

A case of exogenous ochronosis associated with hydroxychloroquine

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Abstract

Exogenous ochronosis is characterized by hyperpigmented skin lesions that arise in association with local suppression of homogentisic acid oxidase enzyme. Although it generally develops in association with topical application of chemical agents, it can occasionally develop in association with antimalarial drugs. Here we present the case of a patient with rheumatoid arthritis who developed hyperpigmentation on the face and neck regions during hydroxychloroquine treatment. Hydroxychloroquine is being widely used in rheumatology practice, and cutaneous hyperpigmentation may develop as an adverse effect. In the present case, we emphasize the potential underlying mechanisms through which it may cause cutaneous hyperpigmentation and determine the clinical and histopathological findings of exogenous ochronosis.

Keywords: Exogenous ochronosis, homogentisic acid oxidase, hydroxychloroquine

Introduction

Ochronosis (alkaptonuria) or black urine disease is an autosomal recessive metabolic disease and occurs due to homogentisic acid oxidase (HGAO) enzyme deficiency. This deficiency causes brown, black, or blue hyperpigmentation of the skin due to accumulation of homogentisic acid (HGA) in the liver and irreversible binding of dermal fibrils to the collagen tissue. Ochronosis may also develop following a long-term exposure of the skin to topical chemical agents and termed as exogenous form. It is an acquired clinical state and is histopathologically and clinically similar to alkaptonuria. The typical appearance is symmetrical, spotted, blue-black or grey-brown macular, popular, or nodular lesions affecting the face and neck regions. Although the pathogenesis is not completely understood, ochronosis may originate from the local suppression of HGAO enzyme activity most often associated with the topical application of phenol, resorcinol, and hydroquinone and less often with oral antimalarial drugs (1). Here we describe the clinical and histopathological findings of ochronosis in a patient with rheumatoid arthritis (RA) using hydroxychloroquine.

Case Presentation

A 60-year-old male, who was followed for almost 20 years with a diagnosis of RA, presented to the rheumatology outpatient clinic with complaints of development of brown- and black-colored changes on the forehead, cheek, and neck regions, which had occurred in the last year (Figure 1). One year before his admission, the patient had started taking 400 mg/day hydroxychloroquine sulphate along with low-dose prednisolone (5 mg/day). The patient had no known systemic diseases other than RA, and he was not taking any other drugs continuously. On physical examination, we observed black hyperpigmented macular skin lesions on the neck and face, mostly on the cheeks and forehead, spreading to the zygomatic notch from the nasal dorsum, sparing the periorbital region. On joint examination, both the wrists and the left knee and ankle were found to be tender and ulnar deviation and boutonniere deformity were present in the hand phalanges. There was no hyperpigmentation in the oral or conjunctival mucosa or in the nails. No abnormality was detected in the fundus examination. The laboratory test results were as follows: serum creatinine, 1.59 mg/dL; erythrocyte sedimentation rate, 45 mm/h; rheumatoid factor, 567 IU/mL; and anti-CCP, 170.7 AU/mL. Because the patient was on long-term corticosteroid therapy, to rule out adrenal insufficiency, serum cortisol and adrenocorticotropic hormone (ACTH) levels were measured and were found to be within normal limits [1.17 (6.2-19.4) µg/dL and ACTH 1.7 (0-46) pg/mL, respectively]. Thereafter, the patient was assessed for endogenous ochronosis. HGA levels were found to be negative, and the urine did not change its color on exposure to the open air. A biopsy sample was obtained from the region of pigmentation on the cheek; histopathological examination showed accumulation of pigment granules within the collagen fibers and macrophages along with the granules present freely in the tissue, which was consistent



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Figure 1. a-c. Hyperpigmentation of the face and neck

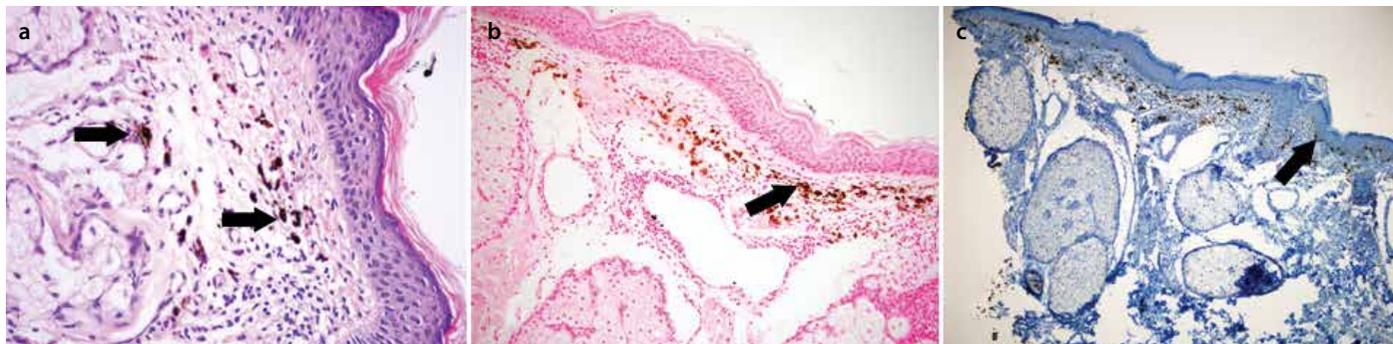


Figure 2. a-c. H&E x400 (a); iron paint x200 (b); MART1 x100 (c)

There were basophilia of the collagen fibers in the upper dermis. Small pigment granules were in macrophages or free in papillary dermis. Also these pigments were seen in the perivascular area of the dermis. The pigments were stained positively with Iron and Mart-1. Perivascular lymphocytic infiltrates were seen in upper dermis.

with exogenous ochronosis (Figure 2). After the clinical and histopathological assessment, these findings were attributed to hydroxychloroquine treatment and the drug was discontinued. The patient was recommended to take protective measures against sunlight. The articular symptoms recovered after a 5-month treatment with 8 mg/kg/month tocilizumab. At the seventh month follow-up examination, an improvement in the intensity and extent of pigmentation was observed; however, it was not completely resolved.

Discussion

Endogenous ochronosis (alkaptonuria) is an autosomal recessive hereditary disorder characterized by HGAO enzyme deficiency, which results in binding of HGA to various tissues. In alkaptonuria, the accumulation of HGA in the connective tissue causes clinical symptoms that are particularly associated with the joints, skin, eyes, and cardiac, genito-urinary, respiratory, and endocrine systems. The exogenous form of ochronosis, which develops due to exposure of the skin to various chemical agents, is associated with clinical findings related to increased pigmentation, particularly in the areas exposed to sunlight (1). Although the relationship between exogenous ochronosis and the topical use of hydroquinone is well reported in literature, to the best of our knowledge, no cases have been reported on the development

of ochronosis in association with the systemic use of hydroxychloroquine (2).

The pigmentation disorders associated with antimalarial drugs have been known for many years; these were first reported during World War II when the color changes developed in the nail beds of soldiers who were administered malaria prophylaxis, and the issue was later more frequently encountered with chloroquine treatment (3). Similar to the cutaneous pigmentation disorders, which develop in association with hydroxychloroquine (used frequently in rheumatology practice), ochronosis could be caused by the affinity of quinine group drugs to melatonin. It could also occur following the accumulation of HGA in the dermal collagen, elastic fibrils, and connective tissue with the local suppression of HGAO enzyme activity. For differentiating the two distinct pathological states, a histopathological assessment of the lesions is necessary. On performing the skin biopsy for exogenous ochronosis, the ochronotic pigment granules were observed to be present freely in the tissue, in the endothelium of vascular walls, in the basal membrane, within macrophages, and in the collagen bands (4).

The patient described here had been under steroid treatment for many years, and following the addition of hydroxychloroquine sulphate 1 year prior to the treatment, brown and

black macular skin lesions developed on the face and neck regions. Although no increase in pigmentation was observed in the axillary and intraoral mucosa, ACTH levels were determined to rule out the possibility of increased pigmentation originating from the hypothalamo-hypophyseal-adrenal axis, and the levels were found to be within normal limits. In the histopathological evaluation of the biopsy sample obtained from the skin lesions, the observation of pigment granules in the collagen fibers and macrophages and granules present freely in the papillary dermis and perivascular area was found to support ochronosis, and the hydroxychloroquine treatment was stopped. Some studies have recommended topical retinoic acid, corticosteroids, and tetracycline together with sun protection and vitamins C and E as antioxidants; however, it has not yet been proven as an effective treatment (5, 6).

By presenting this case of an RA patient who developed hyperpigmentation on the face and neck regions following hydroxychloroquine treatment, we have focused on the various mechanisms, through which hydroxychloroquine, which is commonly used in rheumatology practice, can cause cutaneous hyperpigmentation. We particularly emphasize that in patients complaining of color changes in the face, neck, and upper chest regions, discontinuing hydroxychloroquine treatment and ensuring protective

measures against sunlight are important both in terms of preventing the formation of ochronotic pigment granules and cosmesis.

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