Case 11

A 46-year-old Thai male from Samut Prakan

Present history:

The patient was diagnosed as a case of chronic myeloid leukemia since July 2005. Treatment with imatinib mesylate 400/day was commenced and dose was increased to 600 mg/day 1 year after. In April 2007, he noticed asymptomatic dark-brown discoloration on his face, extensor surface of both forearms and dorsum of both hands.

Personal history:

He works as security guard and his hobby is gardener which both are sun-exposed jobs.

Past history and family history: unremarkable

Physical examination:

Vital signs: Normal

Skin examination: Ill-defined brownish patches on face, extensor area of both forearms and dorsum of both hands.

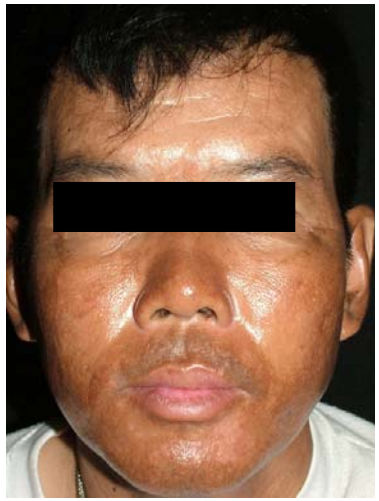

Fig. 11.1

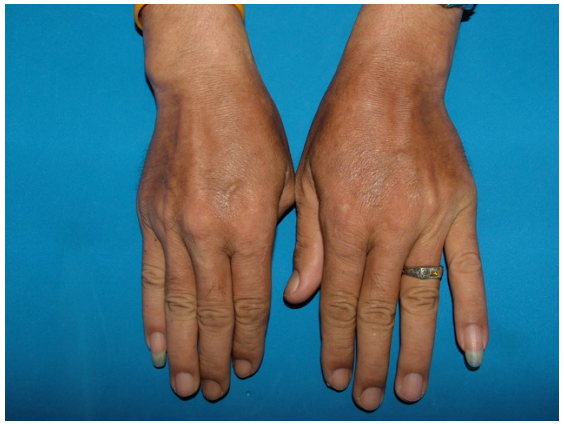

Fig. 11.2

Histopathology (S09-10733) (Fig.11.3, 11.4)

There are sparse superficial infiltrate of mostly melanophages in the upper dermis

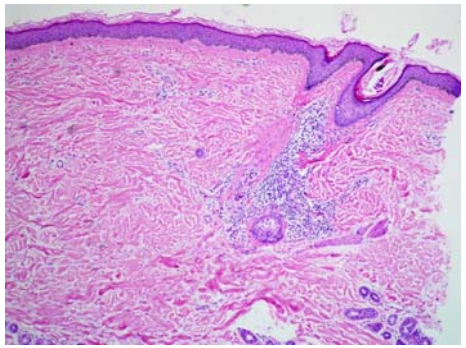

Fig. 11.3

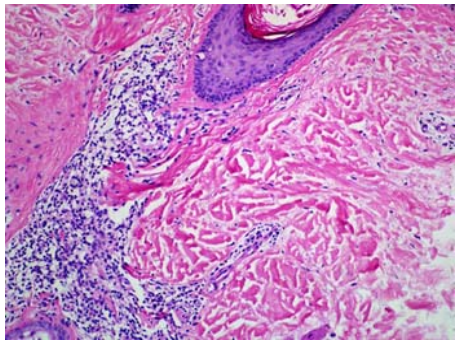

Fig. 11.4

Dignosis: Imatinib-induced photodistributed hyperpigmentation
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Discussion:

Imatinib mesylate (Gleevec®, Novartis Pharmaceuticals) is a tyrosine kinase inhibitor in wide clinical use in chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs) that target TK domain in BCR-ABL protein in CML, c-kit receptor (KIT), and platelet-derived growth factor receptors (PDGFR) [1].

Cutaneous reactions are the most common non-hematological side effects which primarily include skin rash (often pruritic, maculopapular rash) and superficial edema seen in 66.7% and 65% of patients respectively. The prevalence rate of rash increase with daily dose. The relative risk of rash was increase from 3 to 26 for a dose above 400 mg/day. Rerely, it can cause follicular mucinosis, erythroderma, graft-versus-host-like-disease, a mycosis fungoides-like reaction, small vessels vasculitis, generalized exanthematous pustulosis, Stevens-Johnson syndrome, a pityriasis rosea-like eruption, sweet syndrome, and a lichenoid eruption [2, 3]

In the literature there are few data on pigmentary changes during imatinib therapy which hypopigmentation of the skin was observed in the majority of patient (localized of diffuse) and appears to be reversible upon discontinuation or dose reduction [3]. Hyperpigmentation in the skin appears to be much more rare events with only a few patients being reported to date [4, 5]. The largest serie were reported by B. Arora. *et al*, enrolled 188 Indian patients with CML , depigmentation was found in 40.9% of cases and hyperpigmentation in 3.6% of cases. The median time of onset of pigmentary changes was 4 week (range 2-14) after the start of therapy. At the onset the changes were localized, generally becoming diffuse over the next few weeks [4]. Regarding all previous reports, it seems that different skin type may effect Imatinib-induced pigmentary changes as these events only occured in non-Caucasian, ethnically pigmented skin patients.

This clinical paradox of imatinib causing hypo-and hyperpigmentation may be linked to alterations in the c-kit signaling pathway, which plays an important role in melanogenesis. C-kit and its ligand stem-cell factor have a major role in melanogenesis, melanocyte homeostasis and UVB -induced pigmentation. The stimulation of C-kit leads to activation followed by rapid degradation of microphthalmia transcription factor (Mift), which transactivates the tyrosinase pigmentation gene promoter in melanocytes and effects pigment production. PDGF receptor is required for neural crest cell development. How the same drug can produce both hypopigmentation and darkening in the skin is unclear, but a possible explanation may reside in its binding to different receptors in the skin, some with activator, and others with inhibitory effects on melnogenesis. More studies are necessary to elucidate the effects of c-kit and PDGFR inhibition through imatinib to the skin.

References

1. O'Brien SG, Guilhot F, Larson RA 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. Valeyrie L, Bastuji-Garin S, Revuz J, Bachot N, Wechsler J, Berthaud P, et al . Adverse cutaneous reactions to imatinib (STI-571) in Philadelphia chromosome positive leukemias: a prospective study of 54 patients. J Am Acad Dermatol 2003; 48: 201-6.
3. Tsao AS, Kantarjian H, Cortes J, O'Brien S, Talpaz M. Imatinib mesylate causes hypopigmentation in the skin. Cancer 2003; 98: 2483-7.
4. 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.
5. Alexandrescu DT, Dasanu CA, Farzanmehr H, Kauffman L. Persistent cutaneous hyperpigmentation after tyrosine kinase inhibition with imatinib for GIST. Dermatol Online J. 2008 Jul 15;14(7): 7.