Imatinib-Mesylate-Induced Pigment Dilution Effect in a Patient Treated for Dermatofibrosarcoma Protuberans: Case report and Literature Review

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Background

- Dermatofibrosarcoma protuberans (DFSP) is a malignant fibrous tumor with low metastatic potential but is infiltrative with a high rate of local recurrence[1,2].
- The goal of treatment is complete surgical resection with negative histologic margins.
- Resection with negative margins may not always be possible for cases in cosmetically sensitive areas or with risk for functional impairment, or due to tumor extension, size, and metastasis.
- In these cases, radiation and chemotherapy have been used.
- More than 90% of dermatofibrosarcomas have a t(17;22)(q22;q13) translocation, leading to the fusion of collagen type 1 alpha 1 and platelet-derived growth factor (PDGF) subunit β genes[2,3].
- The fusion protein results in continuous activation of the receptor PDGF receptor β tyrosine kinase, promoting tumor growth[1].
- Tyrosine kinase inhibitors, such as imatinib mesylate, are systemic therapies that are effective against DFSP with the t(17;22) translocation.

Case Report

- A 42-year-old female presented with an evolving hyperpigmented nodule on the left temple.
- Biopsy and imaging revealed an 8cm by 8cm by 1cm locally advanced pigmented DFSP.
- The lesion was deemed unresectable due to size and location, and she was started on 400 milligrams (mg) imatinib mesylate daily, which was effective in reducing lesion thickness (Figure 1).
- In follow up, the patient noted a generalized decrease in skin pigmentation, suggesting an imatinib-induced pigment dilution effect.

Figure 1. Dermatofibrosarcoma protuberans in a 40-year-old female
(A) 8cm by 8cm by 1cm locally advanced pigmented dermatofibrosarcoma protuberans on the left temple prior to treatment with imatinib mesylate. (B) Flattened lesion following 3 months of treatment with imatinib mesylate.

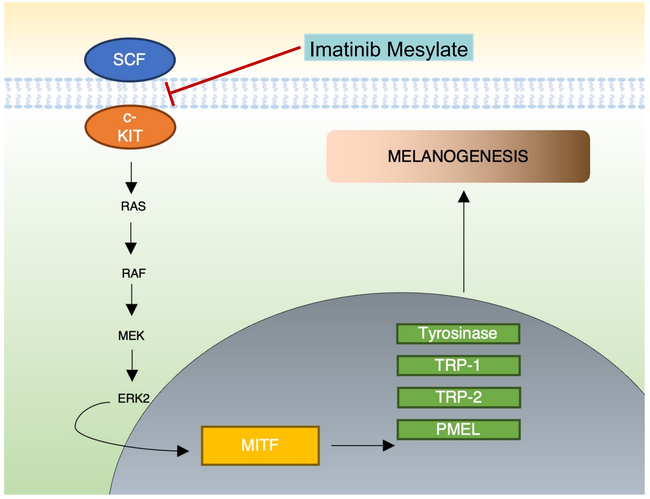

Figure 2. SCF/c-KIT signalling leads to melanogenesis
The binding of stem cell factor (SCF) to tyrosine protein kinase kit (c-KIT) initiates mitogen-activated protein kinase (MAPK) cascades. This leads to MITF expression and activation, inducing the expression of various proteins (Tyrosinase, tyrosinase-related protein 1 (TRP-1), tyrosinase-related protein 2 (TRP-2), and premelanosome protein (PMEL)) which are involved in melanogenesis and melanin synthesis. Imatinib inhibits SCF stimulated c-KIT activation, which has downstream effects on melanogenesis[15-19].

Discussion and Literature Review

- Depigmentation is a side effect of imatinib and has been well documented in patients treated for chronic myeloid leukemia, and the effects are thought to be dose-dependent and reversible[4-6].
- This depigmentation is often gradual and can be generalized or local, causing vitiligo-like lesions, and may also exacerbate preexisting pigmentary disorders[4-6].
- Other cases of imatinib-induced depigmentation following treatment for DFSP have been documented (Table 1)[7,8].

Demographics	Dosage	Depigmentation Effect	Reference
46-year-old Caucasian male	400 mg once daily	Depigmentation surrounding multiple nevi (halo nevi)	Fava et. al., 2010[7]
44-year-old Fitzpatrick V male	400 mg once daily	Graying of the hair	Balagula et. al., 2014[8]
40-year-old Fitzpatrick IV female	400 mg once daily	Generalized depigmentation of the skin	Present case

Table 1. Cases of depigmentation effect following treatment of DFSP with imatinib mesylate

- Imatinib inhibits many different tyrosine kinases including PDGF, BCR-ABL, and c-KIT[9,10].
- C-KIT is involved in melanogenesis and melanocyte homeostasis, and mutations in the c-KIT gene are associated with vitiligo and piebaldism[9-14].
- C-KIT initiates mitogen-activated protein kinase (MAPK) cascades, leading to microphthalmia-associated transcription factor (MITF) activation, and expression of melanogenesis-related proteins such as tyrosinase (Figure 2) [15-17].
- The mechanism for imatinib-induced pigment dilution has been studied in vitro.
- In one in vitro study, imatinib inhibited stem cell factor (SCF)-stimulated c-KIT activation and melanocyte proliferation[18].
- Melanogenesis was suppressed in a dose-dependent manner due to suppressed expression of tyrosinase and MITF[18].
- In a second in vitro study, imatinib significantly reduced the number of melanocytes with high tyrosinase activity[18].
- Patients using imatinib should be warned of the risk of depigmentation and the theoretical increased risk of skin cancer or burns from using this medication[15]. Patients should additionally be encouraged to use sun protection, especially while taking the medication.

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