Alkaptonuric ochronosis presenting as palmoplantar pigmentation

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Summary

We describe a 37-year-old woman who presented with palmoplantar pigmentation, thickening and pitting of 4 years duration. Bluish pigmented patches were seen over the sclera of her eyes. Her lumbar spine showed typical calcification of the intervertebral discs. Addition of Benedict's reagent to a urine sample of the patient gave rise to greenish brown precipitate and brownish black supernatant. Alkalinization of urine turned it black. A biopsy of the palmar lesion demonstrated irregular breaking up, swelling and homogenization of collagen bundles in the reticular dermis. Yellow-brown (ochre coloured) pigment was seen lying within the collagen bundles and also freely in the deeper dermis confirming our clinical diagnosis of alkaptonuric ochronosis. To the best of our knowledge this is probably the second report of alkaptonuria presenting with palmoplantar pigmentation.

Report

Alkaptonuria is a rare inherited disorder due to deficiency of the enzyme homogentisic acid oxidase (HGAO). As a result of this, homogentisic acid (HGA) accumulates in plasma. It is excreted in urine and is deposited as oxidized and polymerized melanin-like pigment in various tissues, mainly cartilage and skin.[1] The skin exhibits a blue-black discoloration most pronounced in sun-exposed areas, in regions of high sweat gland density and cartilaginous structures.[2] The cartilage of the external ear is typically affected and is frequently the first cutaneous site involved. We, however, have recorded a patient with alkaptonuria who presented with palmoplantar pigmentation, thickening and pitting.

A 37-year-old woman presented with asymptomatic progressive pigmentation of the palms, fingertips and soles for last 4 years and dull aching low back pain of 2 years duration. She also had pain in the knees and shoulders of 1 year duration. She denied the use of any topical or systemic substances that could be incriminated as a cause of the pigmentation. She was not aware of her urine leaving a black stain on drying on her undergarment but her cerumen was dark brown in colour. Her parents were not consanguinous and her past medical history was unremarkable.

Physical examination revealed greenish blue pigmentation of the thenar and hypothenar eminences and the fingertips of the hands (Fig. 1) and medial border of the heels, in a bilateral symmetrical pattern, which were associated with thickening and pitting. On close inspection, under bright light, a greenish pigmentation of the pinnae could be detected. Bluish pigmented patches over the sclera were seen in both eyes (Fig. 2). Otorhinolaryngological examination did not reveal any abnormalities. The remainder of the cutaneous examination including mucous membranes and nails was normal. Mobility of the lumbar spine was painful and restricted. Clinical examination of other joints and systems was within normal limits.

Routine haematological and biochemical profile of the patient was within normal limits. Radiography of the dorsolumbar spine showed typical calcification and narrowing of the intervertebral discs with minimal marginal osteophyte formation. Calcification of the supraspinatus tendon was also found. Ultrasonographic examination of the abdomen was normal. On exposure to air the urine darkened and became black; addition of Benedict's reagent produced a greenish-brown precipitate

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Figure 1 Greenish blue pigmentation of thenar, hypothenar eminences and tips of fingers.

and brownish-black supernatant (Fig. 3). Alkalinization of urine also caused it to become black. A biopsy specimen from the palmar lesion showed hyperkeratosis and hypergranulosis of epidermis. There was irregular breaking up, swelling and homogenization of the collagen bundles in the reticular dermis. Yellow-brown (ochre) coloured pigment was seen lying within the collagen bundles and also freely in the deeper dermis confirming our clinical diagnosis of alkaptonuric ochronosis.

Alkaptonuria is a rare metabolic disorder inherited as an autosomal recessive condition.[3] Its incidence in the population is 1 in 10 00 000 persons.[4] It is due to constitutional deficiency of the enzyme HGAO normally found in the liver and the kidney. This leads to the impairment of phenylalanine and tyrosine catabolism and accumulation of HGA in various tissues.[3] As these tissues appear ochre coloured on microscopy, Virchow called this disease, 'ochronosis' (from the Greek for 'yellow disease').[5,6] HGA in the urine is gradually oxidized on exposure to air and becomes black. This reaction can be accelerated by the addition of alkaline solution; hence the term 'alkaptonuria' was coined by

Figure 2 Bluish patch onthe sclera of the eye.

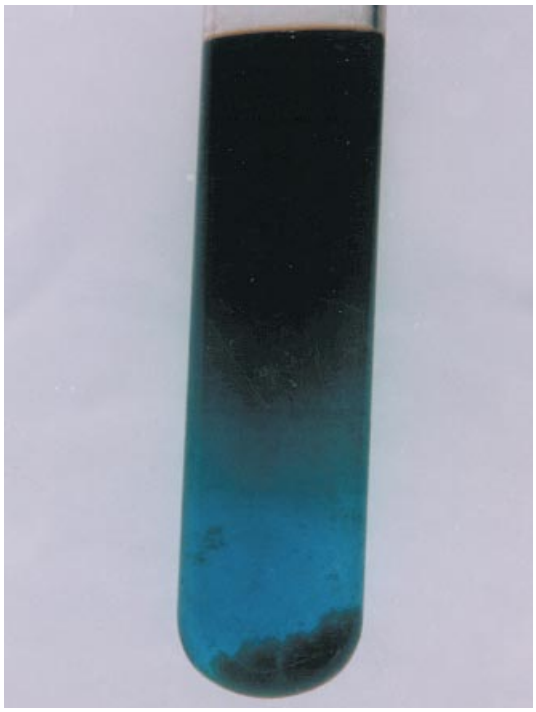

Figure 3 Demonstration of typical change in patient's urine with Benedict's reagent.

Boedecker in 1866.[6] Recently, the HGAO gene locus has been mapped to chromosome 3q(3q21-q23) by consanguinity and by linkage analysis.[3,4] A gene homologous to HGAO has recently been cloned from a fungal model for disorders in phenylalanine metabolism leading the way to cloning of the human gene.[7] This knowledge may provide better insight into the pathogenesis of alkaptonuria and might offer effective therapeutic approaches such as substitution therapy with recombinantly obtained HGAO.

The deposition of HGA-containing pigment in various tissues accounts for the clinical features and chronic progressive course of this disease.[1] Many of early manifestations of this disorder such as dark urine/cerumen (at birth), axillary pigmentation (at puberty), ear lobe skin pigmentation (at 20–40 years) and scleral pigmentation (at 20–40 years) may go unnoticed by the patient. This probably was the reason for late consultation of our case. At that age, our patient had developed palmoplantar pigmentation and arthropathy, which were responsible for bringing her to the hospital. We could trace out only one such case report in the literature with this type of presentation in alkaptonuric ochronosis.[8] Interestingly, that report was also from South India. The reason why alkaptonuric ochronosis manifested first in palms and soles could be due to lighter colour of these areas in dark skinned individuals and the generalized pigmentation being of faint nature and not being apparent through the dark skin of the usual sites such as forehead, cheeks, axillae and genitalia.[8]

Alkaptonuria invariably leads to some degree of arthropathy. It is due to pigment deposition in articular cartilage, joint capsules, tendons and ligaments.[2] Spondylosis accounts for the back pain and limited motion; spinal X-ray demonstrates striking calcification of the intervertebral discs. Rarely, alkaptonuria manifests as cardiovascular disease, renal and prostatic calculi and tympanic membrane involvement.[1] Despite multisystem involvement, this disorder is usually compatible with a normal life span and causes of death are comparable to those of the general population.[6]

The diagnosis, once suspected, can easily be confirmed by performing simple tests on urine. If facilities are available, specific enzyme tests and gas–liquid chromatography of HGA in urine may be performed.[3] Treatment is directed towards reducing connective tissue damage by ascorbic acid (an antioxidant) along with analgesics and physiotherapy for arthropathy.[1,3] A low protein diet limiting phenylalanine and tyrosine is not practicable but can be used intermittently.[3]

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