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Supercilliary madarosis in an Indian male with Chronic Myelogenous Leukemia Treated with Dasatinib - A case report

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ABSTRACT

Dasatinib, a second generation multi-target tyrosine kinase inhibitor (TKI) is active 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 rare case of diffuse cutaneous hypopigmentation and bilateral supercilliary madarosis induced by dasatinib. A 51 year-old Indian male with no co-morbidities and with history of chronic myelogenous leukaemia with complex variant of Philadelphia translocation and E 225 V mutation in P loop domain of bcr-abl transcript who was initiated on imatinib followed by dasatinib as a part of treatment. After 5 months of treatment with dasatinib, he developed supercilliary madarosis bilaterally. Cutaneous side effects may adversely affect patient's quality of life and, therefore, require prompt attention to prevent long-term complications or suboptimal outcomes due to poor compliance.

Keywords: *Chronic Myelogenous Leukaemia, Dasatinib, Supercilliary madarosis*

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 tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib to result in both hypo- and/or hyper pigmentation, especially in same patient, remains unclear. In comparison with the previous standards of care, TKI benefits include more rapid response rate, increased survival, and fewer side effects. The improved long-term outcomes have altered the approach to CML management from a progressive fatal disease with a poor prognosis to a chronic condition.

Prolonged survival increases the need for patient education, support, monitoring, and assistance. Further research is needed to elucidate potential genetic 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 including melanomas. Moreover, the incidence of many cutaneous reactions appears to be related to the cumulative dosage, which further supports a specific pharmacological effect of the drug rather than immunologic or allergic mechanisms. Many of these specific cutaneous toxicities may be regarded as potential indicators of responsiveness to therapy, or even direct markers of treatment outcome, because they indicate biological activity. Cutaneous side effects may adversely affect patients' quality of life and, therefore, require prompt attention to prevent long-term complications or suboptimal outcomes due to poor

compliance. Anecdotal case reports together with profound clinical trials can optimize regular monitoring and management of treatment-related side effects providing better therapy adherence and outcome.

CASE REPORT

A 51 year old male patient, known case of chronic myelogenous leukaemia on treatment with dasatinib, non smoker, non alcoholic and vegetarian by diet was referred to our department. Patient has developed bilateral supercilliary madarosis (**Fig. 1**) for the past 18 months. On examination, the patient was conscious, well oriented, well built with stable vitals. There was no pallor, icterus, cyanosis, clubbing, pedal oedema or lymphadenopathy. Supercialliary madarosis was evident bilaterally. His systemic examination was unremarkable. Patient is on Dasatinib 70mg OD and regular follow-up.

He was apparently well 10 years ago when he developed dry cough and breathlessness, both of which started 15 days prior to the first hospital visit. Cough was non-productive, with no associated fever, haemoptysis or cervical lymphadenopathy. There were no associated diurnal or postural variations. Breathlessness was modified Medical Research Council dyspnoea scale grade II. Both the cough and breathlessness were increased on exertion and were partly relieved on medication.

Figure 1 - Front, right and left lateral profile of patient showing supercilliary madarosis

His routine blood investigations on May, 2005 revealed haemoglobin - 12.5gm/dl, TLC – 188,400/mm^3, DLC - N_{38} $L_2E_2M_0B_2$ with myeloblasts (1%), promyelocytes (3%), myelocytes (15%), metamyelocytes (17%) and band forms (20%). Blood picture revealed normocytic normochromic RBCs with 56% immature cells of myeloid series. Bone marrow aspiration showed increased megakaryocytes, myeloid hyperplasia with predominance of segmented cells, eosinophils and basophils with blasts <5%, thereby diagnosing the patient as a case of CML. Quantitative bcr-abl translocation assay revealed transcript ratio of 91%.

In May 2005, patient was started on tablet imatinib mesylate 400 mg OD. On repeat fluorescence in situ hybridization (FISH) assay, done three months after initiation on imatinib monotherapy, transcript ratio was 0.53%. The transcript ratio on Quantitative bcr abl translocation assay ranged between 0-1% between September 2005 and November 2012. FISH for bcr-abl was positive on two occasions; it was 56% in September 2006 (**Fig. 2**) and 11% in august 2007.

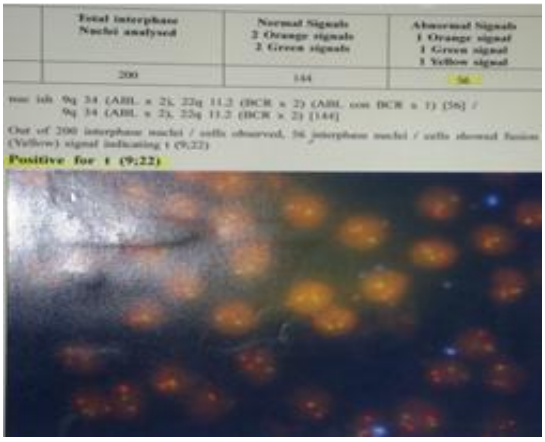

Figure 2 - FISH analysis showing 56 fusion signals Philadelphia Signifying t (9;22)

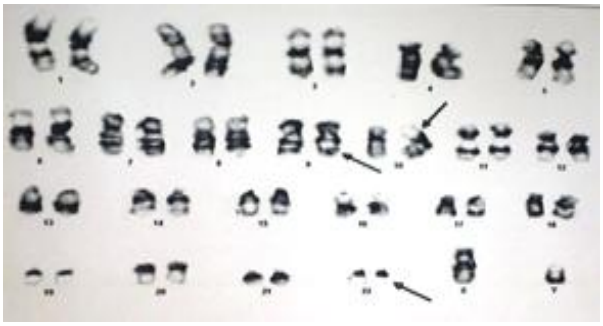

Figure 3 - Complex variant of Philadelphia Translocation

In April 2011, the patient visited a psychiatrist with complaints of anxiety, anger, desire to hurt and self harm and he was initiated on sodium valproate 750mg OD, clonazepam 0.25mg HS and Resperidone 1mg HS. Patient defaulted on imatinib from December 2013 to April 2014. Patient underwent bone marrow biopsy in August 2014 which revealed normal marrow components and reactive

lymphoid aggregates with no evidence of blasts. The chromosome analysis for hematologic malignancy revealed 46XY t (9;10;22) (q34, p11.2, q11.2) i.e. complex variant of Philadelphia translocation (**Fig. 3**). Quantitative bcr abl translocation assay revealed a transcript ratio of 27.38%. Imatinib resistance mutation analysis (IRMA) via RTPCR from peripheral blood was also done which showed E225V mutation in P loop domain of bcr-abl transcript.

Subsequently, patient was started on Dasatinib 100 mg OD on September 7, 2014 but stopped for 12 days (October 16, 2014 to October 28, 2014) following severe drug induced dermatitis and grade I haemorrhoids. It was restarted at a lower dose (50 mg OD) and then escalated to 70 mg OD and is continued till date.

DISCUSSION

Tyrosine kinase inhibitors are used in treatment of various hematologic malignancies as well as solid organ tumours including soft tissue sarcomas. In 2001, the first TKI Imatinib was approved for the treatment of a malignancy, and much has been elucidated about its pharmacokinetics, pharmacodynamics, mechanism of action and adverse reactions including toxities. Dasatinib, a second-generation multi-target TKI is active against many imatinib-resistant bcr-abl mutant forms, Src, and c-Kit tyrosine kinases and platelet derived growth factor receptor b (PDGFR-b) tyrosine kinases [1]. Currently, dasatinib is FDA approved for treatment of CML, but is actively being investigated for other malignancies such as sarcoma.

As mentioned above, various pigmentary abnormalities have been associated with imatinib. Reversible, dose-related hypopigmentation is a well-recognized adverse effect. Histologically there is a reduction or complete absence of melanocytes in association with a partial or total loss of epidermal pigmentation. Superficial perivascular and perifollicular lymphocytic infiltrates are generally absent. In one series, 41% of patients treated with imatinib developed localized or generalized hypopigmentation, at a median of four weeks after initiating treatment. Paradoxical accelerated re-pigmentation and hyper-pigmentation have also been described. In one prospective series, skin hyper pigmentation occurred in 3.6% of ethnically pigmented patients treated with imatinib [2]. The mechanism of paradoxical hyper pigmentation is unclear; however, the variable response to imatinib may depend upon specific c-Kit mutation or interactions with other tyrosine kinase receptors, resulting in increased melanin synthesis [3].

Several dermatologic toxicities have been associated with first generation TKIs such as urticaria, lichenoid reaction, psoriasis, and Stevens-Johnson syndrome [4]. Rarely does it lead to severe epidermal necrolysis, acute generalized exanthematous pustulosis, hyper pigmentation and lichenoid eruption, photo induced dermatoses, pseudoporphyria, pityriasiform/ psoriasiform eruptions, superficial oedema, neutrophilic dermatoses, panniculitides [5-6]. Conversely, dasatinib has very few cutaneous side effects, the most common being non-specific maculopapular rashes and skin exfoliation and irritation [4]. A few cases of dasatinib-induced hair depigmentation have been reported [7,8].

However, skin pigment changes associated with dasatinib have only been reported once in a paediatric leukemic patient who developed achromic patches on neck and dorsal surface of hands, and complete depigmentation of hair, eyelashes and eyebrows [7]. The case described here is noteworthy; as this is the first description of dasatinib-induced supercilliary madarosis which emphasizes role of c-Kit pathway in melanocyte biology.

The proto-oncogene c-Kit is a gene encoding class III tyrosine kinase receptor, while stem cell factor (SCF) is the ligand for c-Kit. SCF and c-kit interaction plays an important role in the development of hematopoietic stem cells, germ cells, mast cells and melanocytes [9]. In particular, SCF is responsible for the permanent survival, proliferation and migration functions in c-Kit receptor-expressing melanocytes, and therefore, plays a critical role in the development of melanocytes from their precursors in the embryonic neural crest cells during embryogenesis and maintenance of melanocyte lineage in adult skin [9]. Inhibition of c-Kit by TKIs is thought to be responsible for hypopigmentation. It is also known that mutations in the c-Kit gene are associated with skin and hair hypopigmentation syndromes, such as piebaldism (autosomal dominant disorder of melanocyte development characterized by white hair and congenital amelanotic patches on forehead, torso and extremities) [10].

In addition, several in vitro and in vivo studies also support the association of c-Kit and its downstream pathway in normal integument pigmentation. For example, imatinib significantly decreases the number of cells with

high tyrosine kinase activity in vitiligo and normal melanocytes, thereby inhibiting melanogenesis [11]. The various interactions between photosensitivity and molecular pathways involved in the response to ultraviolet stress can explain the different phenotype of pigmentary changes caused by TKIs. Pigmentation is associated with c-kit signalling and resultant activation of the tyrosine kinases involved in melanogenesis, such as tyrosinase and tyrosinase-related protein 1.

Hemesath *et al*. suggested that the signal transmission downstream activation of the MAP kinase Erk-2, modulate the pigment production through an effect on the tyrosine pigmentation gene promoter and expression of genes, essential for melanocyte survival and development. The link between the c-kit receptor and melanogenic genes probably occurs through the microphtalmia transcription factor (MITF), which is crucial for melanocyte development [12].

The overlap of target receptors between imatinib and dasatinib likely explains the pigmentary changes seen with dasatinib in this patient. 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 [13]. As most cases of TKIs induced hypo-pigmentation are dose dependent and reversible, return to baseline skin pigmentation is not surprising after discontinuation of TKIs.

REFERENCES

1. Shayani S. Dasatinib, a multikinase inhibitor: therapy, safety, and appropriate management of adverse events. Therapeutic Drug Monitoring (New York). 2010; 32(6): 680-87.
2. Arora B, Kumar L, Sharma A, Wadhwa J, Kochupillai V. Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate. Annals Oncol. 2004; 15(2): 358-59.
3. Balagula Y, Pulitzer MP, Maki RG, Myskowski PL. Pigmentary changes in a patient treated with imatinib. J Drugs Dermatol. 2011; 10(9): 1062- 66.
4. Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. Dermatologic Therapy. 2011; 24(4):386-95.
5. Schaich M, Schakel K, Illmer T, Ehninger G, Bornhauser M. Severe Epidermal Necrolysis after Treatment with Imatinib and Consecutive Allogeneic Hematopoietic Stem Cell Transplant. Annals Hematol. 2003; 82 (5): 303-304.
6. Schwarz M, Kreuzer KA, Baskaynak G, Dorken B, le Coutre P. Imatinib Induces Acute Generalized Exanthematous Pustulosis in Two Patients with Chronic Myeloid Leukemia. Eur J Haematol. 2002; 69(4): 254-256.
7. Sun A, Akin RS, Cobos E, Smith J. Hair depigmentation during chemotherapy with dasatinib, a dual Bcr-Abl/Src family tyrosine kinase inhibitor. J Drugs Dermatol. 2009; 8(4): 395-98.
8. Brazzelli V, Grasso V, Barbaccia V, Manna G, Rivetti N, Zecca M, et al. Hair depigmentation and vitiligo-like lesions in a leukaemic paediatric patient during chemotherapy with dasatinib. Acta Dermato-Venereologica. 2012; 92(2): 218-19.
9. Grichnik JM, Burch JA, Burchette J, Shea CR. The SCF/KIT pathway plays a critical role in the control of normal human melanocyte homeostasis. J Investigative Dermatol. 1998; 111(2): 233-38.
10. Richards KA, Fukai K, Oiso N, Paller AS. A novel KIT mutation results in piebaldism with progressive depigmentation. J Am Academy Dermatol. 2001; 44(2): 288-92.
11. Cario-Andre M, Ardilouze L, Pain C, Gauthier Y, Mahon FX, Taieb A. Imatinib mesilate inhibits melanogenesis in vitro. Br J Dermatol. 2006; 155 (2): 493-94.
12. Hemesath TJ, Price ER, Takemoto C, Badalian T, Fisher DE. MAP Kinase Links the Transcription Factor Microphthalmia to c-Kit Signalling in Melano- cytes. Nature. 1998; 391(6664): 298-301.
13. Robert C, Soria JC, Spatz A, Le Cesne A, Malka D, Pautier P, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. Lancet Oncol. 2005; 6(7): 491-500.

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