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Case Report

Melasma-like facial hyperpigmentation associated with long-term dasatinib therapy in Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia: a rare cutaneous adverse event

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ABSTRACT

Tyrosine kinase inhibitors (TKIs) have significantly improved survival in Philadelphia chromosome-positive leukemias, including chronic myeloid leukemia (CML) and Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Dasatinib, a second-generation TKI, is frequently used in Ph+ ALL due to its potent BCR-ABL inhibition and ability to cross the blood-brain barrier. While common adverse effects of dasatinib include cytopenias and fluid retention, cutaneous side effects are rare, particularly pigmentary changes, and among these, melasma-like hyperpigmentation has seldom been reported. We report the case of a 29-year-old woman diagnosed with high-risk Ph+ B-cell ALL with baseline CNS-III involvement, who was treated with the augmented BFM 2009 protocol along with dasatinib (100 mg once daily). After achieving complete molecular remission and transitioning to maintenance therapy, the patient developed progressive, asymptomatic, brown-gray hyperpigmented macules and patches over the malar areas, forehead, nasal bridge, and upper lip consistent with a centrofacial melasma-like pattern. No history of sun exposure, hormonal therapy, cosmetic products, or systemic illness was identified. A dermatologic evaluation attributed the lesions to dasatinib-induced hyperpigmentation, and the patient was treated with topical fluticasone and 2% hydroquinone, along with strict photoprotection. Cutaneous pigmentary changes induced by TKIs are typically hypopigmentary and most commonly associated with imatinib, whereas hyperpigmentation, especially with melasma-like features, remains a rare adverse effect of dasatinib; the pathogenesis is believed to involve inhibition of the c-KIT/stem cell factor signaling pathway, which is vital for melanocyte function. In this patient, the delayed onset of pigmentation nearly four years after dasatinib initiation highlights the unpredictable nature of TKI-induced skin changes, and given the importance of dasatinib in disease control, continuation of therapy with symptomatic dermatologic management was deemed appropriate. This case underscores the importance of recognizing rare dermatologic adverse effects of TKIs, such as melasma-like hyperpigmentation associated with dasatinib; early identification and management are essential to prevent cosmetic distress and ensure treatment adherence, and further research is needed to elucidate the mechanisms underlying such pigmentary changes and to guide optimal management strategies.

Keywords: Dasatinib, Skin rash, Philadelphia chromosome, Toxicity

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of Philadelphia chromosome-positive leukemias, significantly improving survival outcomes in both chronic myeloid leukemia (CML) and Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL).[1] Dasatinib, a second-generation TKI, occupies a particularly important niche in Ph+ ALL. Beyond its

potent inhibition of BCR-ABL, its capacity to cross the blood-brain barrier makes it the preferred agent in patients with, or at risk for, central nervous system involvement.[2]

While dasatinib is generally well tolerated, it is associated with a spectrum of adverse effects, most commonly hematologic, gastrointestinal, and fluid retention-related.[3] Cutaneous adverse effects, though less frequently reported, are increasingly recognized and can range from non-specific maculopapular rashes to more unusual presentations such as drug-induced pigmentation and melasma-like lesions.[4] These pigmentary changes, although benign, can pose significant cosmetic and psychological distress, especially in young patients, and may affect adherence to long-term therapy.

Noncutaneous adverse effects of dasatinib are well documented with cytopenias and fluid retention being the most common, but pigmentary abnormalities have been reported only rarely. Pigmentary alterations with TKIs are mechanistically linked to c-KIT inhibition, since the c-KIT/stem cell factor axis is essential to melanocyte proliferation, migration, and survival. Disruption of this pathway most often manifests as hypopigmentation, but paradoxical hyperpigmentation including melasma-like patterns has been described sporadically, predominantly with imatinib and, less often, dasatinib.[4] Here, we report a rare case of facial melasma-like hyperpigmentation in a young woman with Ph+ B-cell ALL, developing after prolonged dasatinib therapy during the maintenance phase. This case highlights the importance of recognizing and managing cutaneous adverse effects of TKIs to ensure continued adherence and patient quality of life.

CASE REPORT

We present the case of a 29-year-old lady, follow-up case of Philadelphia chromosome-positive (Ph+) B-cell ALL, high risk, who developed new-onset hyperpigmentation over face.

The patient was initially diagnosed in August 2021 with Ph+ B-cell ALL, with baseline CNS-III involvement. She was started on the augmented BFM 2009 protocol in combination with a tyrosine kinase inhibitor (dasatinib). She achieved measurable residual disease (MRD) negativity by flow cytometry at the end of induction and was MRD-negative by PCR at the end of early intensification She was continued on therapy as per the BFM protocol. During the course of treatment, she was admitted twice for pneumonia, managed appropriately and therapy was continued. The patient was started on maintenance phase along with dasatinib at a dose of 100 mg once daily in November 2022, and remained in regular follow-up.

Approximately two months prior to presentation she noticed new onset dark patchy lesions over face involving cheeks and forehead which progressively darkened over time. There was no associated itching, burning, or scaling. Although asymptomatic, the pigmentation was of significant cosmetic concern to the patient. There was no prior history of melasma, facial pigmentation, or similar lesions in the past. The patient denied photosensitivity, excessive sun exposure or change in skincare products or medications. There was no history of hormonal therapy or oral contraceptive use. Cutaneous examination revealed multiple, symmetrical, hyperpigmented macules and patches over the malar prominences, forehead, nasal bridge, and upper lip, consistent with a centrofacial distribution. The pigmentation appeared brown to gray-brown in color, with irregular borders. These lesions were flat, non-scaly, and non-tender. There was no associated erythema, edema, or scaling

No pigmented lesions were noted on the limbs, trunk, or other areas. There were no signs of photosensitivity, pruritus, or lichenification. Rest of the systemic examination was normal.

Clinical photograph of the patient in Figure 1 showing symmetrical, brown hyperpigmented macules and patches distributed over the malar prominences, forehead, nasal bridge, and upper lip-consistent with a centrofacial melasma-like pattern.

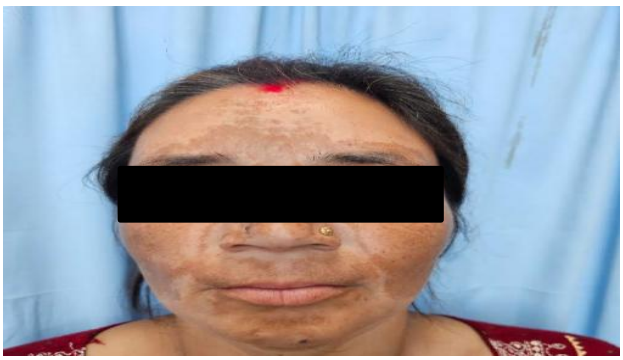

Figure 1: Clinical photograph of the patient.

Management

After consultation with dermatology team, the pigmentation was considered to be consistent with dasitinib-induced melasma-like hyperpigmentation. The patient was started on topical fluticasone cream and advised to use broad-spectrum sunscreen daily. She was counselled regarding the benign nature of the condition and the importance of sun protection, and was scheduled for regular outpatient follow-up. Topical 2% hydroquinone cream was started, advised to use sunscreen and follow up in OPD after counselling the patient.

DISCUSSION

TKIs, particularly dasatinib, are now central in the management of Ph+ ALL, offering significant improvement in survival and disease control.[5] Dasatinib's ability to cross the blood-brain barrier and its activity

against BCR-ABL, c-Kit, and Src family kinases distinguish it from first-generation TKIs, expanding its clinical applications to cases with CNS involvement.[6]

Adverse effects such as cytopenias, pleural effusionare well-documented in the literature.[7] In contrast, cutaneous side effects are rare and underreported, with pigmentary changes being particularly uncommon. In addition to targeting BCR-ABL, dasatinib inhibits several other tyrosine kinases, including SRC family kinases, c-KIT, platelet-derived growth factor receptors (PDGFR), and ephrin-A receptor kinases.[8] Among these, the proto-oncogene c-KIT and its ligand, stem cell factor (SCF), play a vital role in the proliferation, migration, and survival of melanocytes.[9] Interference in this pathway disrupts normal melanogenesis and commonly leads to hypopigmentation. However, paradoxical pigmentary effects, including hyperpigmentation after hypopigmentation or de novo, have been described.[10] Inhibition of the c-KIT/SCF signaling pathway is believed to contribute to the pigmentary alterations seen in patients receiving tyrosine kinase inhibitors, most commonly seen with imatinib. Maculopapular eruptions and nonspecific rashes are more typical, whereas pigmentary changes are much rarer, with hypopigmentation being most common.[4]

Hyperpigmentation, especially with a melasma-like morphology, remains exceedingly unusual and has only been described in isolated patient reports, making this case significant.[11] A 2024 case series further suggested that at least some TKI-associated hyperpigmentation may not be purely a melanocyte-intrinsic phenomenon at all, but rather secondary to a lichenoid drug eruption with pigment incontinence histologically and clinically overlapping with lichen planus pigmentosus rather than representing pure melanogenic dysregulation.[12] This raises the possibility that "hyperpigmentation" in this drug class is mechanistically heterogeneous rather than a single entity. In our patient, the temporal association between prolonged dasatinib use and the gradual onset of centrofacial hyperpigmentation in the absence of other causative factors such as hormonal therapy, sun exposure, or other medications supports a drug-induced etiology.

The onset of pigmentary adverse effects associated with TKI therapy typically occurs within the first two months of treatment initiation, as reported in several studies.[13] However, the timeline can be variable. Webb et al. described a case of dasatinib-induced facial depigmentation that developed almost three years after the start of therapy.[10] In contrast, our patient developed melasma-like hyperpigmentation approximately 3 years 9 months after initiation of dasatinib. This variation suggests that pigmentary changes may not follow a strict temporal pattern and can arise even with prolonged use. Moreover, pigmentary effects associated with TKIs are thought to be dose-dependent and, in many cases, reversible upon dose reduction or discontinuation of therapy. However, in scenarios where the drug plays a critical role in disease control as in our patient, continuation with symptomatic management may be the most appropriate strategy.[14]

Management typically includes patient reassurance, the use of topical therapies such as depigmenting agents and broad spectrum sunscreen.[15] A recent narrative review of TKI-associated pigmentary change reinforces this conservative approach as standard across the drug class, while noting that the underlying mechanisms remain incompletely defined.[16] In most cases, these measures lead to stabilization or gradual improvement of the lesions. In rare instances where pigmentation is severe, persistent, or accompanied by other drug-related toxicities, dose reduction or discontinuation of the TKI may be considered.[17] However, such decisions must be made cautiously, carefully weighing the dermatologic benefits against the potential impact on oncologic outcomes.

This case reinforces two points we think are under-emphasized in the existing literature. First, that TKI-associated pigmentary change can present with a substantially longer latency than the "early toxicity" framing common in prior reports; and second, that the underlying mechanism may not be uniform across cases, with at least some instances better explained by a lichenoid pigment-incontinence process than by direct melanocyte c-KIT inhibition.[12]

This case further underscores the continuing need to recognize and document rare adverse effects of novel TKI, It also supports the emerging view that TKI-induced skin pigmentary changes may be under-recognized, and that their underlying mechanisms, particularly factors predisposing to hyperpigmentation require further research. The phenomenon of dasatinib-induced hyperpigmentation in patients with Ph+ ALL is rare and early recognition is crucial for counselling and supportive care, reinforcing the importance of a multidisciplinary approach to optimize both treatment outcomes and patient quality of life.

CONCLUSION

This case highlights a rare but important dermatologic adverse effect of prolonged dasatinib therapy; melasma-like facial hyperpigmentation in a young woman with Ph+ B-cell ALL. While dasatinib is indispensable in the treatment of Philadelphia chromosome-positive leukemias, particularly those with CNS involvement, clinicians should be aware of its potential to cause pigmentary skin changes, which may be cosmetically distressing and impact adherence. Recognition of such cutaneous manifestations is crucial for timely dermatologic evaluation, patient counseling, and supportive management. As pigmentary changes can occur late and unpredictably, ongoing monitoring is warranted throughout the course of TKI therapy. This report adds to the limited literature on dasatinib-induced hyperpigmentation and underscores the need for further research into its pathophysiology, incidence, and optimal management strategies.

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