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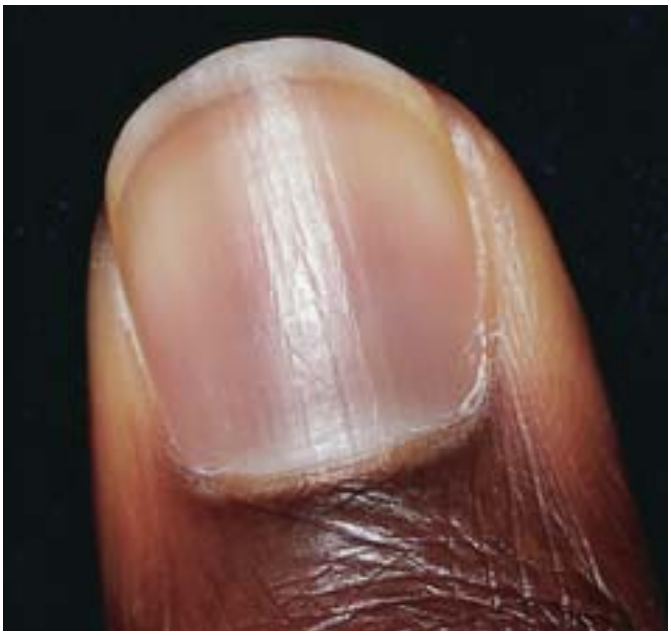

A patient with acne developed nail bed pigmentation.

What is your diagnosis?

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The Diagnosis: Pigmentation Due to Minocycline

Minocycline, a second generation, semisynthetic, broad-spectrum antibiotic of the tetracycline family, is a yellow crystalline material that turns black when exposed to oxygen in an alkaline medium in vitro.[1] Minocycline chelates with iron to form insoluble complexes.[2] It is the most lipophilic of the tetracyclines, which accounts for its high concentration in the brain, saliva, thyroid, lung, liver, bone, and fat.[3]

Since the introduction of minocycline in 1967, it has been widely used in the treatment of recalcitrant acne vulgaris, rosacea, and other dermatoses. Adverse effects are uncommon but can be serious. As with other tetracyclines, minocycline can cause gastrointestinal toxicity, intracranial hypertension, nephritis, and hepatitis and is deposited in growing bones and teeth.[4] Because minocycline is highly lipid soluble and readily penetrates the blood-brain barrier, patients may experience dose-related vertigo, tinnitus, ataxia, nausea, and vomiting. Markers for minocycline-induced systemic lupus erythematosus and autoimmune hepatitis include a flulike syndrome; seronegative, nonerosive polyarthritis and arthralgias of the hands, wrists, and knees; and elevated liver function tests.[5,6]

Transient skin pigmentation secondary to minocycline was described in 1972.[7] Persistent minocycline pigmentation may involve the skin,[8] oral mucosa,[3] nails,[9-13] teeth,[2] and sclera.[3,9] Unusual presentations such as a black tongue[14,15] and acquired mongolian spot[16] have been described. Pigmentary changes occur in 2.4%[17] of patients. Pigmentary change of the thyroid is also a well-recognized long-term adverse effect of minocycline[18-21]; however, the pigment does not appear to have any clinically significant effect on thyroid function.[4] Nail pigmentation usually coincides with pigmentation at other sites[9-13] but may occur as an isolated finding. Blue-black discoloration of the proximal nail bed is the most commonly described pigmentary change.[11,22] In addition, photo-onycholysis,[23] longitudinal melanonychia,[22-24] and periungal hyperpigmentation mimicking Hutchinson's sign[25] have all been reported in association with minocycline.

Skin pigmentation due to minocycline can be subdivided into 4 clinical types.[26] Focal, bluish-black macules appear principally in acne scars but also in areas of inflammation and previously traumatized areas on the face. A second type consists of blue-gray circumscribed macules and patches on normal skin that affect most of the body, especially the lower legs. A third type consists of diffuse and generalized muddy brown hyperpigmentation in sun-exposed areas. A fourth type resembles fixed drug eruption.[16]

The onset of pigmentation is not strictly dose related nor does the extent always correlate with the cumulative dose. Pigmentation has occurred as early as 1 week in the case of the black tongue[14] and 3 weeks in areas of prior cutaneous inflammation on the legs.[27] Dwyer et al[4] reported that 27 of 54 patients taking the drug for more than 3 years developed pigmentation when the cumulative dose was more than 100 g.[4] Concomitant medications such as amitriptyline[28] and Diane®-35[29] (cyproterone

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acetate and ethinyl-estradiol) may have a synergistic effect that contributes to pigmentation.

The composition of the pigment granules varies. Iron, melanin, minocycline, and a minocycline-complex chelated to iron have all been reported. Histologically, numerous pigment-laden macrophages are found in the papillary dermis, particularly around vessels.[10] Pigment is distributed in various sized aggregates and may stain with both Prussian blue and Masson-Fontana silver stains.[8,9,13,16,19,21,25,30,31] Electron microscopic examination of aggregates of pigment reveals electron dense granular material within the cytoplasm of dermal macrophages.[8,27,30] Energy-dispersive x-ray microanalysis indicates that the granules contain iron.[8,10] Minocycline has been detected by high performance liquid chromatography in extracts from pigmented skin.[8]

Minocycline binds to iron, but minocycline and its metabolites do not contain iron.[32] Minocycline may bind to hemosiderin deposited in skin after tissue damage.[10] In some cases, the pigment appears to represent a complex of minocycline metabolites with iron.[8,30,33] Melanin has been demonstrated by some authors[9,16,31] but not by others.[8,27] Spindle cells containing compound melanosomes and a nonmelanin substance in the dermis and around vessels have been noted.[16] Minocycline may accentuate melanin pigmentation stimulated by sunlight.[32]

The resolution of the pigmentation is uncertain and varies by the site of pigmentation. Slow spontaneous resolution may occur after discontinuation of minocycline. Rapid onset pigmentation patterns are most likely to resolve completely.[14-16,27] Diffuse pigmentation may continue to improve even after 5 years, although resolution is generally incomplete.[3,4,11,12,25,30] Tooth pigmentation is generally permanent, showing little resolution after 5 years.[2,12] The natural history of nail pigmentation is less well described.

Four patients with diffuse blue-black facial pigmentation were treated effectively with the Nd:Yag laser (532-nm wavelength).[34] Ascorbic acid (vitamin C) has recently been shown to protect rats from thyroid pigmentation when given minocycline.[35] As current treatment options are less than optimal, it is important to identify minocycline pigmentation early so the drug can be discontinued.

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