Disappearing pigmentary mosaicism during imatinib treatment for gastrointestinal stromal tumors

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INTRODUCTION

Imatinib is a first-generation tyrosine kinase inhibitor of *bcr-abl*, *PDGF* receptor, and c-*kit*, approved for the treatment of chronic myelogenous leukemia and other malignancies such as metastatic or unresectable gastrointestinal stromal tumors (GISTs).[1] Several dermatologic adverse events have been associated with its use including maculopapular eruptions, periorbital edema, lichenoid dermatitis, and pigmentary alteration.[1] We report a case of disappearing pigmentary mosaicism in the form of segmental speckled lentiginous nevi during imatinib therapy for GISTs.

Abbreviation used:

GIST: gastrointestinal stromal tumor

CASE REPORT

A man in his 20s with multifocal small bowel GISTs was referred to the dermatology department for evaluation of hyperpigmentation that developed shortly after birth. On examination, he had tan patches speckled with brown macules on the bilateral arms and legs, shoulders, chest and back (Fig 1, *A* and *B*) consistent with segmental speckled lentiginous nevi. His GISTs harbored a *c-kit* mutation in exon 11 (KIT L576P), which is associated with clinical response to imatinib therapy, which was started at 400 mg/d. Six months later, he noted progressive fading of his pigmented lesions.

He returned to the dermatology clinic with diffuse pigmentary dilution and disappearing speckled lentiginous nevi (Fig 1, *C* and *D*), which was highlighted under Wood's lamp examination. A biopsy was obtained of residual pigmentation and found pigment incontinence with melanophages in the papillary dermis (Fig 2, *A* and *B*). Genetic evaluation of blood leukocytes was negative for germline mutations in *c-kit* or other genes linked to familial GIST syndrome (*KIT, NF1, PDGFRA, SDHA, SDHB, SDHC, SDHD*). Direct sequencing of melanocyte DNA from skin biopsy using laser capture and melanocyte culture was negative for the *c-kit* L576P mutation. The patient remained on imatinib without adverse events and with interval decrease in the size of GISTs on serial imaging.

DISCUSSION

Imatinib is associated with pigmentary alteration with hypopigmentation and depigmentation occurring more frequently than hyperpigmentation (41% vs 3.6% of patients).[2] In addition, vitiligo exacerbation and fading of lentigines has been previously described.[3] Interestingly, we report a case of disappearing pigmentary mosaicism associated with its use.

Our patient's speckled lentiginous nevi may be a manifestation of aberrant *c-kit* expression resulting in both GISTs and hyperpigmentation. Prior reports of familial GISTs have demonstrated a link with cutaneous hyperpigmentation.[4] This association may be explained by constitutive activity of c-*kit*,

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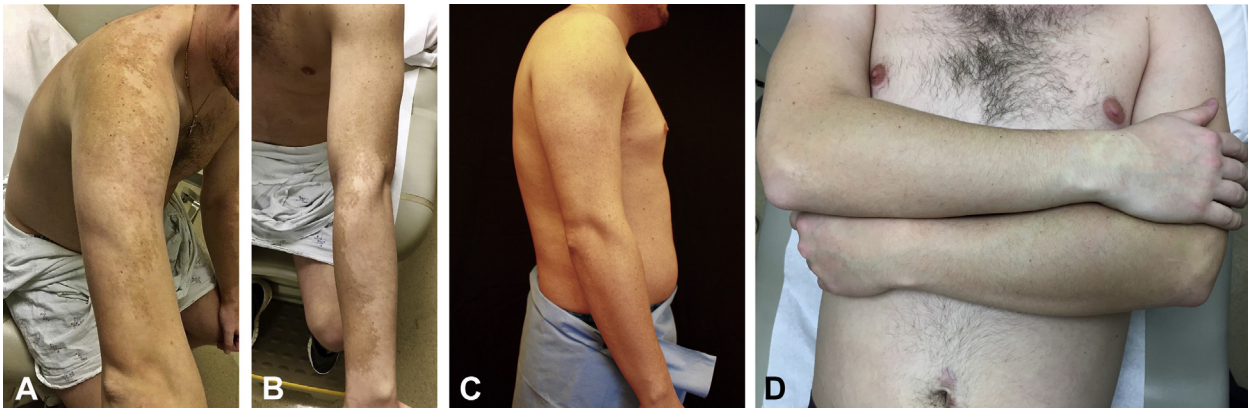

Fig 1. Clinical appearance of pigmentary mosaicism before and during imatinib therapy. **A** and **B**, The patient had tan patches with speckled macules in a segmental distribution on the bilateral arms and legs, shoulders, chest, and back shortly after birth. **C** and **D**, Disappearing pigmentary mosaicism with diffuse pigmentary dilution developed 6 months after initiation of imatinib.

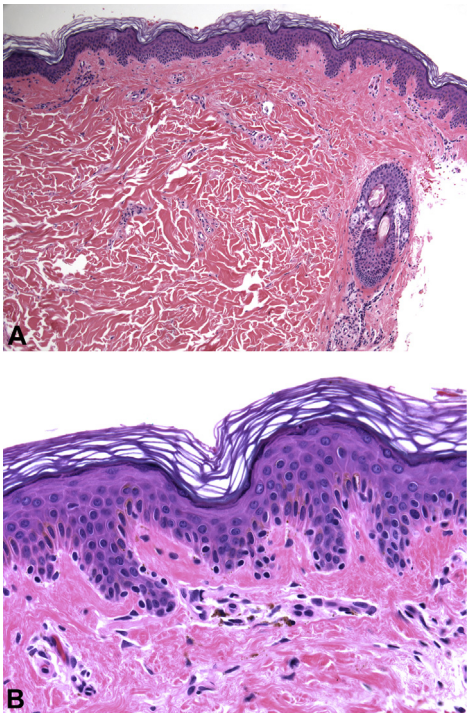

Fig 2. Histopathologic findings. **A** and **B**, Skin biopsy within an area of fading pigmentation found pigment incontinence with melanophages in the papillary dermis. (Hematoxylin-eosin stain; original magnifications: **A**, ×10; **B**, ×40.)

which promotes the development, migration, and survival of melanocytes, as well as interstitial cells of Cajal from which GISTs originate.[4] Interestingly, mosaicism for the gene encoding the KIT ligand, SCF, resulting in increased epidermal *c-kit* expression, has been identified in a case of linear and whorled nevoid hypermelanosis, which manifests with hyperpigmentation along Blaschko lines.[5]

In our case, the constellation of multiple GISTs in association with hyperpigmentation in a young patient suggested a familial GIST syndrome. However, genetic analysis failed to detect a germline mutation in *c-kit* or other genes linked to familial GISTs. Thus, mosaicism was favored and supported by the segmental distribution of pigmented lesions. It is possible that genetic sequencing of melanocytes before imatinib treatment may have detected the same *c-kit* mutation found in our patient's GISTs, or perhaps these melanocytes harbor another *c-kit* mutation.

The exact pathomechanism of imatinib-induced pigmentary changes remains unknown but may be speculated based on other disorders that harbor *c-kit* mutations.[6] In piebaldism, *c-kit* expression is increased in hyperpigmented skin but absent in hypopigmented areas.[6] In imatinib-treated skin, in vitro studies have found decreased melanocytes with high tyrosinase activity and reduction of melanocyte proliferation in fibroblasts.[7]

This case suggests that the *c-kit*-SCF pathway may play an important role in the development of pigmentary mosaicism in the context of GISTs. Further genetic studies are required to investigate this and the pathogenesis of imatinib-associated pigmentary alterations.

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