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Case Report

An Uncommon Clinical Presentation of a Rare Disease-Alkaptonuria: Case Report

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ABSTRACT

Palmoplantar pigmentation is a rare clinical presentation of alkaptonuria, a rare inborn error of phenylalanine and tyrosine metabolism. Alkaptonuria occurs owing to deficiency of an enzyme homogentisic acid oxidase inherited as an autosomal recessive disorder. We report a case of alkaptonuria, which presented with palmoplantar pigmentation pigmentary nail changes and the involvement of the spine and joints. He was advised of ascorbic acid along with symptomatic management and detailed counselling.

Keywords: Alkaptonuria, Endogenous ochronosis, Palmoplantar pigmentation.

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INTRODUCTION

The literature has described Unusual palmoplantar pigmentation as associated with various disorders, including peutz-jeghers syndrome, systemic lupus erythematosus, arsenical poisoning & chemotherapeutic agents.[1-2] Very few case reports on alkaptonuria present clinically as palmoplantar pigmentation.[3]

Alkaptonuria is also known as endogenous ochronosis, a rare disease inherited as an autosomal recessive disorder. The genetic mutation results in a deficiency of homogentisic acid oxidase, a key enzyme in the metabolism of phenylalanine/tyrosine.[4] This results in a buildup of homogentisic acid in various body tissues. The disease manifests as a classical triad of dark-coloured urine (homogentisic aciduria), blue-black pigmentation of the skin (ochronosis) and precocious degenerative arthropathy.[5]

At this moment, we report a case of endogenous ochronosis (alkaptonuria), which was referred to our department of dermatology for evaluation of abnormal palmoplantar pigmentation.

CASE REPORT

A 58-year-old male patient was referred to our skin department complaining of progressively increasing bluish-black pigmentation of his palms and soles for the last twenty-two years. The pigmentation started as a small patch on the right index finger, which progressed over time to involve both palms and soles. It was also associated with blackish discolouration of nails, ears and eyes. He also developed progressively worsening backache and knee pain for the last four years and became so handicapped that he was unable to walk for the last six months. On further questioning, he also gave a history of dark-coloured urine, which he first noticed in his early twenties. There was no significant history of any long-term medication other than painkillers, which he used off and on for his aches and pains. His parents had a cousin marriage, but all his siblings and children were unaffected.

On examination, blue-black discolouration was present on his palms and soles bilaterally, more on his palms than on soles (Figures-1a and 1b), and blue-black pigmentary changes were also observed in the nails of his hands and feet (Figures-2a and 2b).

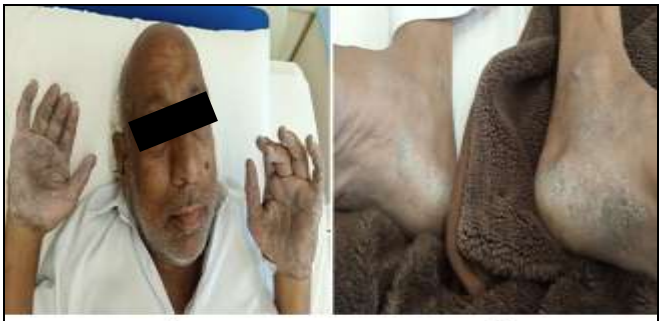

Figure-1: Blue-black Pigmentation of (a) Palms (b) Soles

Marginal thickening of hands (acrokeratoelastoidosis) was also observed bilaterally. Brown-black discolouration (Osler's sign) was present in the sclera of both eyes (Figure-3). Nodular thickening, along with blackish discolouration, was present in both ears. The patient was unable to stand, and there were visible deformities in both knee joints. His chest expansion was normal, and no abnormalities were found on auscultation of his heart and lungs.

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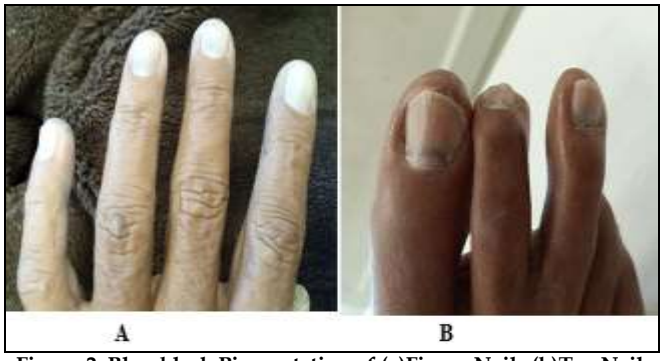

Figure-2: Blue-black Pigmentation of (a)Finger Nails (b)Toe Nails

Figure-3: Brownish-black Discoloration of Sclera (Osler's Sign)

His full blood count and routine blood biochemistry, i.e. renal function tests, liver function tests, serum calcium and phosphate, were within normal limits. His ECG, 2D echocardiogram, and abdomen ultrasound were also unremarkable. His urine turned brownish-black on prolonged standing (Figure-4).

Figure-4: Darkening of Urine on Standing

A radiological examination of his supine showed marked osteoporosis, multiple intervertebral disc calcifications, syndesmophyte formation & narrowing of multiple disc spaces (Figures-5a & 5b).

Based on the classical clinical and radiological presentation and dark discolouration of urine, he was diagnosed with endogenous ochronosis (alkaptonuria), so further testing was not performed partly to avoid patient discomfort and partly due to our laboratory restraints. He was advised oral ascorbic acid supplementation along with symptomatic management and detailed counselling.

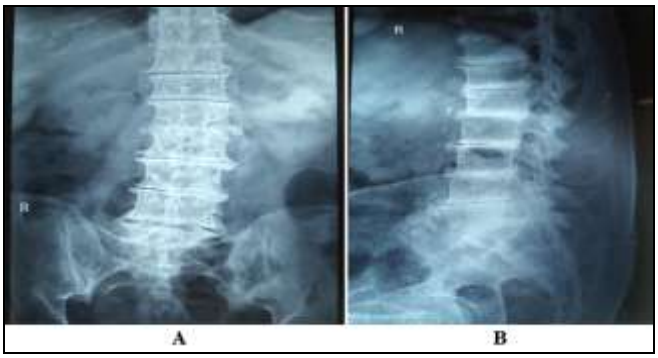

Figure-5: Radiographic Images of Spine (a) Antero-posterior View (b) Lateral View

DISCUSSION

Alkaptonuria (endogenous ochronosis) is a rare autosomal recessive hereditary disorder resulting in abnormal metabolism of phenylalanine/tyrosine. This occurs due to a deficiency of the enzyme homogentisic acid oxidase.[6] The disease has a worldwide incidence of 1:250000 live births, predominantly occurring in Czechoslovakian and German populations. Very few cases of alkaptonuria have been reported from Pakistan.[7]

Alkaptonuria was originally defined by Archibald Garrod in his famous Croonian Lectures in 1908. The enzyme deficiency was identified in 1958 by La Du *et al.* Mapping of the gene responsible for the disease was done by Pollak *et al.* to chromosome 3q2.[8] Mutation in the gene results in deficiency of the enzyme homogentisic acid oxidase, accumulating homogentisic acid in various fibrocartilaginous tissues of the body and excretion of excessive amounts of the same in urine.

Homogentisic acid is deposited intracellularly and extracellularly, oxidising to benzoquinone acetate, which polymerises into the melanin-like polymer. Deposition of these polymers can be seen on histopathology as dark yellow (ochre) coloured acellular, often banana-shaped deposits, hence named ochronosis.[9]

Patients of alkaptonuria mostly remain asymptomatic during the early years except for the darkening of their urine on standing (occurring due to oxidation of excessive homogentisic acid). Dark urine stains on diapers or dark discolouration of urine-soaked

clothing on washing with detergents are usually the first signs of disease in childhood. Other than this, most individuals remain symptom-free till the early third to fourth decade of life.

One of the earliest signs is brown-black pigmentation of the sclera, especially near the insertion of the lateral rectus muscle, called Osler's sign. Slate-grey to blue-black pigmentation of the skin of the face, ears, nose, hands and feet is usually seen in the fourth decade of life. Skin pigmentation is more pronounced on sun-exposed sites. Less common pigmentation of palms, soles and genitalia has also been described in the literature, as was the case with our patient.[10] Bluish discolouration of mucosae and pigment of tendons have also been observed in alkaptonuria patients.

The most troublesome feature of the disease is ochronotic arthropathy, which mostly appears after the fourth decade of life. This involves weight-bearing joints of the spine, knees and sometimes shoulders. With the advancement of age, arthritis occurs in almost all individuals affected with the disease, and it is the most disabling condition in these patients. The disease may rarely affect heart valves, endocardium, coronaries or aortic intima. Heavy depositions can also occur in the tracheobronchial tree, larynx or oesophagus, resulting in dysphagia or hoarseness of voice.

Diagnosis of the disease is usually clinical. However, different tests can be performed for diagnosis, including alkalisation of urine, skin biopsy for histopathology and radiographic imaging of the spine, joints and chest. Measurement of homogentisic acid levels in blood or urine using enzyme spectrophotometry or gas-liquid chromatography is confirmatory. Screening for mutations can done through genetic testing using polymerase chain reaction technique after DNA extraction from whole blood.

No effective treatment is available for alkaptonuria. Dietary restriction of phenylalanine and tyrosine, along with oral vitamin C (ascorbic acid) supplementation in a dose of 1gm/day, is the mainstay of treatment. Dietary advice includes reduced intake of meat, milk, poultry, eggs, cheese, and nuts.

Nitisinone, a herbicide and inhibitor of 4-hydroxyphenylpyruvate dioxygenase, has recently been used to treat alkaptonuria. It inhibits the synthesis of homogentisic acid and has been shown to reduce its urinary excretion in diseased individuals. However, its long-term efficacy and safety still need to be fully understood, which needs further long-term studies.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

YAAQ: Conception, study design, drafting the manuscript, approval of the final version to be published.

NAM: Data acquisition, study design, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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