicated in our case of eruptive nevi.

In summary, we report a rare case of darkening of existing nevi and development of melanoma in situ during treatment with erlotinib. The patient's therapeutic timeline and concurrence of other well-documented side effects provided support for erlotinib as the causative agent in our patient. Additional support is provided through reports of other medications affecting the same pathway as erlotinib

causing eruptive nevi, darkening of existing nevi, and melanoma in situ.⁷⁻¹⁰ Through c-KIT immunostaining, we demonstrated that increased expression of c-KIT might be responsible for the changes in nevi in our patient. We, therefore, suggest frequent full-body skin examinations in patients treated with erlotinib to monitor for the possible development of malignant melanomas.

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