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Letter

Sorafenib Induced Eruptive Melanocytic Lesions

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Abstract

Sorafenib is a multikinase inhibitor FDA-approved for the treatment of advanced renal cell and hepatocellular carcinoma. Dermatologic side effects include hand-foot skin reaction, facial and scalp erythema and desquamation, splinter subungual hemorrhages, alopecia, pruritus, xerosis, keratoacanthomas, and squamous cell carcinomas. We report sudden eruption of melanocytic nevi diffusely in a patient receiving sorafenib.

Key Words: eruptive nevi, sorafenib, kinase inhibitor, BRAF mutation

Introduction

Sorafenib inhibits multiple kinases, inhibiting the Ras/Raf/MEK pathway. The Ras/Raf/MEK pathway is a signaling cascade that controls cell growth and survival. Activation via growth factors on the cell surface translates to the nucleus ultimately affecting cellular proliferation, apoptosis, differentiation, and transformation. Raf is a serine/threonine kinase that is a downstream effector enzyme of Ras. Raf activates MEK1 and MEK2 kinases, which in turn phosphorylate and activate ERK1 and ERK2 that translocate to the nucleus where they stimulate pathways required for translation initiation and transcription activation leading to proliferation. Raf kinase inhibitors are used in a variety of cancer therapies as an anti-proliferative. [1,2]

Case Presentation

A 62-year-old male presented with the sudden appearance of multiple scattered monomorphic benign-appearing pigmented lesions distributed diffusely over his body without preceding cutaneous inflammation or eruption. These appeared one month after starting sorafenib for metastatic renal cell carcinoma. He had previously been treated with nephrectomy and brachytherapy before discovering metastasis to lung parenchyma. He denied previous personal or family history of skin cancer.

On physical exam, there were multiple scattered monomorphic pigmented macules, small and symmetric, on the scalp, neck, upper trunk, and extremities. (Figures 1-2) After initial examination and clinical determination of benign nevi, the patient was observed closely in clinic at monthly intervals with no change in number or clinical appearance of lesions. Biopsy was deferred and the patient died from his metastatic renal cell cancer 9 months after beginning treatment with sorafenib.



Figures 1 and 2. Multiple new nevi.

Discussion

Sorafenib is a multikinase inhibitor FDA-approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma. Dermatologic side effects include hand-foot skin reaction, facial and scalp erythema and desquamation, splinter subungual hemorrhages, alopecia, pruritus, and xerosis. Solitary, multiple, or eruptive keratoacanthomas and squamous cell carcinomas have also been reported to develop shortly after starting sorafenib [1-3].

Eruptive benign melanocytic lesions occurring with sorafenib have been rarely described in the literature. Five patients were reported with an eruption of 100 to greater than 200 nevi on the trunk and extremities after a mean duration of treatment of 9.2 months [4]. Another case reported onset of palmar/plantar nevi after 2 months of sorafenib; histology confirmed nests of normal melanocytes at the dermal-epidermal junction. The final reported case described onset of truncal, extremity, and palmar/plantar lentigenes after 1 month of sorafenib treatment; histology revealed proliferation of melanocytes at the epidermal basal layer [5].

Sorafenib inhibits multiple kinases including CRAF, wild-type and mutant BRAF, c-KIT, VEGFR-2 (vascular endothelial growth factor receptor), PDGFR- β (platelet derived growth factor receptor), and FLT-3. Inhibition of RAF effectively inhibits the RAF-MEK-ERK signaling pathway. Constitutive activation of this pathway is found in several cancers, promoting cell proliferation and survival. Kong et al suggested that differential inhibition of wild-type versus mutant BRAF by sorafenib may promote the development of nevi and lentigenes. [5]

Changes to nevi in patients on vemurafenib, a more selective inhibitor that targets mutant BRAF, may also help elucidate pathophysiology. Patients on vemurafenib have been reported to develop both new dysplastic nevi and new primary melanomas that are wild type BRAF[6,7,8]. It is hypothesized that inhibition of mutant BRAF by vemurafenib may cause compensatory upregulation of upstream and downstream effectors and paradoxically activate cellular proliferation.

Further studies exploring the effects of targeted molecular inhibitors such as sorafenib may yield new insights into the biology of nevi.

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