Int.j.pathol.2017; 15(1)26-30

Case Report

An Unusual Case of Pigmentation of Face and Hands

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Abstract: Alkaptonuria is a rare metabolic disorder caused by deficiency of homogentisate dioxygenase; which leads to deposition of homogentisic acid which gets deposited in connective tissue as a melanin like pigment. We had a female patient who presented to us with abnormal pigmentation on her face and hands which was not cosmetically acceptable to her. Upon exploring, she had a history of darkening of urine. Her skin biopsy demonstrated fragmented collagen and deposits of pigment in connective tissue. Subsequently she was found to have high levels of homogentisic acid in urine. We recommend that every case of abnormal hyperpigmentation should be looked for the possibility of alkaptonuria.

Key Words: Alkaptonuria, Pigmentation, Ochronosis

Introduction

The word 'Alkaptonuria (AKU)' has its origin from the Arabic word alkapton for "alkali" and Greek word "to suck up oxygen greedily in alkali" based on the observation that the urine becomes black on standing when it becomes alkaline[1]. AKU is an autosomal recessive condition[5]. HGD is the only gene associated with it and it encodes homogentisate 1,2-dioxygenase. Mutations in it leads to deficiency of homogentisate 1, 2-dioxygenase, an enzyme that converts homogentisic acid (HGA) to maleylacetoacetic acid in the tyrosine degradation pathway[4]. Some of the excess HGA excretes through the urine which turns dark on exposure to oxygen or alkalization occurs. Rest of accumulated HGA oxidizes initially, and subsequently gets deposited within the connective tissue irreversibly as a melanin-like pigment[7].The incidence is approximately 1:250,000 to 1:1,000,000 live births[7]. It is increased in certain countries including the Dominican Republic and Slovakia[3].

The three major features of alkaptonuria are the presence of HGA in the urine, ochronosis and arthritis[2]. Patients usually are asymptomatic in childhood[3]. Ochronosis is a term used to describe the darkening of tissues due to accumulation of HGA and its metabolites and commonly develops after age 30[5].

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Manifestations include blue or brown pigmentation, which starts with ears and sclerae. Then it may involve the nose, cheeks, forehead, extensor surfaces of hands, axillary and inguinal areas. Perspiration can stain clothing. Arthritis often manifests as lower back pain due to involvement of spine and may lead to kyphosis. Intervertebral disc calcification may be seen. Larger joints such as the hips, knees, and shoulders are sometimes involved. Alkaptonuria also may cause cardiac valvular disease and coronary artery disease and lead to an increased incidence of myocardial infarcts. They also have a higher incidence of renal and prostatic stones[3]. Homogentisic acid levels are elevated in the blood, urine, and tissue specimens in alkaptonuria. So diagnosis is confirmed by measuring urine homogentisic acid levels[3].

Treatment is mainly centered on symptomatic care and may include administering analgesics, ascorbic acid, diet restrictions or surveillance. As disease progresses, invasive procedures such as joint surgeries or organ transplantations may be recommended. Physiotherapy and lifestyle counseling are also important[5].

Case Report

A 35-year-old lady presented to us for cosmetic reasons with unusual pigmentation on face and hands. These asymptomatic bluish grey papules were present for past 3 years. They started as small papules on malar area of both cheeks and later on involved dorsum of hands. There was no pigmentation in sclerae. She also suffered from low back pain and stiffness for past 10 years. She also

mentioned pain in right hip joint for last 1 year. Upon specific inquiry, she told that she has noticed blackish discoloration of her urine on standing for a past few years. She is the only sister of three brothers but there was no history of similar findings in any of them or her parents. Dermatological examination revealed firm, non-compressible, non blanchable bluish grey papules on nasal bridge and malar areas of cheeks (figure 1). Bluish tinge of auricular cartilage is also noted at concha, triangular fossa and antihelix of ear (figure 5). On hands, blue linearly arranged hyperkeratotic papules were found on thenar and hypothenar eminence, radial and ulnar borders of thumbs and index fingers (figure 3 & 4). Firm non compressible bluish papules also located on medial part of dorsum of hands (figure 2). Rheumatological examination of spine demonstrated reduced forward flexion of spine..

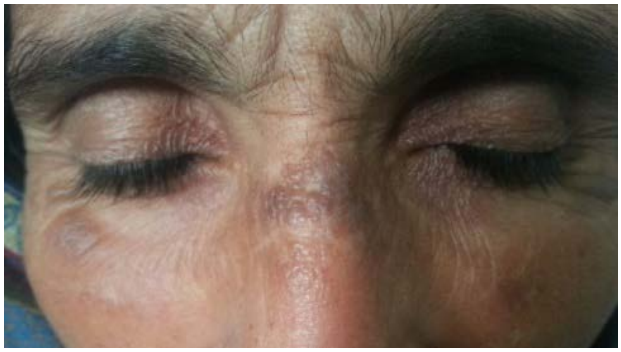

Figure-1: Bluish pigmentation of nasal bridge and malar areas

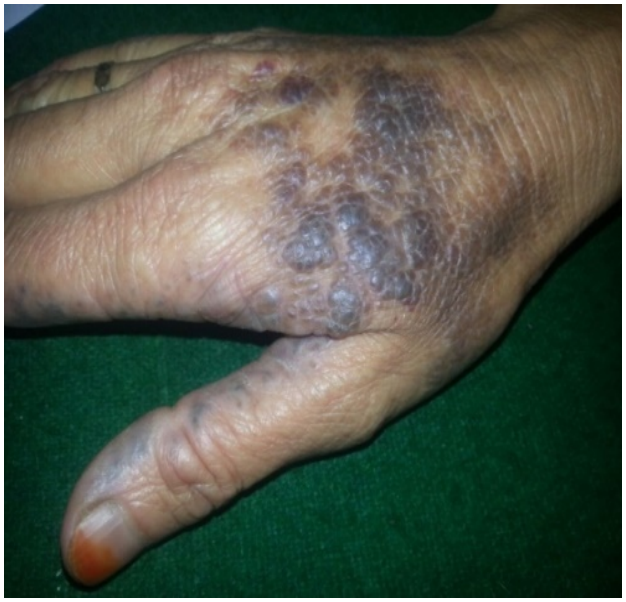

Figure-2: bluish papules on dorsum of hands

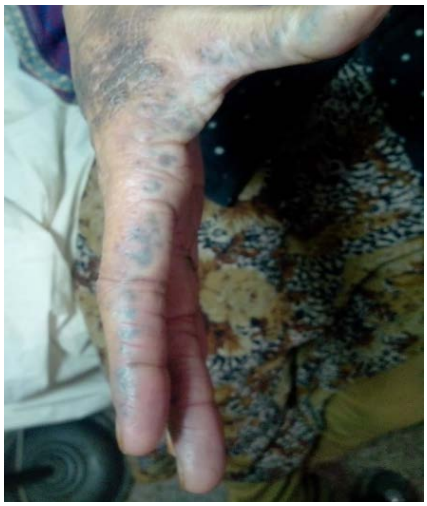

Figure-3: Linear blue hyperkeratotic papules on sides of fingers and thumbs

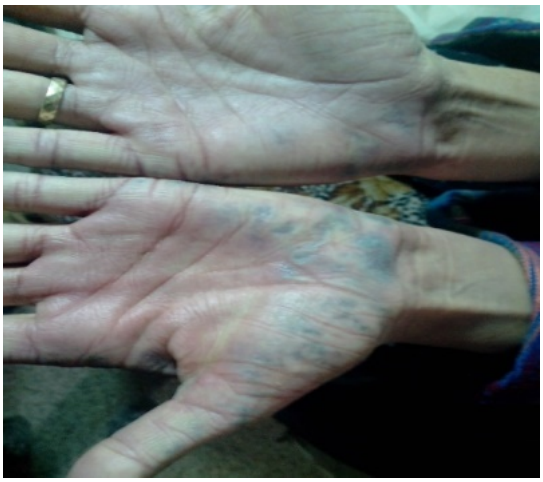

Figure-4: Blue hyperkeratotic papules of thenar and hypothenar eminence

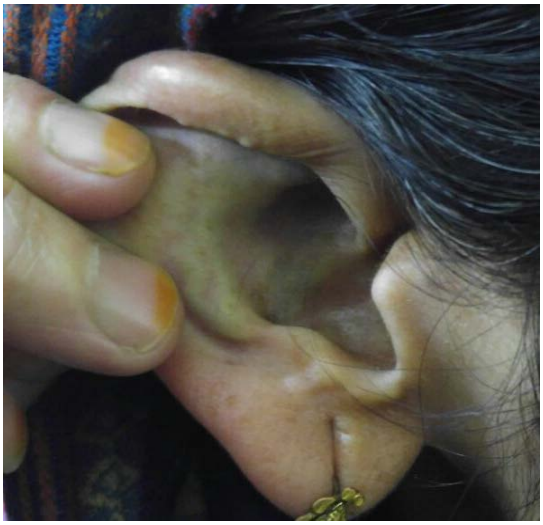

Figure-5: pigmentation of auricular cartilage

Her blood counts and metabolic profile was normal. Urine was negative for reducing sugars. Her echocardiography also turned out to be normal. X rays of both hip joints were also normal but X ray of her thoracolumbar spine showed intervertebral disc calcification at multiple levels with disc space narrowing. Straightening of spine is also noted (figure 6)

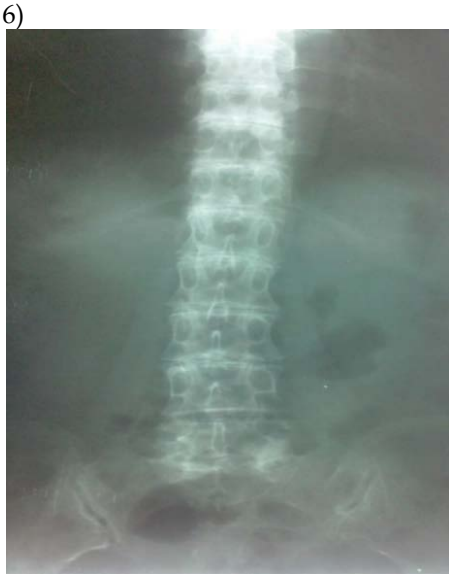

Figure 6: X ray of thoracolumbar spine showing calcified discs

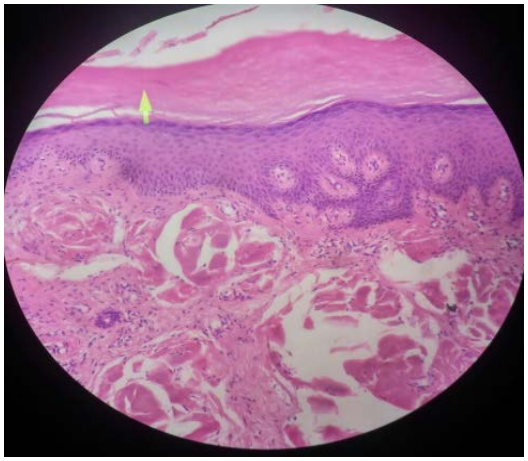

Figure 7: The skin biopsy showing hyperkeratosis (arrow), degeneration & fragmentation of collagen in dermis. Empty spaces represent deposition homogentisic acid (H&E X100)

Her skin biopsy revealed significant dense hyperkeratosis, no para keratosis, mild focal atrophy as well as focal acanthusis. There was significant fragmentation and degeneration of collagen with frequent empty areas representing deposits of homogentisic acid. Also focal typical yellow brown pigment deposition is seen at a few places in the collagen bundles. No increase in melanin or melanocytes is seen (figure 7 & 8)

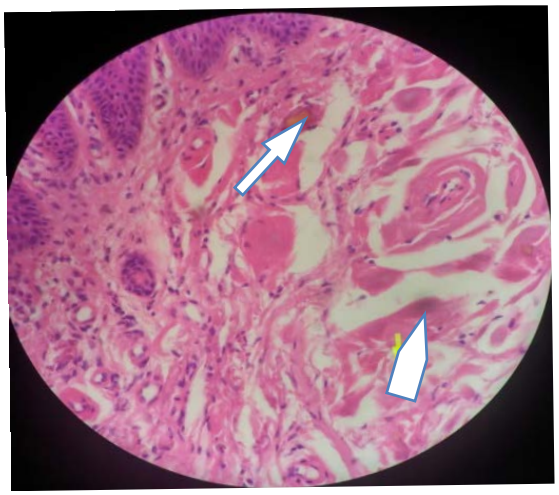

Figure-8: Yellow brown pigment deposition is seen in collagen bundles (arrows) (H&E X400)

As many of her investigations were suggestive of alkaptonuria so her urine was specifically sent for organic acids. A large peak of homogentisic acid is identified by gas chromatography mass spectrometry (GC-MS). Patient was then started oral ascorbic acid 500mg twice daily and referred to physiotherapy and rehabilitation department for strengthening exercises and management of backache and hip joint pain.

Discussion

Alkaptonuria is a metabolic disorder caused by an absence of the enzyme homogentisate 1,2-dioxygenase (HGD) leading to accumulation of homogentisic acid (HGA) in the tissues. Theoretically, human hepatobiliary system produces enough HGD to metabolize over 1.5 kg of HGA daily, so a loss of more than 99% of the enzyme activity is needed in order to display alkaptonuric symptoms. This pigment is deposited with high affinity in the hyaline cartilage tissues of large joints, sclera and intervertebral discs[8].

Slow deposition of homogentisic acid and its oxidation products as a dark pigment in tissues is called ochronosis and it may affect the musculoskeletal, cardiovascular, genitourinary system, the sclera and the skin[12].

Ochronotic discoloration is commonly seen in the cartilage of pinna which become thickened and in

later stages gross calcification can be seen. Ear wax also becomes reddish brown or jet–black. Cutaneous pigmentation can be detected on the nasal tip, extensor tendons of hands (which appear as a coal black–like tattoo work, sometimes may be associated with pitting and hyper pigmented plaques with adherent scales), cheeks, axilla, fingernails and buccal mucosa. Grey–brown or blue black pigmentation of the sclera (often confused with choroidal melanoma) can also be seen[2]. It was however absent in our case. The skin markers in our case were the progressive pigmentation of the both sides of hands, cheeks and auricular cartilages. The hyperkeratotic, linear blue papules along the lateral aspects of fingers, a rare presentation[9], were present in our patient.

Characteristic feature of urine of alkaptonuric patient is that its initially normal and then turns brown or black after standing or after alkanization. This darkening is due to the oxidation of homogentisic acid. Cloth diapers of affected infants may turn brown after washing with alkaline solutions[3]. However diagnosis may be delayed until adulthood, when arthritis or ochronosis occurs as acidic urine does not become dark even after many hours of standing[10]. This may be the reason our patient has not noticed darkening of urine till adulthood.

The differential diagnosis of the cutaneous findings of alkaptonuria includes exogenous ochronosis[3]. Exogenous ochronosis is clinically and histologically similar to its endogenous counterpart; however, it exhibits no systemic effects and is not an inherited disorder. It most commonly results from use of products containing hydroquinone. It can also occurs following use of antimalarials and products containing resorcinol, phenol, mercury or picric acid. Other differentials of cutaneous findings include argyria, chrysoderma, and drug-induced hyperpigmentation[2].

Histopathological examination of a skin biopsy in classical ochronosis reveals the characteristic ochre or yellow-brown pigment from which the condition gets its name. The pigment is strikingly present within collagen bundles, which tend to fracture transversely resulting in pointed ends and have been described as banana or comma-shaped. Finally there is collagen degeneration, and an occasional granuloma may be seen. Fine granules of ochronotic pigment may also be seen intracellularly in the endothelium, macrophages and secretory cells of sweat glands, as well as extracellularly, particularly in basement membranes. Melasma, another differential, does not show this pigment; instead melanin is found to be significantly increased in all the epidermal layers. Unlike melanin, ochronotic pigment does not stain with silver nitrate, and blackening on methylene blue or cresyl violet staining is a useful method to characterize it[11].

Currently there is no specific and effective treatment for alkaptonuria. Some suggest dietary protein restriction (mainly phenylalanine and tyrosine), and ascorbic acid to reduce urinary homogentisic acid excretion and possibly reverse bone abnormalities. These observations have not been confirmed in other studies. A newer drug nitisinone shows direct pharmacologic reduction of homogentisic acid production. it is a triketone herbicide and potent inhibitor of 4–ydroxy–phenylpyruvate dioxygenase which is responsible for catalyzing the formation of homogentisic acid from hydroxyphenylpyruvic acid. Nitisinone reduced urinary homogentisic acid excretion by approximately 70% in two patients with alkaptonuria. However, long-term side effects of nitisinone therapy are still under consideration[2].

Conclusion

AKU is a rare metabolic disorder but it should be considered in differential diagnosis of cases with unusual pigmentation. A thorough history, examination and homogentisic acid measurement is the key to the right diagnosis.

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Date Received:	13-07-2017
Date Sent for Reviewer:	1407–2017
Date Received Reviewers' Comments:	18-07-2017
Date Received Revised Manuscript:	23-07-2017
Date Accepted:	2507–2017

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C. Analysis/Interpretation/Discussion
D. Manuscript Writing
E. Critical Review
F. Facilitated for Reagents/Material/Analysis