



Medical Case Report

IDIOPATHIC VARIANT OF SKIN OCHRONOSIS

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ABSTRACT

The formally accepted meaning of the term ochronosis is musculoskeletal and skin manifestation of alkaptonuria. Additionally, exogenous ochronosis has been reported following long-term application of skin-lightening creams, which contain hydroquinone, phenol or resorcinol. It exclusively affects black individuals, particularly in South Africa, but with an increasing number of reports on a worldwide scale.

We describe a 57-year-old female patient with a 3-year history of asymptomatic, dark-brown macules on the skin of the eyelids and the malar regions. Histopathological examination of HE sections revealed light to dark-brown granules presenting as free bodies, which were mainly situated in the papillary dermis. Despite the very detailed history, taken from the patient, it was impossible to identify any exogenous cause for her condition. The investigation of blood and urine samples excluded alkaptonuria. On the basis of the presented data we propose the existence of an idiopathic variant of skin ochronosis. This presents with a negative for precipitating factor patient history, monomorphic lenticular macular lesions and brown granules in the papillary dermis without close association with collagen fibres and easily stained black with methylene blue. Our results may expand the aetiopathogenesis as well as the clinical and histopathological spectrum of this irreversible disfiguring cosmetic problem.

Key words: skin ochronosis, idiopathic form

INTRODUCTION

Exogenous ochronosis is a condition characterised by hyperpigmentation of the skin, usually over the malar regions, secondary to the use of bleaching creams containing hydroquinone, phenol or resorcinol. It affects exclusively black individuals particularly in South Africa, but with an increasing number of reports from all over the world. Histopathologically it presents with a collection of yellowish-brown granules in the papillary dermis (2).

Most of the reports describe exogenous ochronosis as a secondary effect resulting from the application of skin-lightening products (3-7). Clinical cases of ochronosis following treatment with antimalarials have also been reported (8). Furthermore, Dupre et

al. (5) describe the same condition after exposure to benzenoid substances.

We present a patient with clinical and histopathological evidence for skin ochronosis, which has no apparent cause. We discuss the possible existence of a new, idiopathic type of this disorder.

CASE REPORT

A 57-year-old female patient visited the University Dermatology Clinic in Stara Zagora in April 1997. She presented a 3-year history of asymptomatic, dark-brown spots on the skin around the eyes. Apart from very rare episodes of high blood pressure in the last seven years, which had been treated with Nifedipine, her medical history was unremarkable. There was no family history of abnormal mucocutaneous pigmentation and gastrointestinal polyposis. The patient denied having used skin-lightening creams or taking antimalarials. She was a schoolteacher and so had never been exposed to benzenoid

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substances.

Physical examination of the skin revealed multiple dark-brown lenticular macules (1-3 mm in diameter) located symmetrically on the skin of the eyelids and the malar regions.

Close inspection of the uninvolved skin and the eyes, as well as the oral, vulvar, vaginal and perianal mucosa showed no changes. Blood and urine tests were all normal. X-ray examination of the bones and the large joints did not display any abnormalities.

Histopathological examination of HE sections revealed light to dark-brown granules presenting as free bodies mainly situated in the papillary dermis (**Figure 1**). Masson-Fontana staining, a specific staining for melanin, showed no increase of the pigment in the basal cell layer and did not change the colour of the granules. These particles, not bleached by 10% H₂O₂, stained black in methylene blue.

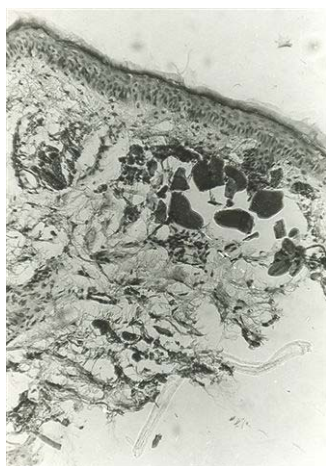


Figure 1. Light to dark granules presenting as free bodies situated in the papillary dermis - HE.

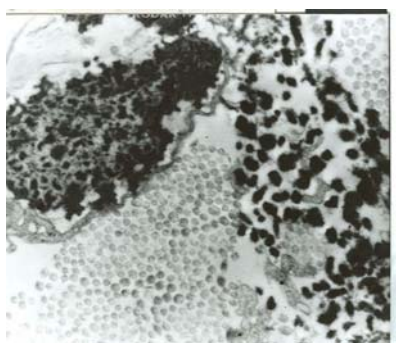


Figure 2. Dark non membrane-bound granules localised in extracellular space – Magnification x 12 000.

Electron microscopically, the homogeneous smaller-sized deposits tended to associate into larger non membrane-bound bodies (**Figure 2**). No pathological changes were observed in

the adjacent structures of the skin under the light and electron microscope.

COMMENT

It is generally accepted that ochronosis is the musculoskeletal manifestation of alkaptonuria which affects especially the large joints (1). The extra-articular involvement comprises ocular and skin pigmentations as well as genitourinary calculi and cardiovascular complications. This autosomal recessive inborn error of metabolism is due to deficiency of homogentisate 1, 2-dioxygenase (10).

In our patient, the laboratory evaluation of blood and urine samples revealed absence of alkaptonuria. Therefore, the endogenous nature of the disease was unlikely. Moreover, the haematogenous origin of the pigment in the case is excluded by the negative results from the bleaching test.

Additionally, exogenous ochronosis has been reported following long-term application of skin-lightening creams (3, 7), which contain hydroquinone, phenol or resorcinol (1). The disorder can also be caused by professional contact with benzenoid substances, glues, varnish, dyes and oral or intramuscular administration of antimalarials for treatment of malaria and connective tissue diseases (5, 8).

In spite of the very detailed history taken from the patient we were unable to identify any specific cause for this condition. The only cream she had ever used was a cosmetic product with cucumber extract not containing hydroquinone, resorcinol or phenol. The patient worked as a literature teacher, so was not professionally exposed to benzenoid substances, glues, varnish or dyes. She had never suffered from malaria or a connective tissue disease and had never taken antimalarials.

Jordaan and Van Niekerk (2) describe two clinical types of exogenous ochronosis. The mild one is characterised by coarsening and darkening of the skin while the severe one presents with caviar-like black papules and skin atrophy.

The clinical picture in our patient was monomorphic. We observed well-demarcated lenticular dark-brown macules on the skin of the eyelids and malar regions. Their surface was smooth and typical for the age-related small wrinkles and without coarsening. Caviar-like black papules and signs of atrophy were not found.

Most of the authors describe the typical histological picture with ochronotic collagen

fibres and eventual formation of ochronotic colloid milium (2, 4). A variable cellular infiltrate, which may be granulomatous is also observed. Besides, Jordaan and Van Niekerk report a transfollicular elimination of ochronotic fibres (2).

The histopathological findings in our case are characterised by the presence of abnormal brown granules in the papillary dermis without clear association with collagen fibres. It is unlikely that the particles are artefacts because we obtained two separate biopsy specimens for light and electron microscopy and these were present in both. On the other hand, Masson-Fontana staining revealed no increase in the melanin quantity. Therefore, the only possible explanation for the discoloration of the skin could be the presence of ochronotic pigment in the dermis. The latter suggestion is further supported by the characteristic black staining of the granules with methylene blue.

On the basis of the overall data presented in this study, we propose the existence of an idiopathic variant of skin ochronosis which can be characterised by a negative for precipitating factor patient history, monomorphic lenticular macular lesions and brown granules in the papillary dermis with no close association with the collagen fibres and typically stained in black with methylene blue. The results of the present study may further expand our knowledge about the aetiology of this condition and shed some new light on the clinical and histopathological spectrum of this irreversible disfiguring cosmetic problem.

REFERENCES

1. Braun-Faleo O, Plewig G, Wolff HH, Winkelmann RK. *Dermatology*, 4 ed. Berlin Heidelberg: Springer; 1991.
2. Jordaan HF, Van Niekerk DJ. Transepidermal elimination in exogenous ochronosis- A report of two cases. *Am J Dermatopathol*; 13:418-424, 1991
3. Howard KL, Fumer BB. Exogenous ochronosis in a Mexican-American woman. *Cutis*; 45: 180-182, 1990
4. Martin RF, Sanches JL, Gonzales A, Lugo-Somolinos A, Ruiz H. Exogenous ochronosis. *P R Health Sci J.*, 2:23-26, 1992.
5. Dupre A, Bonafe JL, Viraben R, Arque MT. Idiopathic pigmentation of the hands. Professional exogenous ochronosis? *Arch Dermatol Res.*, 266:1-9, 1979.
6. Lawrence N, Bligard CA, Reed R, Perret WJ Exogenous ochronosis in the United States. *J Am Acad Dermatol*, 18: 1207-1211, 1988
7. Hardwick N, Van Gelder LW, Van der Merwe CA, Van der Merwe MP. Exogenous ochronosis: an epidemiological study. *Br. J Dermatol*, 120:229-238, 1989
8. Bruce S, Tschien JA, Chow D. Exogenous ochronosis resulting from quinine injections. *J Am Acad Dermatol.*, 15:357-361, 1986.
9. Konttinen YT, Holkka V, Landtman M, Saari H, Santavirta S, Metsarinne K, Seegmeiller JE- Ochronosis: a report of a case and a review of literature. *Clin Exp Rheumatol*; 7:435-444, 1989
10. Granadino B, Beltran-Valero de Bernabe D, Fernandez-Canon JM, Penalva MA, Rodriguez de Cordoba S. The human homogentisate 1, 2-dioxygenase (HGO) gene. *Genomic*; 43:115-122, 1997.