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# What Explains This Man's Nail Discoloration?

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A 69-year-old man was evaluated at an outpatient clinic for his type 2 diabetes mellitus. The man is a retired construction worker with a history of hypercholesterolemia, hypertension, and essential thrombocythemia. He denied any history of arterial or venous thrombosis.

Physical examination findings and vital signs were unremarkable except for the patient's hands, which showed multiple longitudinal brown-black pigmented bands on some of the fingernails bilaterally (**Figure**). His nails also appeared thickened, which he ascribed to his profession. The patient had noticed the nail discoloration for many years but had paid no attention to it. His toenails were not affected, and no other mucocutaneous pigmentations were seen. He was on aspirin, metoprolol, metformin, and hydroxyurea, the latter at a dosage of 500 mg/day for the past 1 year. Results of all routine laboratory investigations were normal except for mild anemia (hemoglobin, 12.8 g/dL; platelet count,  $300 \times 10^3/\mu\text{L}$ ). A biopsy was deemed unnecessary.



**What is the cause of this man's brownish nail discoloration?**

- A.** *Pseudomonas aeruginosa* infection
- B.** Hydroxyurea-induced melanonychia
- C.** Subungual melanoma
- D.** Subungual hematoma

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## Answer: Hydroxyurea-induced melanonychia

Changes in nail color often indicate the presence of underlying local or systemic diseases. In fact, any change in structure and growth characteristics of the nail may be the first clue to an underlying pathological process.

Discoloration of the nails is called chromonychia.<sup>1</sup> Melanonychia is a type of chromonychia that is characterized by brown to black discoloration of a fingernail or toenail in diffuse, transverse, or longitudinal band patterns. Longitudinal melanonychia describes a pigmented band and is due to melanin within the nail plate.<sup>2</sup>

The differential diagnosis of longitudinal melanonychia affecting multiple nails includes iatrogenic causes such as drug-induced hyperpigmentation, and physiological causes such as repetitive trauma, subungual hematoma, onychomycosis, pseudomonal infection, or underlying systemic disease.<sup>3,4</sup>

It is important to also consider exogenous causes of nail pigmentation when a patient presents with nail dyschromia. Trauma resulting in a persistent hematoma, fungal infection (onychomycosis) caused by *Aspergillus* or *Scopulariopsis* species, and bacterial infections with persistent *Pseudomonas aeruginosa* are important nonmelanocytic origins of dyschromia.

In our patient's case, a subungual melanoma was unlikely due to the absence of micro-Hutchinson and Hutchinson signs. The Hutchinson sign is the periungual extension of brown-black pigment from the nail bed and nail matrix onto the surrounding tissues, which usually occurs during the radial growth phase of subungual melanoma.<sup>5</sup> There was no periungual extension of the pigmentation in this patient's case. However, experience has demonstrated that the Hutchinson sign, although valuable, is not an infallible predictor of melanoma. Periungual pigmentation is present in a variety of benign disorders and therefore may lead to overdiagnosis of subungual melanoma. Periungual hyperpigmentation occurs in at least one nonmelanoma skin cancer, Bowen disease of the nail unit.

Clinicians should keep in mind that the presence of the Hutchinson sign may be a specific finding when present but is not sensitive enough to ignore when absent.

A subungual hematoma was also unlikely in the absence of a history of trauma and given that multiple nails were involved. Fingernails grow at a rate of 0.1 mm/day; thus, any evidence of trauma would likely be gone by 100 to 120 days. Therefore, subungual hematoma is an unlikely diagnosis in this patient.

*Pseudomonas aeruginosa* infection of the nails commonly occurs in elderly, debilitated patients. Specifically, *P aeruginosa* infections are seen in persons who are exposed to damp environments in which the bacteria may reside. Once infected, the nails of patients feature a blue-green pigmentation (pyoverdine and pyocyanin). This specific discoloration was not seen in this patient's case.

Nail changes as a result of antineoplastic drugs are asymptomatic and entirely reversible within few months after withdrawal of the offending agents. The most frequent presentation of chromonychia induced by antineoplastic drugs is melanonychia, which may coexist with diffuse pigmentation of skin, also known as melanoderma.

Hydroxyurea or hydroxycarbamide is an antineoplastic cytostatic drug used in myeloproliferative disorders (eg, chronic myeloid leukemia, polycythemia vera, essential thrombocythemia) and at times in the treatment of psoriasis (as a second-line systemic agent). The medication is converted to a free radical nitroxide in vivo and results in inactivating the enzyme ribonucleotide reductase, which ultimately results in inhibition of DNA synthesis, thus producing cell death. Melanonychia develops in approximately 4.3% of patients receiving hydroxyurea therapy.<sup>3</sup> The onset of the melanonychia varies from 4 weeks to 5 years after initiation of hydroxyurea. There are currently few drugs to consider as second-line therapy in essential thrombocytosis for patients who cannot tolerate hydroxyurea; these include pegylated interferon alfa, busulfan, and anagrelide.

The adverse mucocutaneous effects of hydroxyurea can include hyperpigmentation, alopecia, leg ulcers, lichenoid eruptions, and nail discoloration as described above. The mechanism of hydroxyurea-induced melanonychia is still unknown.<sup>6</sup> Several hypotheses have been suggested, including genetic predisposition, the toxic effect of hydroxyurea on the nail bed, and focal stimulation of melanocytes at the nail bed. Some evidence suggests that fingernails are more frequently involved because they have more exposure to the sun. The discoloration generally fades following the withdrawal of the medication; however, because of our patient's underlying medical problem, he was unable to suspend the drug permanently. Besides the discoloration, there are no known long-term consequences of this condition.

It is especially important to educate patients about the need to return for follow-up if there is extension of the discoloration to the adjacent skin (the Hutchinson sign), skin ulceration, or other adverse effects

of the medication. Our patient's case has been followed for a year now, and he has had no other hydroxyurea-associated adverse effects.

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