Exogenous ochronosis hydroquinone induced: a report of four cases *

Ocronose exógena induzida por hidroquinona: relato de quatro casos

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Abstract: Exogenous ochronosis is an infrequent dermatosis characterized as a dark blue hyperpigmentation localized where the causing agent was applied. It may be caused by the use of systemic medication such as antimalarials and by the use of topic substances such as phenol, resorcinol, benzene, or hydroquinone, which is a fenolic compound with depigmentation action, largely used in the treatment of melasma and other hyperpigmentation. The physiopathology of this process is not well clear up to this moment, and the therapeutic measures are not satisfactory either. Here we present four cases of female patients that developed hyperpigmentation on their faces after the use of hydroquinone containing compounds, characterized clinically and histological as ochronosi. We emphasize the possibility of exogenous ochronosis cases being misdiagnosed as a melasma treatment failure. We also emphasize the risks of the indiscriminated use of hydroquinone containing compounds, used, in many instances, without medical prescription.
Keywords: Hydroquinones; Hyperpigmentation; Melanosis; Ochronosis

Resumo: A ocronose exógena é uma dermatose, aparentemente pouco frequente, caracterizada por hiperpigmentação negro-azulada fuliginosa, localizada na região onde foi aplicado o agente causador. Pode ser causada por uso de medicamentos sistêmicos, os antimaláricos e de uso tópico, como fenol, resorcinol, benzeno, ácido pícrico e a hidroquinona - que é um composto fenólico, com propriedade despigmentante, muito utilizado em formulações dermatológicas para o tratamento de melasma e outras hiperpigmentações. A fisiopatogenia deste processo ainda não está esclarecida e as abordagens terapêuticas são insatisfatórias. Relatam-se quatro casos de pacientes do sexo feminino que, após uso de preparados contendo hidroquinona, desenvolveram hiperpigmentação acentuada na face, caracterizadas no exame dermatológico e histopatológico como ocronose. Enfatiza-se a possibilidade de casos de ocronose exógena estarem sendo diagnosticados erroneamente, como falha de tratamento de melasma, e também para os riscos do uso indiscriminado de formulações, contendo hidroquinona, muitas vezes, sem acompanhamento médico.
Palavras-chave: Hidroquinonas; Hiperpigmentação; Melanose; Ocronose

INTRODUCTION

The term ochronosis was described by Virchow in 1866,[1] referring to a brownish-yellow pigment (ochre), that was deposited in the connective tissue of various organs such a : cartillage in the articulations, ears and nose, ligaments, tendons, sclera and skin. Ochronosis is classified as endogenous and exogenous. The endogenous echronosis or alkaptonuria is caused by an alteration of the metabolism of aminoacids and purines, of recessive autossomal inheritance resulting from defficiency of the enzyme homogentisic acid oxidase responsible for the oxidation of the homogentisic acid, a metabolite of the aminoacids tyrosine and phenylalanine. The deficit of this enzyme causes deposit of this polymerized acid in all structures that contain collagen, forming ochronotic pigments. A triad is observed in the clinical condition: dark urine, hyperpigmentation (sclera, axillae skin and inguinal region, articulations) and arthropathies.[2] Ochronotic arthropathy occurs in big articulations and vertebral column, other findings include deafness , urinary obstruction and cardiovascular complications such as calcifications and aortic stenosis.

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Exogenous ochronosis was first related in 1906 by Pick.[3] In 1912, Beddard and Plunter,[4] described the disease when a patient used fenol for the treatment of an ulcer on the leg. In 1976 Findlay described exogenous ochronosis in patients that used topic clarifying agents containing hidroquinona.[5]

Various reports of exogenous ochronosis have been described among the Black population of South America, as a result of the application of clarifying products, mainly containing hidroquinona and its derivatives. derivados. It is unknown the exact incidence of ochronosis as the patients that use the product on a self medication basis have not been properly informed about the problem and health professionals not always are able to recognise the early clinical manifestations of the disease. There was a consensus among authors that ochronosis would occur exclusively among the Black population that was making use of solutions containing high concentrations of hidroquinona above 4%, for a long period of time. However, there are reports of exogenous ochronosis pratically among all ethnic groups even when using hidroquinona in low concentrations, (2%) and for short periods of time (6 months).[6]

Penneys, attributed the cutaneous hyperpigmentation of exogenous ochronosis to the inhibition of the enzyme homogentisic acid oxidase by hidroquinona, resulting in accumulation of the homogentisic acid that polymerizes itself to form the ochronotic [7] pigment. Eletronic microscophy showed deposition of ochronotic pigment around and inside collagen and elastic fibers. Collagen fibers are substituted in the final stage of the disease by the ochronotic pigment.

Hidroquinona is an active substance commomly used for its clarifying effect of the skin. It is used in the chemical industry and its derivatives are also used in photographies, plastic resins, cosmetics, medications and in acrylic resin dental prosthesis.

This compound can cause exogenous ochronosis in patients exposed in industries being called pseudochronosis and in patients that use clarifying creams containing hidroquinona. Since 1950, creams containig hidroquinona have been used for treating hypermelanosis, senile lentigo, pigmented areas of vitiligo and melasma. It acts like a competitor in the production of melanina, by inhibiting the sulfhydryl group and acts like substratum to tyrosine, resulting in a selective action in the metabolism of melanocytes inhibiting the production of melanin. Acts in the sinthesis of DNA and RNA, by the melanocyte, and might degrade the melanocyte acquiring a cytotoxic characteristic.

The main adverse effects caused by its chronic use are: depigmentation confetti type, exogenous ochronosis, dermatitis, pigmentation of sclera and nails, squamous cell carcinoma on the exogenous ochronosis site and reduction of the healing capacity of the skin and cataract.

The clinical condition of ochronosis is charaterized by hyperpigmentation of areas photo exposed of a dark blue colouration and fuliginous aspect, asymptomatic, on the malar region, on the cervical region, temples and cheeks, where hidroquinona was employed. Subsequently, the affected areas look shiny, plain and inelastic

In 1979, Dogliotte,[8] described 3 stages of the exogenous ochronosis disease 1- Erythema and light pigmentation; 2- Light colloid hyperpigmentation, atrophia; 3- Nodule-papular lesion.

In the histologic exam we can observe in the incisions coloured by hematoxylin-eosin a brown pigment in the shape of thin free granules in the dermis and collagen bundles with the ochronotic pigment and a bizarre aspect similar to bananas. Sarcoidi granulomas with gigantic mulinuclear cells that phagocyte ochronotic particles have been observed. Transfolicular elimination of ochronotic fibers are also described. It is not observed ochronotic pigment in the histological condition of melasma. Other exam that can be used in the diagnosis is dermatoscopy differenciating areas of the skin affected by melasma or ochronosis.

Various treatments have been used for exogenous ochronosis such as retinoic acid, azelaic acid, kojic acid, dermabrasion, cryotherapy, laser with CO2, ruby laser Q among others. However, the results are not satisfactory.

CASE REPORTS

Case 01: Female patient, aged 36, skin phototype III, presenting facial melasma for more than 8 years which had begun after gestation. Dermatologic examination showed brownish macula on the malar region, bilateral, symetrical, on the dorsum of the nose and supralabial. The patient had been treating with hidroquinona (2%) for 5 years and reports progressive hyperpigmentation on the face for 4 years. (Picture 1).

Case 02: Female patient, aged 56, skin phototype IV, presenting for more than ten years greybrownish macula on the lateral region of the face with lesions showing depigmentation in the centre of the spot, confetti type. The patient reported that during 8 years she had had topic application with different clarifying creams, and that among those creams various had concentrations of hidroquinona varying from 2 to 6%. Initially, the patient presented discreet clarifying of the maculae, evolving lately to hyperpigmentation.

Case 03: Female patient, aged 58, skin phototype IV, presenting facial melasma for 22 years, using

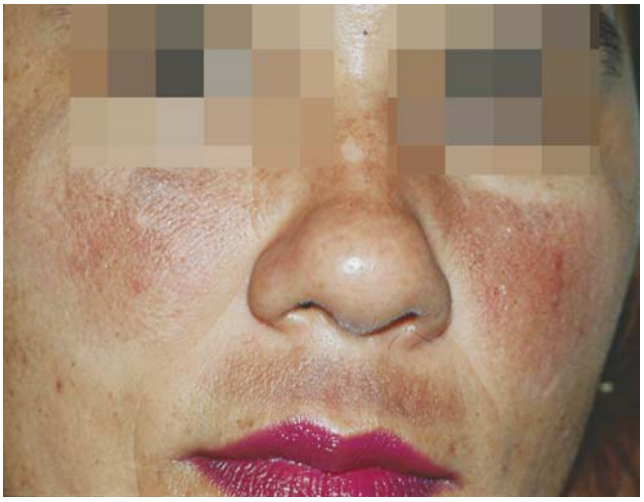

Figure 1: Brownish macule in the malar and supralabial regions and nasal dorsum

hidroquinona in concentrations that varied from 2 to 5% in the last 10 years, with good response at the beginning of the treatment. In the last 4 months, even using concentrations of hidroquinona of 5%, the patient reported worsening of hyperpigmentation. Her dermatological examination showed fuliginous blueish-black maculae on the lateral region of the face (bilateral) and on the forehead. (Picture3).

Case 04: female patient, aged 38, skin phototype III with facial melasma for 5 years, presenting brownish macula on the malar and lateral region of the face, symetrical and bilateral. The patient reported she had been using a facial cream containig hidroquinona in concentrations varying from 2 to 4% (Picture 4) for 3 years, presenting partial response

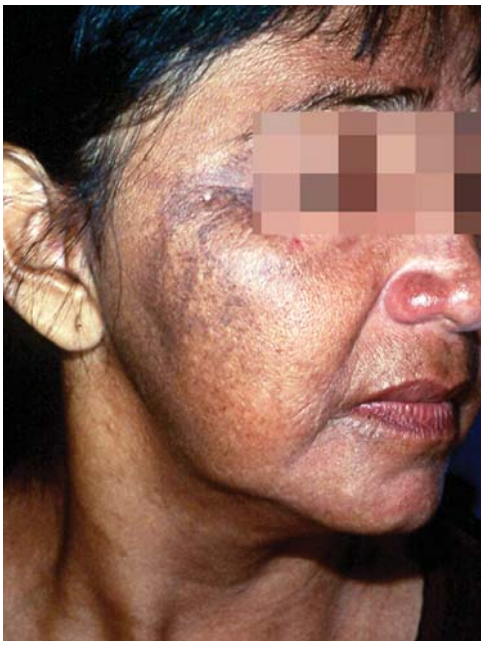

Figure 2: Brown-gray macule in the lateral region of the face with centered depigmented lesions, like confetti

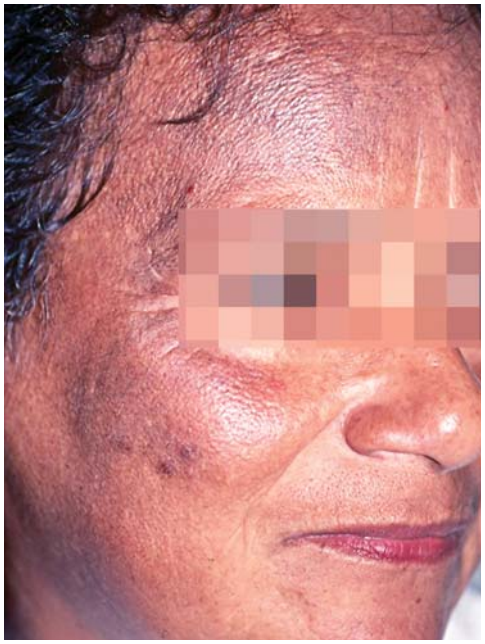

Figure 3: Fuliginous blue-black macule in the lateral region of the face and forehead

with frequent relapses without the use of the the clarifying formula. In the last 6 months she reported worsening of hyperpigmentation even though she was still in treatment.

DISCUSSION

None of the patients presented in this study had other complaint associated to facial hyperpigmentation as: arthralgia, alterations in the colour of urine, hyperpigmentation of sclera, axillae, sexual organs or articulations. The four patients had applications of formulations containing hidroquinona in various concentrations for long periods of time and referred to exposition to solar radiation without regular use of sunscreen. Histologic exam carried out in the four

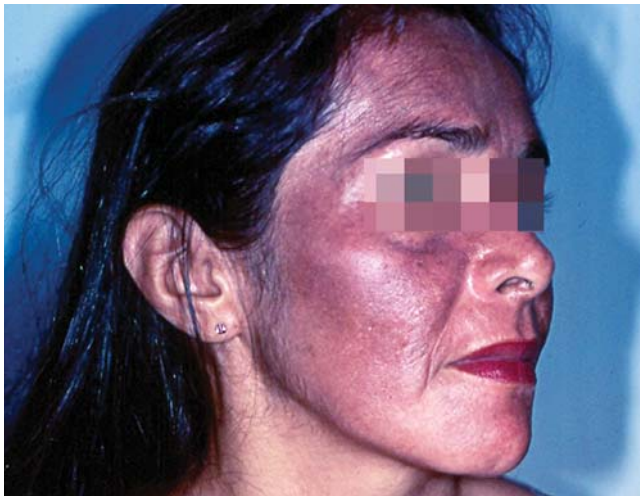

Figure 4: Brown macule in the malar region and lateral region of the face

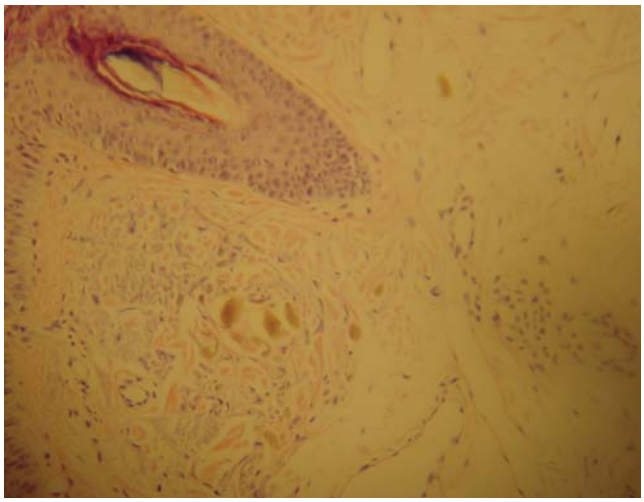

Figure 5: Ochronotic pigment in the dermis with basophilic degeneration (H&E 10x)

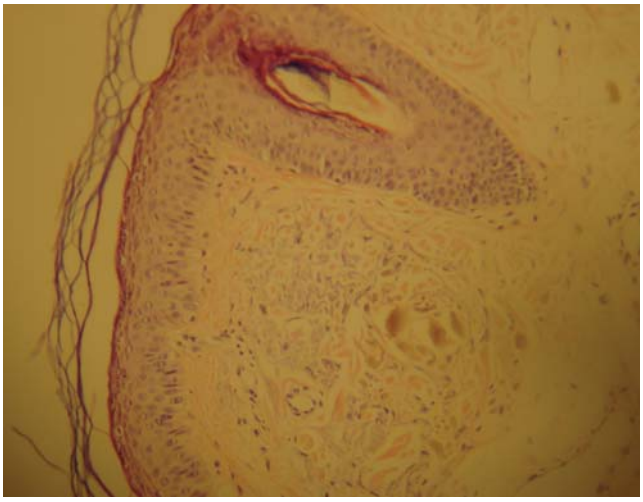

Figure 6: Ochronotic pigment in the dermis with basophilic degeneration (H&E 10x)

patients confirmed the presence of ochronotic pigment in the dermis confirming the diagnosis of exogenous ochronosis (Pictures 5 and 6).

The concentrations of hidroquinona used by patients varied from 2 to 6% and were used for long periods of time which is in accordance with data from the medical literature. The patients had not been warned about the possibility of this adverse effect and it took a long time to have a final diagnosis. If we consider that inumerous formulations containing hidroquinona in various concentrations are commercialized without medical prescription it should be expected to have the report of many more cases of ochronosis. The apparent subnotification might be happening as a result of the permissiveness in the use of medication without medical prescription, due to the fact that patients are not warned about the possibility of such adverse effect and as a consequence of the diffilcuty in making a differential diagnosis with the melasma.

It is suggested that dermatologists should be attentive to the possibility of these diagnoses in refractory cases of melasma; that they should adequately inform the patients about the adverse effects of medication and make suggestions to the health authorities to stablish policies for better control of the use of the product in a similar way they have done for the control of the use of retinoids. ❑

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