Darkening and Eruptive Nevi During Treatment With Erlotinib

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Case Presentation:

Patient: 70 year-old Caucasian male.

History of Present Illness: Our patient developed eruptive nevi and darkening of his existing nevi three months after beginning erlotinib for treatment of non-small cell lung carcinoma. The patient’s prior chemotherapeutic regimen was discontinued five weeks before starting erlotinib. A complete cutaneous exam after completion of these chemotherapeutic agents and prior to initiation of erlotinib was unremarkable for abnormally dark or eruptive nevi. Of note, the patient had not had a melanoma diagnosed since 2006. However, since the start of erlotinib the patient had ten biopsies performed on clinically suspicious dark nevi, two of which were favored to be melanoma in situ and one an atypical nevus.

Medical History/Surgical History: Non-small cell lung cancer (May 2012), invasive melanomas x3, atypical nevi, hypertension, diabetes, diverticulitis, gastroesophageal reflux disease, chronic obstructive pulmonary disease, left lower lobectomy and lung biopsy dissection (July 2012), pacemaker and defibrillator placement, gastric bypass, appendectomy, cholecystectomy.

Medications: Erlotinib (started May 2013), lansoprazole, metformin, aspirin, simvastatin, niacin, nifedipine, bisoprolol, hydrochlorothiazide, furosemide


Physical Examination: Numerous dark brown to black macules on the trunk and bilateral extremities. Scattered papules and pustules with generalized xerosis on the trunk and extremities.

Studies: c-KIT immunostaining revealed a mild to moderate increase in intensity in nevi and melanomas post-darkening compared to similar pre-darkened lesions.

Biopsy: Biopsies revealed atypical melanocytes.

Discussion:

Erlotinib is a small molecule tyrosine kinase inhibitor that functions by blocking the intracellular portion of the epidermal growth factor receptor (EGFR). This blockade prevents tyrosine kinase phosphorylation, melanomas, eruptive nevi, and darkening of existing nevi. Erlotinib is indicated in the treatment of non-small cell lung cancer and advanced stage pancreatic cancer. A number of cutaneous side effects have been reported including an acneiform eruption (63%), xerosis (7.7%), pruritus (3.8%), and paronychia (6%).

Eruptive nevi have been reported in one patient treated with erlotinib, and in seven patients treated with sorafenib, a multikinase inhibitor that also affects the MAPK pathway. Vemurafenib, a selective inhibitor of BRAF in the MAPK pathway, has been reported to produce dysplastic nevi, melanomas, eruptive nevi, and darkening of existing nevi. Changes in nevi were noted within a few months of initiating treatment with these medications. The effects of vemurafenib have been ascribed to a paradoxical up-regulation of MAPK, which has been well documented and demonstrated in vivo. Perhaps erlotinib has a similar potential to paradoxically up-regulate MAPK or other enzymes in the pathway, thus stimulating cellular proliferation and survival.

We did not observe c-KIT, a tyrosine kinase receptor that activates the MAPK pathway and is critical for the development and survival of melanocytes. Stimulation of c-KIT tyrosine kinase can also induce melanocyte proliferation and pigment production/melanogenesis. Activating mutations of c-KIT have been described in some cases of melanoma. In our patient, c-KIT immunostaining revealed a mild to moderate increase in intensity in nevi and melanomas post-darkening compared to similar pre-darkened lesions. Increased expression of c-KIT, possibly reactive to downstream inhibition of the EGFR pathway, provided support for erlotinib as the causative agent in our patient. We therefore suggest that frequent full body cutaneous examinations to monitor for possible melanocytic atypia or development of malignant melanoma.

References: