Case report

Nail pigmentation due to hydroxycarbamide

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Abstract

A 47-year-old male developed both longitudinal melanonychia and periungual hyperpigmentation 6 months after initiation of hydroxycarbamide (synonym: hydroxyurea) therapy for chronic myeloproliferative disease. Based on the clinical symptoms observed in this patient, the broad differential diagnostic spectrum of hyperpigmentation of the nails is briefly reviewed here. In individuals who undergo hydroxycarbamide treatment, melanonychia might sometimes be seen as side effect and always has to be differentiated from subungual malignant melanoma.

Introduction

Hydroxycarbamide is used in the treatment of chronic myelogenous leukemia (CML), polycythemia vera, essential thrombocythemia, sickle cell anemia, and other myeloproliferative disorders.[1] This drug inhibits DNA synthesis through its action on ribonucleoside diphosphate reductase, which catalyzes the reduction of ribonucleotides.[2] Long-term hydroxycarbamide therapy can produce different cutaneous abnormalities including nail changes such as onycholysis, onychodystrophy, and melanonychia.[3,4]

Here, we describe a patient who developed longitudinal melanonychia and periungual hyperpigmentation on his finger- and toenails several months after initiation of hydroxycarbamide therapy.

Case Report

A 47-year-old negroid male presented to our outpatient clinic with a 4 week history of slow but progressive hyperpigmentation of his fingernails. He first noted the color changes 6 months after initiation of hydroxycarbamide therapy for chronic myeloproliferative syndrome.

On physical examination, we saw multiple longitudinal brownish-black bands with a width of 1–2 mm spanning the nail matrix to the most distal edge of all nails. Additionally, the adjacent skin showed hyperpigmentation proximal of the nail matrix (Fig. 1a,b). The nails did not appear thickened or atrophic, and dermatoscopy revealed a regular distribution pattern of melanin pigment. The rest of the integument did not show hyperpigmentation.

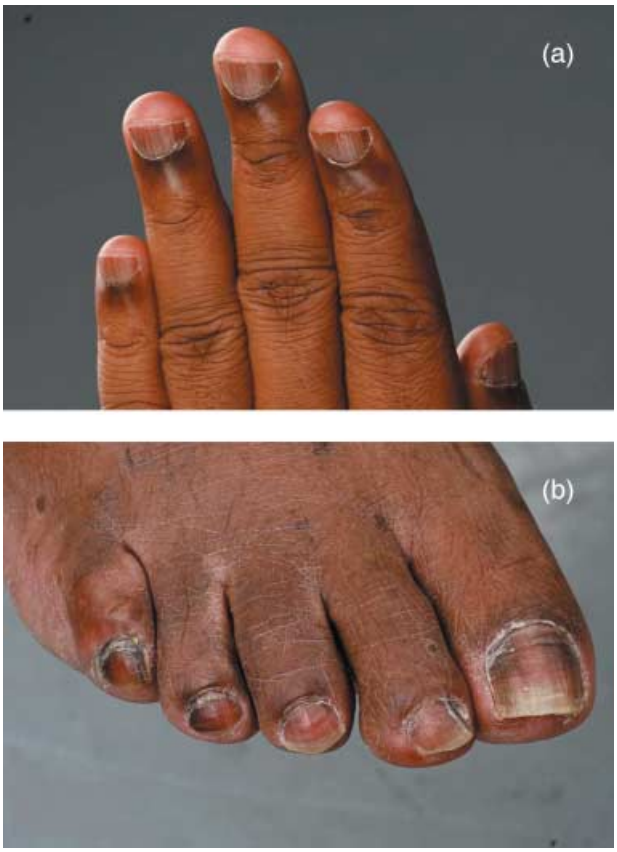

Figure 1 Longitudinal hyperpigmentation of the nails on (a) hands and (b) feet

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Table 1 Possible causes of longitudinal melanonychia

Microorganisms	Drugs	Melanocytic lesions	Metabolic disorders	Other dermatologic diseases
Fungal infection	Tetracycline	Benign naevus	Morbus Addison	Verruca vulgaris
Trichophyton soudanense	Chloroquine	Lentigo simplex	Hemosiderosis	Hematoma
Alternaria tenuis	Phenytoin	Laugier–Hunziker syndrome	Vitamin E deficiency	Morbus bowen
Fusarium oxysporum	Hydroxycarbamide	Malignant melanoma	Vitamin B12 deficiency	Basal cell carcinoma
Scytalidium dimidiatum	Virostatics	Metastasis of malignant melanoma		Ungual lichen ruber planus
Bacterial infection	Dithranole			Ungual lichen striatus
Pseudomonas aeruginosa	Silver nitrate			
Proteus species				

Mycological examination was negative, both on direct microscopy and on culture of nail specimens.

Discussion

Pigmentation of finger- and toenails constitutes a wide range of differential diagnostic considerations. They can be of infectious, melanocytic, and exogenous origin, caused by metabolic disorders or reflect an adverse effect of therapy with specific drugs (Table 1).[5,6]

Hydroxycarbamide-induced nail hyperpigmentation can occur as early as 4 months and as late as 5 years after initiation of therapy and is due to deposition of melanin pigment subungually that can only be visualized histopathologically. Longitudinal bands seem to be the most common pigmentation distribution pattern, although multiple patterns, including transversal melanonychia, may occur simultaneously in one patient. The interval between start of therapy and first signs of nail pigmentation might depend on the velocity of nail growth; this would explain the later and less frequent appearance of pigmentation changes in the toenails.[7,8]

Although the pathogenesis of melanonychia is not well understood, yet several hypotheses have suggested, for example, genetic predisposition, that it is due to the toxic effect of hydroxycarbamide on the nail bed and matrix, photosensitization, and focal stimulation of melanocytes at the level of the nail matrix.

The differential diagnoses include bacterial infections with *Pseudomonas aeruginosa* and *Proteus* species, subungual hemorrhages, melanocytic naevi, and subungual malignant melanoma (Table 1).[5,6] Brown or black discoloration spreading from under the nail or proximal to nail fold into the surrounding skin, referred to as Hutchinson's sign, should be a reason to rule out malignant melanoma.[9] Idiopathic longitudinal melanonychia is a physiologic sign in dark-colored individuals (skin types IV–VI; according to Fitzpatrick) and in patients with mucocutaneous pigmentation as in Laugier–Hunziker syndrome.[10] Drug-induced hyperpigmentation of the nails occurs sporadically, mostly induced by cytostatics, antibiotics, and antimalarials, such as chloroquine.[11,12]

Hydroxycarbamide, also known as hydroxyurea, is the chemotherapy of choice for myeloproliferative diseases like CML, polycythemia vera, essential thrombocythemia, and sickle cell anemia.[13,14] Besides hyperpigmentation of the nails, it can cause other reversible cutaneous, mucosal, and systemic adverse effects including cutaneous hyperpigmentation, xerosis cutis, skin atrophy, dyskeratosis, oral mucositis, oral ulcers, gastrointestinal complaints, lymphocytopenia, and kidney disease.[15–17] Of note, the development of basal cell and squamous cell carcinoma has also been reported following long-term administration of hydroxycarbamide.[18]

In patients who develop isolated ungual or periungual hyperpigmentation, the most important differential diagnosis that has to be ruled out is subungual malignant melanoma and acrolentiginous melanoma. Since our patient showed a uniform hyperpigmentation pattern on all finger- and toenails we, considered a malignant melanoma less probable. The nail changes observed rather resembled melanonychia that can sometimes develop in the course of hydroxycarbamide therapy.

Conflicts of interest

The authors have declared no conflicts of interest.

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