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Case Report

Skin pigmentation, a window to diagnose Alkaptonuria: a very rare entity

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ABSTRACT

Alkaptonuria (AKU) or endogenous ochronosis is a very rare inborn error of tyrosine metabolism inherited by autosomal recessive mode. There is complete absence of homogentisic acid oxidase enzyme which results in accumulation of homogentisic acid in cartilaginous connective tissue thus produces ochronotic clinical manifestations. Here we reported a 36 year old woman with bluish pigmentation of pinnae, index fingers (lateral aspect), nails, teeth and sclera. Detailed clinical and investigative workup was done to diagnose patient. Skin biopsy showed changes of ochronosis and urine examination revealed detectable level of homogentisic acid. Classical ocular findings, ochronosis on clinical and HPE and positive urinary tests for homogentisic acid confirmed the diagnosis of alkaptonuria. The highlight of our case is that an asymptomatic patient was detected early by ochronosis prior to development of musculoskeletal or cardiac complications.

Keywords: Aciduria, Alkaptonuria, Homogentisic, Ochronosis

INTRODUCTION

Alkaptonuria was described by Garrod in his Croonian lectures of 1908 as an inborn error of tyrosine metabolism. It is a progressive disease characterized by a classical triad of dark urine since birth, ochronosis becoming evident around fourth decade and osteoarthritis of major joints developing around sixth decade of life.[1]

The interesting fact about this disease is that it was identified in 1500 BC in an Egyptian mummy (Harwa) but the first original description was published by Rudolph Virchow in 1866.[2] Further it is one of the first condition in which mendelian recessive inheritance was proposed and described under the heading of 'Inborn errors of metabolism'.[3] The reported incidence of AKU is one in 250,000 to 1: 1000000 all over the world. But this disorder is relatively common in Slovakia where incidence is 1 in 19000.[4] AKU is caused by mutation in gene on chromosome 3q2 coding for homogentisate-1, 2-dioxygenase (HGO) enzyme of tyrosine/phenylalanine catabolic pathway.[5]

Deficiency of this enzyme results in accumulation and deposition of homogentisic acid and its oxidation product (benzoquinone acetate) in cartilaginous connective tissue. Dark pigmentation of the skin, sclera and nails along with osteoarthritis and cardiac involvement are the main complications of AKU.[6] Diagnosis of AKU is made by collaboration of clinical manifestations, HPE and further confirmed by detection of homogentisic acid in urine by qualitative or quantitative biochemical tests.

CASE REPORT

A thirty-six-year-old woman presented with complaints of change in skin color of both ears and index fingers (lateral aspect) for a period of one year. There was no history of similar complaints amongst her parents, siblings or offsprings. Further patient didn't reveal any other systemic problem or any history of topical or systemic drug intake. On physical examination, her vitals were normal. Dermatological examination revealed diffuse bluish pigmentation of both ears (conchae) (Figure 1) and lateral aspects of index fingers. Bluish dots were also noticeable on visible sclera (Figure 2) of both eyes in a symmetrical fashion.

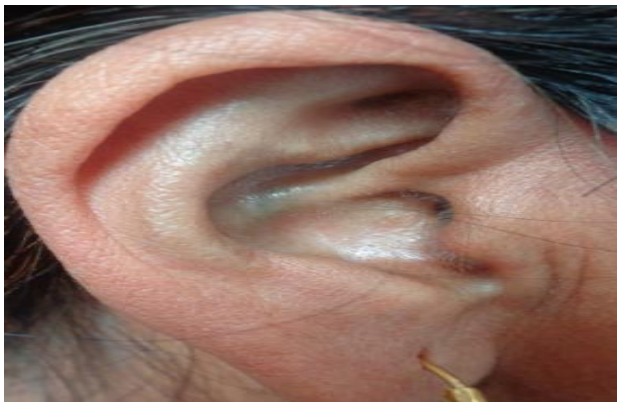

Figure 1: Bluish- grey discoloration of ear cartilage visible over concha.

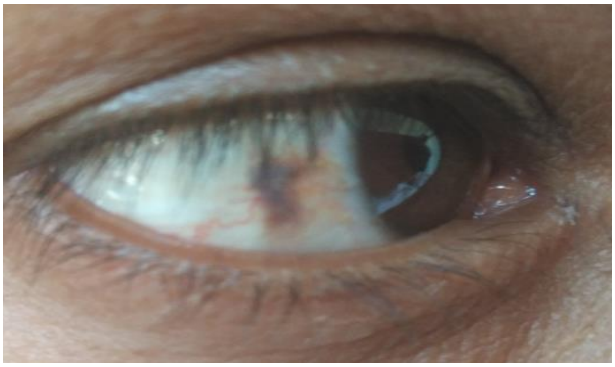

Figure 2: 'Osler sign' showing dot like bluish pigmentation of visible sclera.

Slit lamp examination showed brownish deposits of same pigment over cornea and conjunctiva. Patient's teeth and nails were found discolored, while her oral and genital mucosae were normal in color. Musculoskeletal and gross systemic examination didn't reveal any relevant findings.

Routine investigation and radiological evaluation (X-rays of chest, knee, ankle joints and lower back, echocardiography for cardiac involvement and ultrasonography for genitourinary stones) were performed to look for systemic ochronosis but they were unremarkable. Patient's urine was found normal straw colored immediately after voiding but when examined after twenty-four hours of exposure to air, it had changed into cola color (Figure 3). Histopathology of biopsy specimen from affected finger showed features of ochronosis in the form of thick compact horny layer, moderately sclerotic upper dermis along with several yellow coloured structures surrounded by thickened collagen (Figure 4).

Figure 3: Change in colour of urine from normal straw colour to cola color after 24 hours of standing.

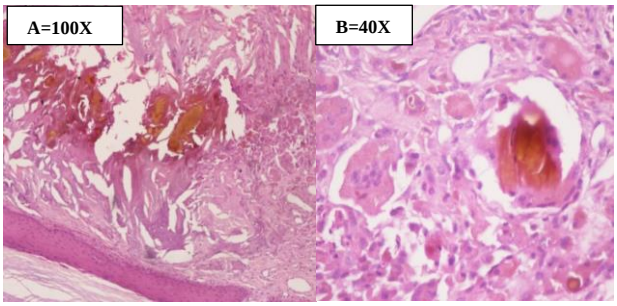

Figure 4 (A and B): Yellow- brown pigment deposits surrounded by thick collagen and giant cell reaction in dermis on hematoxyline and eosin staining.

To confirm our diagnosis urine sample of the patient was sent to detect homogentisic acid by various qualitative and quantitative tests. Sunlight standing test, alkaline test, ferric chloride test, silver nitrate test and benedicts test showed positive results and simultaneously homogentisic acid levels were detected in urine by chromatography. Patient was started on ascorbic acid 1000mg daily in two divided doses and asked for annual follow up examination for cardiac and musculoskeletal problems.

DISCUSSION

AKU is a very rare autosomal recessive disorder known by different nomenclatures like "black urine disease, black bone disease and endogenous ochronosis" due to its variable clinical manifestations. In 1859 Boedecker used the term 'alkapton' (alkapton means substance having high affinity for alkali) for reducing substances found in patient's urine, which later on identified as homogentisic

acid by Wolkow and Bauman in 1891.[7] La Du et al identified the deficient enzyme in 1958, while Pollak et al located the mutated gene on 3q2 chromosome.[8] So far 67 genetic missense mutations of AKU gene have been identified.[9] This metabolic disorder is prevalent worldwide, with case reports from USA, UK, Germany, Lebanon, Sudan, Saudi Arabia, Pakistan, Turkey and India.[10] As per literature 626 cases has been reported from all over the world till 2011.[11] Cases reported from India are very few in number and their exact number is not known as data reveal only isolated case reports sporadically. Although seven cases of AKU were reviewed by Parikh et al, over a period of six years at genetic clinic in Mumbai.[12] In AKU there is complete absence of homogentisic acid oxidase oxidase (HGAO) enzyme, which converts HGA into maleyl acetoacetate and benzoquinone acetoacetic acid (Figure 5). Thus HGA and benzoquinone acetic acid accumulates and have high affinity for cartilaginous connective tissue.

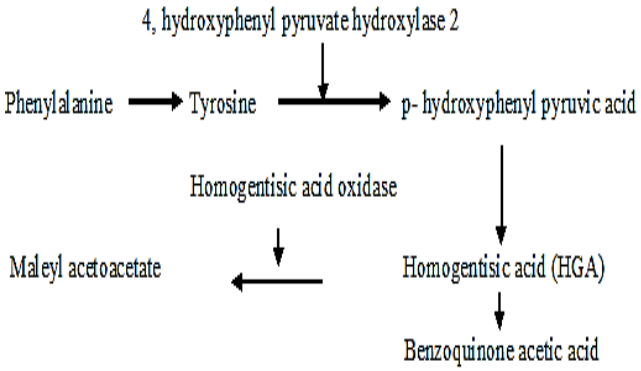

Figure 5: Phenylalanine/tyrosine catabolic pathway.

AKU- Homogentisic acid oxidase enzyme is absent Nitihistone- Blocks 4, hydroxyphenyl pyruvate hydroxylae 2, thus decrease HGA but elevate level of tyrosine and phenylalanine which can be toxic to our body.

The auto-oxidation and polymerization of HGA in connective tissue is an irreversible process which not only stains tissues with ochre color (so known as endogenous ochronosis) but also initiate the process of degeneration and dystrophic calcification. HGA levels are not detectable in blood as it is rapidly excreted in urine where it is colorless but it rapidly oxidizes to black and brown pigments on exposure to air or after addition of alkali. Therefore, urine appear normal on voiding but turns brown black on standing, but sometimes if urine is strongly acidic it doesn't change color even after long hours of standing. This is one of the reasons to explain that only 20% of cases of AKU are diagnosed in infancy by homogentisic aciduria, while 80% have delayed presentation in adulthood with ochronosis.[13]

Earliest sign to suspect AKU is staining of diapers in infancy after exposure to air, while in childhood and early adulthood disease is quiescent so remain undetectable. Symptoms of ochronosis become evident and gradually progressive after the age of thirty years.[7,13] They commonly manifest in skeletal, cardiovascular, genitourinary, cutaneous and ocular systems. Air exposed and thinned cutaneous sites like cheeks, forehead, earlobes, axilla and genitalia develop blue to grey pigmentation.[14] Teeth, nails, oral and genital mucosa may also show dusky discoloration.[15] In third and fourth decade almost all patients start to develop symptoms of ochronotic arthropathy resembling to osteoarthritis or to rheumatoid arthritis. Till the age of 50 years approximately 50% of the patients have undergone at least one joint replacement.[13] Earliest symptoms appear in major weight bearing joints and lumbar spine is most commonly affected.[16] Involvement of small joints of hands and feet is rare and sacroiliac joint is usually spared. Clinically arthritis is most common presentation but patient can develop ligament/tendon rupture, joint stiffness, deformity and disabilities.[17] Radiographic evaluation reveals calcification, joint/disc space narrowing, osteoporosis and osteophytosis (characteristically in lumbar spine). Universal calcified discs and osteoporosis in young individuals is the pathognomic X- ray change seen in AKU.[9] Proposed mechanisms implicated in pathogenesis of ochronotic arthropathy include chemical irritation by HGA and its oxidation products, disturbed metabolism of chondrocytes and alteration of cross linkage of collagen fibrils.

Involvement of cardiovascular system is common and primarily the ochronosis of aortic and mitral valve is seen.[18] Incidence of valvulitis, stenosis and dystrophic calcification due to ochronosis is quite high. Although cardiac ochronosis is a benign disease but myocardial infarction is leading cause for mortality in patients of AKU.[19] In respiratory system, ochronotic pigment is deposited in laryngeal, tracheal and bronchial cartilage. Hoarseness and dyspnoea are initial symptoms but end result is restrictive lung disease due to irreversible fibrosis of cartilages. In genitourinary system, other than homogentisic aciduria, HGA accumulation can results in renal, urinary bladder and prostatic calculi.[20] At least two third patients of AKU can have ocular ochronosis but it doesn't affect vision. Scleral pigmentation oftenly referred as 'Osler sign' is most common and most prominent finding.[21] While pigmentation of cornea at limbus also known as corneal 'oil drops' is less frequent but pathognomic sign of ochronosis.[22]

AKU is a close mimicker of exogenous ochronosis due to various drugs and chemicals like phenol, hydroquinone, quinine, hydroquinone, anti- malarials, minocycline and methyl- dopa.[23] Homogentisic aciduria and systemic ochronosis is absent in exogenous ochronosis. The distinction between two is necessary because management and prognosis of both conditions is quite different. Some of the screening tests which can be performed in suspected cases of AKU and their family

members include: [24] 1) Alkali test- on addition of NaOH to urine, it turns black. 2) Ferric chloride test- transient green color is noticeable. 3) Ammonical silver nitrate test-forms black precipitate of silver. 4) Benedict's test-shows black supernatant and red brown precipitate of cuprous oxide at the bottom. 5) N-butane test-pink brown color is formed. However, the gold standard test is to detect homogentisic acid in urine by enzymatic spectrophotometer /gas liquid chromatography or by high pressure liquid chromatography.[25] Other investigations which can detect systemic ochronosis include: simple radiography of spine and major joints which can identify degenerative arthropathies. Further radiographs and ultrasonography can also pick up kidney stones. Magnetic resonance imaging can show thickening of Achilles tendon. CT and echo-cardiographic studies can reveal vascular calcifications and cardiac valve defects respectively.

Currently there is no definitive cure for AKU and most of the treatment modalities are symptomatic. Diet low in tyrosine/phenylalanine has been recommended to delay the joint ochronosis. Vitamin C (an anti-oxidant) in doses of 500mg twice a day can reduce connective tissue damage by altering the polymerization of HGA.[26] However no clinical studies have shown the long-term efficacy of above two measures. Ochronotic arthropathy needs rest, physiotherapy, and analgesia. Surgical intervention in the form of joint replacement may be required in advanced disease. Nitihistone, a triketone herbicide is a newly proposed drug for AKU. It is a potent blocker of 4-hydroxy- phenyl-pyruvate dioxygenase which inhibit production and excretion of HGA but indirectly raises body levels of tyrosine/phenylalanine.[27] Although nitisinone is approved by the Food and Drug Administration for the treatment of tyrosinemia type I but long term studies are required to prove its safety and efficacy in alkaptonuria.[28] As the gene responsible for AKU has been identified, gene replacement therapy is a potential upcoming treatment for AKU.[29] Although AKU inevitably progress to ochronosis and ochronosis to degenerative arthritis but overall prognosis is good as life span of alkaptonurics is comparable to general population. We can help our patients by doing active surveillance for cardiac, renal and musculoskeletal complications after fourth decade of life by advising annual follow up examinations.

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