Cutaneous Hyperpigmentation Due to Chronic Quinine Ingestion

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Striking hyperpigmentation developed on the arms of a 66-year-old man following protracted oral ingestion of quinine. Although this phenomenon is well described in conjunction with other similar drugs, including quinidine, it has not been well documented following exposure to quinine. This adverse event is cosmetic in nature and is not associated with functional impairment.
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Cutaneous hyperpigmentation may vary in shade, ranging from dark black to bright yellow. The differential diagnosis is quite extensive and most prominently includes genetic disorders (café au lait and mongolian spots, lentigines, incontinentia pigmenti); metabolic disorders (hemochromatosis, Wilson disease, porphyria, Gaucher disease, alkaptonuria); endocrine disorders (tumors that produce adrenocorticotropic hormone or melanocyte-stimulating hormone, pregnancy); inflammatory disorders (lichen planus, discoid lupus erythematosus, tinea versicolor, postinflammatory hyperpigmentation); nutritional causes (kwashiorkor, pellagra, vitamin B_{12} deficiency); neoplastic diseases (melanoma, acanthosis nigricans); and physical causes (irradiation, trauma).[1]

Also included among the causes of cutaneous hyperpigmentation is a long list of drugs, some that produce a characteristic pattern and others that do not.[2-4] Arsenic has been described as producing a "rain drop" appearance of diffuse macular bronze pigmentation on the trunk.[2,3] Ingestion of silver can produce argyria, typically characterized by generalized blue-gray pigmentation with accentuation of exposed areas.[3,4] The tetracycline antibiotics are known to cause hyperpigmentation on the teeth, nails, and previously traumatized or inflamed skin.[2] Melasma is a well-recognized and common side effect of oral contraceptive use. Also well documented is the hyperpigmentation associated with many of the cancer chemotherapeutic agents, the appearance varying with the agent used. Among the drugs known to produce hyperpigmentation, the antimalarials as a class are well described; quinine, however, has only rarely been reported in this regard in the readily available medical literature. We report a case of cutaneous hyperpigmentation due to quinine use and review this phenomenon as it relates to structurally similar drugs.

Case Report

A 66-year-old white man presented to the dermatology clinic for routine biannual examination for actinic keratoses. Prominent, nonblanching, macular, blue-black hyperpigmentation was noted on the dorsum of the patient's forearms with sparing of the wristwatch area. The patient stated that the asymptomatic discoloration had occurred over several years but had become more prominent during the past year and a half. The patient's medical history included a cerebrovascular accident in 1983 and a long history of leg cramps for which he had been ingesting oral quinine 975 mg/d for the past 10 years. There was no historical indication of recurrent bouts of solar purpura.

Results of a physical examination revealed large, blue-black, well-demarcated patches covering both forearms and the left lower limb (Figure). Diffuse actinic changes also were seen. The sclerae and pinnae were normal in appearance, and the patient's urine did not darken spontaneously upon standing.

Results of histopathologic examination showed severe solar elastosis, telangiectatic vessels, and an absence of inflammation. Marked yellow-brown, granular, pigmentary deposition was present in the reticular dermis, both within macrophages and between collagen bundles. Results of special staining procedures were positive for both iron and melanin. The quinine level in the skin was not measured.

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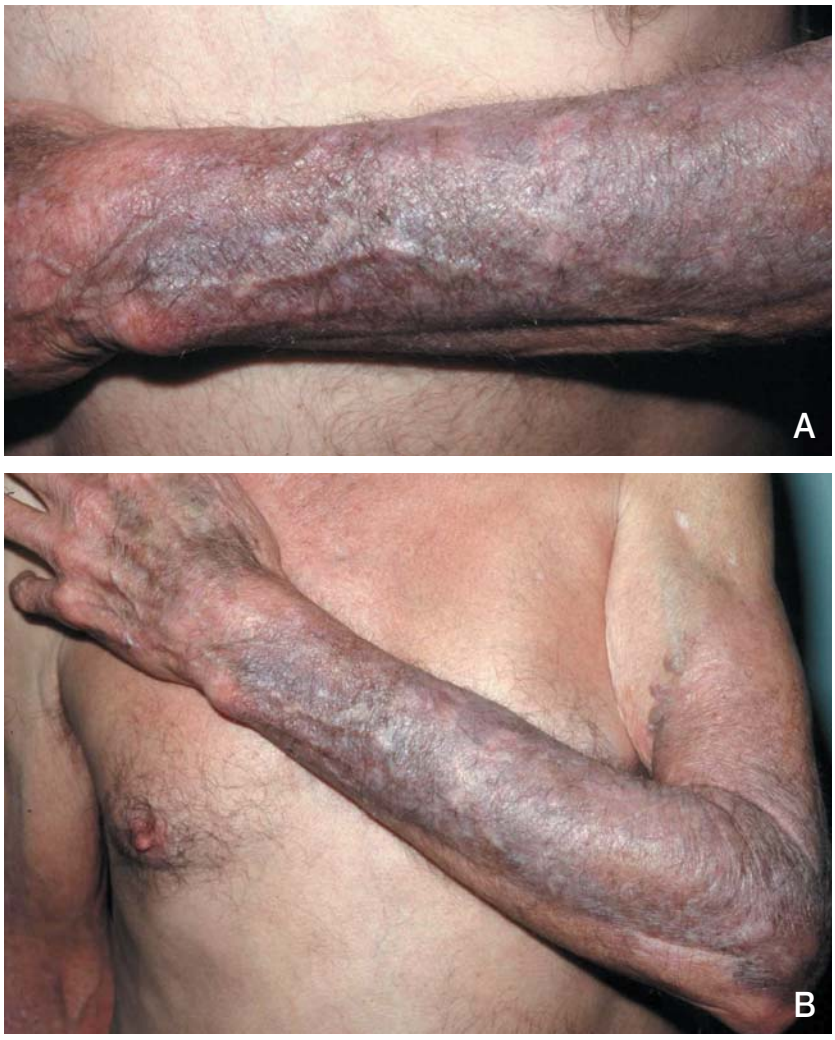
Comment

Quinine is an alkaloid derived from the bark of the cinchona tree. Its basic chemical structure is a quinoline group attached to a quinuclidine ring through a secondary alcohol linkage. It was the first antimalarial drug and the only effective treatment of malaria until the early to middle part of the 20th century. During World War II, with the quinine supply interrupted, synthetic antimalarials were developed. Quinacrine, chloroquine, and hydroxychloroquine are all variations of the same basic aminoquinoline ring structure. Their unique chemical properties are related mainly to substitutions on side chains. These drugs are now commonly used in the treatment of various disorders other than malaria, including giardiasis, nocturnal leg cramps, rheumatoid arthritis, discoid lupus erythematosus, polymorphic light eruption, solar urticaria, and porphyria cutanea tarda.[5] Quinidine is a related compound whose gluconate and sulfate salts are used as cardiac antiarrhythmics because of sodium channel blockade selective for cardiac muscle. All these structurally related drugs can cause hyperpigmentation involving the oral mucosa,[6-9] face,[6-10] forearms,[10,11] pretibial areas,[8,11,12] and nails.[6,9,10,12] The typical clinical appearance consists of blue-gray macular lesions involving one or more of the above-mentioned locations. In one patient taking quinidine, lesions were limited to sun-exposed areas[11]; this pattern also was described in another report involving amodiaquine[9] use but, to our knowledge, has not been described elsewhere. Lesions involving the hard palate usually demonstrate a characteristic sharp line of demarcation between the hard and soft palate.[8] Nail lesions consist of either transverse bands[6,10,12] or diffuse[6] hyperpigmentation. Diffuse lemon-yellow coloration of the skin has been described only in patients receiving quinicrine.[6]



Hyperpigmentation on the dorsal forearm (A and B). Note the sparing of the area routinely covered by a wristwatch.

Development of hyperpigmentation does not appear to be greatly influenced by gender. However, Campbell[9] described decreased density of pigmentation among female patients as compared with male patients. Age does not appear to be a factor in antimalarial-induced hyperpigmentation among adults, with patients ranging in age from late teens and early 20s[8,13] to older than 80 years.[10] However, a study of children receiving antimalarial therapy noted only palatal hyperpigmentation without involvement of other characteristic locations.[9] An increased incidence in white patients as compared with Hispanic or black patients was described by Tuffanelli et al.[8] The cases cited did not report any specific correlation between the drug, the dosage, and the appearance of hyperpigmentation. Duration of treatment with antimalarial drugs may be an important factor in the development of pigmentary changes. Although hyperpigmentation has been described after both short-term[7,8] and prolonged[6,8,10,11] courses of antimalarial drugs, Hendrix and Greer[2] and Campbell[9] noted that the incidence

of this phenomenon increased directly with the duration of therapy.

The histologic findings in quinidine-induced lesions include deposition of yellow-brown to brown granules within dermal macrophages and free within the dermis, with positive staining for both melanin and iron.[10-12] Chloroquine produced lesions with a similar histologic pattern[8] but also with increased melanin in the epidermis.[7] In one patient, elevated levels of chloroquine were detected in lesional skin as compared with uninvolved areas.[8] A prior reported case of quinine-induced hyperpigmentation involved isolated bluish-black macular lesions on the buttocks of a patient who had received intramuscular injections of quinine for the treatment of malaria decades earlier.[13] The results of a pathologic examination showed yellowish-brown irregularly shaped bundles within connective tissue consistent with exogenous ochronosis.[13] The present case differs in the route of administration and in the sun-exposed accentuation of pigmentation on the limbs as compared with isolation of pigmentation to areas surrounding injection sites.

Our case is a dramatic example of cutaneous hyperpigmentation induced by oral quinine therapy. Although the patient had pronounced hyperpigmentation, he had no functional impairment. Our patient continues to take quinine at the same dosage; the hyperpigmentation shows slight darkening but no extension, and the patient has no other ill effects. Therefore, if an antimalarial drug is essential for the treatment of cardiac arrhythmia, leg cramps, porphyria cutanea tarda, or discoid lupus erythematosus, it appears that the medication can be continued. Owing to the wide variety of uses for quinine and its related compounds, the primary care physician and selected specialists need to recognize this potential, though benign, complication.

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