DOI: 10.7860/JCDR/2014/8055.5160

Case Report

Oncology Section

# Diffuse Hypopigmentation Followed by Hyperpigmentation in an African American Woman with Hemangiopericytoma Treated with Dasatinib

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## ABSTRACT

Dasatinib is a second-generation multi-target tyrosine kinase inhibitor (TKI) that has activity against many imatinib-resistant BCR-ABL mutant forms, Src, and c-Kit tyrosine kinases. While skin hypopigmentation is a well recognized adverse effect of first generation TKIs; it has rarely been reported with dasatinib. We report a unique case of diffuse cutaneous hypopigmentation induced by dasatinib followed by hyperpigmentation occurring in the same patient. A 52-year-old African American female with a history of metastatic hemangiopericytoma was initiated on dasatinib as part of a clinical trial. After 2 months of treatment, she developed generalized skin hypopigmentation. Within 1 month of discontinuing the drug, the patient's skin pigmentation returned to normal. However, she then developed diffuse skin hyperpigmentation over the next couple of months. The hyperpigmentation was self-limited, and eventually resolved after several months.

**Keywords:** Sarcoma, Skin pigmentation, Tyrosine kinase inhibitor (TKI)

## CASE REPORT

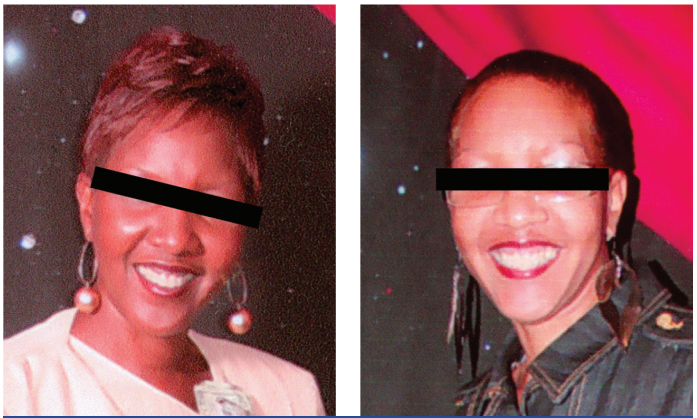
The patient is a 52-year-old African American female with a history of hemangiopericytoma, an uncommon histologic subtype of soft tissue sarcoma, originating in the left flank status post multiple resections of local recurrences. Because of progressive metastatic disease to bone, lung, and body wall, 10-years after the initial diagnosis, she was initiated on dasatinib, a second-generation tyrosine kinase inhibitor (TKI), as part of a Sarcoma Alliance for Research through Collaboration (SARC) clinical trial. She was treated with dasatinib at a dose of 70mg twice daily per clinical trial protocol. She tolerated therapy well with only minimal side effects initially including mild fatigue, periorbital oedema, and mild anaemia. After approximately 2-months of treatment with oral dasatinib, she began to notice diffuse lightening of her skin. This hypopigmentation was generalized over the entirety of her skin, but was most noticeable centrally over her chest, abdomen, and thighs. She denied any rashes or other skin changes, and also denied any changes in hair, nail, or mucous membranes. Physical examination was notable for global hypopigmentation of the skin, most prominent over central areas rather than peripherally, except for two 1-2 cm hypopigmented patches over the right lower shin. Hair depigmentation was not present. The patient denied any family history of vitiligo, and denied the use of any topical medications or bleaching agents. The hypopigmentation progressed slowly over the next several months, most noticeably at her fingertips and nailbeds, as well as over her scapulas posteriorly. This caused the patient significant psychosocial distress as family and friends began to notice the changes in her pigmentation. The patient is shown before initiating treatment with dasatinib [Table/Fig-1] and after completing 9 months of treatment [Table/Fig-2].

After approximately 12 months of treatment, the patient was removed from clinical trial and dasatinib was discontinued due to disease progression. Within 4-6 weeks of discontinuing treatment, the skin hypopigmentation began to resolve and the patient reported improvement in her skin color back to normal. However over the next couple of months, off of any systemic anti-cancer therapy, her skin tone continued to darken beyond her baseline, and the patient then experienced diffuse skin hyperpigmentation. The hyperpigmentation persisted for several months but eventually dissipated, and the patient's skin pigmentation returned to baseline once again. Unfortunately, during this time period, the patient's disease progressed in her spine causing cord compression with resultant paraplegia. The patient continues to follow up with her medical team, and is looking forward to physical rehabilitation in hopes of regaining some lower extremity function.

## DISCUSSION

Tyrosine kinase inhibitors (TKIs) are used in the treatment of various hematologic malignancies as well as solid organ tumors including soft tissue sarcomas. Imatinib was the first TKI approved for treatment of a malignancy in 2001, and its mechanism of action and toxicities have been well characterized. Dasatinib is one of multiple second generation TKIs, which has activity against many imatinib-resistant BCR-ABL mutant forms, as well as Src, c-Kit, and platelet derived growth factor receptor β (PDGFR-β) tyrosine kinases [1]. Currently, dasatinib is approved for treatment of chronic myelogenous leukemia, but is actively being investigated for other malignancies such as sarcoma.

Several dermatologic toxicities have been associated with first generation TKIs such as imatinib including urticaria, lichenoid reaction, psoriasis, and Stevens-Johnson syndrome [2]. Notably,



**[Table/Fig-1]:** Baseline pigmentation before treatment with dasatinib
**[Table/Fig-2]:** Hypopigmentation after 9 months of dasatinib

hypopigmentation has been frequently reported, affecting up to 41 percent of treated patients [3]. Conversely, very few cutaneous side effects have been reported with dasatinib, the most common being non-specific maculopapular rashes and skin exfoliation and irritation [2]. A few cases of dasatinib-induced hair depigmentation have been reported [4,5]. However, skin pigment changes associated with dasatinib have only been reported once in a pediatric leukemic patient who developed vitiligo-like lesions [5]. The case described here is noteworthy, as this is the first description of dasatinib-induced diffuse skin hypo- and hyperpigmentation occurring in the same patient, and emphasizes the role of the c-Kit pathway in melanocyte biology.

The proto-oncogene c-Kit is a gene encoding a class III tyrosine kinase receptor, while stem cell factor (SCF) is the ligand for c-Kit. The interaction between c-Kit and SCF plays an important role in the development of hematopoietic stem cells, germ cells, mast cells and melanocytes [6]. In particular, SCF exerts permanent survival, proliferation and migration functions in c-Kit receptor-expressing melanocytes, thereby playing a critical role in the development of melanocytes from their precursors in the embryonic neural crest cells during embryogenesis and maintenance of the melanocyte lineage in adult skin [6]. Inhibition of c-Kit is thought to be responsible for hypopigmentation in patients receiving TKIs. Indeed, mutations in the c-Kit gene are associated with skin and hair hypopigmentation syndromes, such as piebaldism, an autosomal dominant disorder of melanocyte development characterized by white hair and congenital amelanotic patches on the forehead, torso, and extremities [7]. In addition, several invitro and invivo studies also support the significance of c-Kit and its downstream pathway in normal integument pigmentation. For example, invitro, the first generation TKI imatinib significantly decreases the number of cells with high tyrosine kinase activity in both vitiligo and normal melanocytes, thereby inhibiting melanogenesis [8].

As mentioned above, various pigmentary abnormalities have been associated with imatinib. Reversible, dose-related hypopigmentation is a well-recognized adverse effect. In one series, 41 percent of patients treated with imatinib developed localized or generalized hypopigmentation, at a median of four weeks after initiating treatment [3]. Paradoxical accelerated re-pigmentation and hyperpigmentation have also been described. In one prospective series, skin hyperpigmentation occurred in 3.6 percent of ethnically pigmented patients treated with imatinib [3]. The mechanism of paradoxical hyperpigmentation is unclear; however, the variable response to imatinib may depend upon specific c-Kit mutation type or interactions with other tyrosine kinase receptors, possibly resulting in increased melanin synthesis [9].

The overlap of target receptors between imatinib and dasatinib likely explains the pigmentary changes seen with dasatinib in this patient. As most cases of TKI-induced hypopigmentation appear to be reversible and dose-related, the return to the patient's baseline skin pigmentation is not surprising; however, the subsequent hyperpigmentation seen in this patient is difficult to explain. One can propose a role for drug-related immune dysregulation, with cytotoxic responses to epidermal cells leading to melanin pigment incontinence and clinically persistent hyperpigmentation [9]. Also, as TKIs appear to interfere with molecular mechanisms involved in response to ultraviolet stress, chronic inhibition of c-Kit may impair the protective cutaneous response to ultraviolet light, which may lead to hyperpigmentation of sun-exposed areas [10].

## CONCLUSION

With tyrosine kinase inhibitors being increasingly used for the treatment of various malignancies, it is important for physicians to become familiar with the adverse effects of these chemotherapeutic agents. Tyrosine kinase inhibition through blockade of the c-Kit/SCF signal transduction pathway likely plays a key role in dasatinib-induced cutaneous pigmentary changes. The paradoxical ability of TKIs such as imatinib and dasatinib to result in both hypo- and/or hyperpigmentation, especially in the same patient, remains unclear. Further research is needed to elucidate potential mechanisms responsible for cutaneous pigmentary changes and the interference caused by TKIs, and may greatly contribute to understanding and potentially treating a variety of pigmentation disorders.

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**FINANCIAL OR OTHER COMPETING INTERESTS:** None.

Date of Submission: **Nov 17, 2013**
Date of Peer Review: **Jan 28, 2014**
Date of Acceptance: **Apr 09, 2014**
Date of Publishing: **Nov 20, 2014**