National Journal of Physiology, Pharmacy and Pharmacology

CASE REPORT

Blue nails in chronic myeloid leukemia – Is it usual?

Jaydeep Raj Damor[1], Jaya Chakravarty[1], Madhukar Rai[1], Manaswi Chaubey[1], Priyanka Kumari[1], Akash Rai[1], Ashish Anand Pushpakar[1], Praveen Kumar Chaturvedi[2]

[1]Department of Medicine, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, [2]Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Correspondence to: Manaswi Chaubey, E-mail: manashwi123@gmail.com

Received: June 26, 2020; **Accepted:** August 01, 2020

ABSTRACT

Nail toxicity is an uncommon cutaneous adverse effect of imatinib mesylate. Here, we have described a 45-year-old female, a diagnosed case of Philadelphia positive chronic myeloid leukemia, who was on imatinib mesylate for the past 3 months and developed bluish discoloration of the nails. This discoloration was related to the drug imatinib mesylate because the patient was only on imatinib and thyroxine medication. No any other skin-related diseases was present, which can lead to her nail changes.

KEY WORDS: Bluish Nail; Imatinib; Chronic Myeloid Leukemia

INTRODUCTION

Imatinib mesylate is the first-line drug for chronic myeloid leukemia (CML). Patients receiving imatinib experience both hematological as well as non-hematological side effects. The most common non-hematological side effect of the drug is skin changes, but nail changes have also been described, though less commonly (3%).[1] Imatinib can cause both hypo- and hyperpigmentation of nails. However, hypopigmentation is relatively more common (40%) than hyperpigmentation and incidence of isolated nail hyperpigmentation is extremely low.[2]

We present a case of a 45-year-female patient who was diagnosed as a case of Philadelphia positive CML, who was on imatinib for the past 3 months and developed hyperpigmentation of nails subsequently.

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2020.10.06167202001082020	

CASE REPORT

A 45-year-old female came in our outpatient department in August 2019 with complains of feeling of heaviness in the left side of the abdomen for the past 3 months and loss of appetite for the past 2 months. She was a known case of primary hypothyroidism for the past 4 years and was on 100 μg of oral thyroxin medication. There was no history of fever, weight loss, rashes, bleeding from any site, intraretinal hemorrhages, hair fall, or swelling anywhere in the body. She was a vegetarian, non-alcoholic, and non-tobacco chewer.

On examination, the patient was conscious, well-oriented to time, place, and person. Vitals and general examination were within normal limits. On per abdominal examination, massive splenomegaly was present approximately 10 cm below the costal margin. The rest of the systemic examination were within normal limits.

Her investigations revealed hemoglobin (Hb) – 9.3 g/dl, total leucocyte count (TLC) –1,78,000/mm^3, and platelet count – 1,91,000/mm^3. Liver and kidney function tests were normal. Urinary findings were also within normal limits. Hence, the possibility of chronic myeloproliferative disorder was kept, and BCR ABL and Philadelphia chromosome analysis were

National Journal of Physiology, Pharmacy and Pharmacology Online 2020. © 2020 Manaswi Chaubey, *et al*. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creative commons.org/licenses/by/4.0/), allowing third parties to copy and redistribute the material in any medium or format and to remix, transform, and build upon the material for any purpose, even commercially, provided the original work is properly cited and states its license.

sent. BCR-ABL1 mRNA transcript came out to be positive in the peripheral blood by reverse transcription-polymerase chain reaction and Philadelphia chromosome was found in 100% cells. Hence, a final diagnosis of CML was made, and imatinib 400 mg/day was started. In a subsequent follow-up, a complete hematological response was seen within 1 month of treatment. After 1 month of therapy, her Hb improved to 10.6 g/dl, TLC reduced to 7580/mm^3, and platelet count was 1,41,000/mm^3. Spleen also regressed after 2 months of initiation of treatment.

After 4 months of treatment initiation, she noticed hyperpigmentation of nails of both hands and feet. It started at the nail bed and gradually involved proximal one-third of the nails. Initially, it was light blue in color, but subsequently, it became dark blue. All fingernails and toenails were affected [Figure 1]. Fingernails were more darkened than toenails. There was no change in the skin and mucous membrane elsewhere in the body. As the patient was not on any other treatment except imatinib and thyroxin, so the diagnosis of imatinib-induced hyperpigmentation was made and the patient was counseled and the drug was continued.

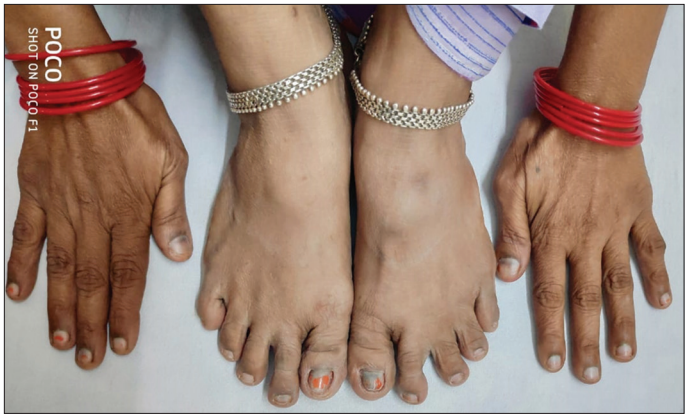

Figure 1: Hyperpigmentation of nails of both hands and feet

Table 1: Common drugs causing melanonychia

Drugs	Characteristics
Anticancer agents: Cyclophosphamide, doxorubicin, hydroxyurea, busulfan, taxanes, capecitabine, cisplatin, bleomycin, daunorubicin, dacarbazine, 5FU, and methotrexate	Seen 1–2 months after initiation One or more transverse or longitudinal bands Cyclophosphamidediffuse black, longitudinal, or dark grey pigmentation of proximal nail plate[6] Doxorubicin: Alternating bands of dark brown and white lines, and transverse bands.[6] Hydroxycarbamide: Distal or diffuse, dark brown[6]
Antiretroviral drugs zidovudine and lamivudine	Diffuse bluebrown, transverse, or longitudinal bands Fingernails > toenails Appears after 38 weeks Reversible within 6–8 weeks, may persist for months
Antimalarials: Amodiaquine, chloroquine, mepacrine, and quinacrine	Melanonychia due to melanin and ferric dyschromia[5]
Others: Biologicals, clofazimine, infliximab, psoralens, phenytoin, fluconazole, cyclins, ketoconazole, phenothiazines, and sulphonamides Metals arsenic, thallium, Mercury	Diffuse pigmentation, multiple nails

DISCUSSION

Melanonychia is defined as brownblack discoloration of the nail plate due to pigment "melanin." Drug-induced melanonychia often coexists with other mucosal and cutaneous pigmentations. Three patterns of nail discoloration have been described – nail bed pigmentation, transverse bands and longitudinal melanonychia. The pattern of melanonychia depends on the causative drug. These patterns can be seen either alone or together.[3]

However transverse melanonychia, although uncommon, almost exclusively seen with drugs.[4] It involves several nails, and reversibility following drug withdrawal is either partial or complete.[5] Reversibility may occur within 6–8 weeks, but may take several months to years.[3] The common drugs causing melanonychia is listed in Table 1.

Among these drugs, the most common cause of nail discoloration is chemotherapeutic drugs.[3] Imatinib mesylate is a tyrosine kinase inhibitor used in the treatment of the chronic, accelerated and blastic phases of CML, Philadelphia chromosome-positive acute lymphoblastic leukemia and gastrointestinal stromal tumors.

Imatinib mesylate is associated with mild to moderate toxicity which is mostly reversible by either reducing the dose or stopping the drug. Most of the side effects are observed within the first 2 years of initiation of treatment; however, late effects may occur.

Superficial skin edema (mild to moderate regional fluid retention limited to periorbital region and leg), skin rashes, hypopigmentation, and pruritus are the common skin findings which are encountered in imatinib-induced skin toxicity.[1] Rarely, severe toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and hyperpigmentation may occur.[7-9] According to a study in India on CML patients, imatinib can lead to hypopigmentation in 40.9% patients. However, hyperpigmentation of the skin was reported just once.[7]

Pigmentary changes in the nails have been reported very rarely,[10-12] but the mechanism is same as that for the skin pigmentary changes. Imatinib acts on tyrosine kinases of BCR-ABL, platelet-derived growth factor receptor-α, and c-kit. C-kit, which is a stem cell factor, is expressed in many

sites, including skin basal cells and melanocytes.[7] It regulates melanogenesis, melanocyte homeostasis, and pigmentation.[11] Other postulated mechanisms are deposition of drug-metabolite chelated to iron or melanin and drug-induced immune dysregulation, leading to melanin pigment incontinence.[13] However, the molecular mechanism for hyperpigmentation is still unknown. These nail changes are mainly dose-related and they are reversible after discontinuation of the drug.[12]

The temporal relation between administration of imatinib and the onset of nail changes, as well as the absence of other iatrogenic, paraneoplastic, or endocrinological causes, supports the cause as imatinib mesylate-induced persistent hyperpigmentation of nails in our patient.

CONCLUSION

Patients taking imatinib should be thoroughly examined for the dermatological side effects of the drugs and periodic assessment should be performed. These patients need reassurance and imatinib should not be stopped.

REFERENCES

1. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, *et al*. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2003;348:994-1004.
2. Vinay K, Yanamandra U, Dogra S, Handa S, Suri V, Kumari S, *et al*. Long-term mucocutaneous adverse effects of imatinib in Indian chronic myeloid leukemia patients. Int J Dermatol 2018;57:332-8.
3. Andre J, Lateur N. Pigmented nail disorders. Dermatol Clin 2006;24:32939.
4. Jefferson J, Rich P. Melanonychia. Dermatol Res Pract 2012;2012:952186.
5. Sobjanek M, Michajlowski I, Wlodarkiewicz A, Roszkiewicz J. Longitudinal melanonychia in a northern Polish population. Int J Dermatol 2014;53:e412.
6. Finch J, Arenas R, Baran R. Fungal melanonychia. J Am Acad Dermatol 2012;66:83041.
7. Arora B, Kumar L, Sharma A, Wadhwa J, Kochupillai V. Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate. Ann Oncol 2004;15:358-9.
8. Schaich M, Schakel K, Illmer T, Ehninger G, Bornhauser M. Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplant. Ann Hematol 2003;82:303-4.
9. Schwarz M, Kreuzer KA, Baskaynak G, Dorken B, Le Coutre P. Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. Eur J Haematol 2002;69:254-6.
10. Jain A. Imatinib induced blue nails. Indian J Hematol Blood Transfus 2020;36:432-3.
11. Di Tullio F, Mandel VD, Scotti R, Padalino C, Pellacani G. Imatinib-induced diffuse hyperpigmentation of the oral mucosa, the skin, and the nails in a patient affected by chronic myeloid leukemia: Report of a case and review of the literature. Int J Dermatol 2018;57:784-90.
12. Prabhash K, Biswas G, Prasad N, Karant N, Sastry PS, Parikh PM. Imatinib-induced nail hyperpigmentation in chronic myeloid leukemia. Indian J Dermatol Venereol Leprol 2006;72:63-4.
13. Tsao AS, Kantarjian H, Cortes J, O'Brien S, Talpaz M. Imatinib mesylate causes hypopigmentation in the skin. Cancer 2003;98:2483-7.

How to cite this article: Damor JR, Chakravarty J, Rai M, Chaubey M, Kumari P, Rai A, Pushpakar AA, *et al*. Blue nails in chronic myeloid leukemia – Is it usual? Natl J Physiol Pharm Pharmacol 2020;10(12):1160-1162.

Source of Support: Nil, **Conflicts of Interest:** None declared.