International Journal of Medical and Pharmaceutical Case Reports
6(4): 1-5, 2016; Article no.IJMPCR.22710
ISSN: 2394-109X, NLM ID: 101648033

SCIENCEDOMAIN *international*
www.sciencedomain.org

A Case of Alkaptonuria Diagnosed in Late Adulthood

Nayyereh Saadati[1], Mandana Khodashahi[1*] and Bahram Naghibzadeh[2]

[1]Rheumatology Department of Internal Medicine, Ghaem Hospital, Medical Sciences University of Mashhad, Iran.
[2]Rheumatic Disease Research Center (RDRC), Ghaem Medical Center, Mashhad, Iran.

Authors' contributions

This work was carried out in collaboration between all authors. Author NS wrote the draft of the manuscript. Author MK managed the literature searches. Author BN designed the figures, managed literature searches and contributed to the correction of the draft and the figures and supervised the work. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2016/22710
Editor(s):
(1) Nurhan Cucer, Medical Biology Department, Faculty of Medicine, Erciyes University, Turkey.
(2) Rakesh Kumar Tiwari, Chapman University School of Pharmacy, Chapman University Harry and Diane Rinker Health Sciences Campus, Irvine, CA, USA.
(3) Rahul S. Khupse, Pharmaceutical Sciences, University of Findlay, USA.
Reviewers:
(1) Mutlu Cayırli, Mevki Military Hospital, Ankara, Turkey.
(2) Ayhan Goktepe, Selcuk University, Konya, Turkey.
(3) Anonymous, Dicle University, Turkey.
Complete Peer review History: http://sciencedomain.org/review-history/12941

Case Study

Received 21st October 2015
Accepted 19th December 2015
Published 11th January 2016

ABSTRACT

Background: Alkaptonuria (AKU), also known as black urine disease, ochronosis as well, is a rare Mendelian autosomal recessive disorder, located on chromosome 3q21-q23, caused by deficiency of the homogentisate 1,2 dioxygenase (HGO), an enzyme which normally catalyses the conversion of homogentisic acid (HGA) into maleylacetoacetic acid, in the tyrosine degradation pathway. It results in accumulation and deposition of homogentisic acid in cartilage, eyelids, forehead, hand, axillae, genital regions, nail beds, buccal mucosa, larynx, tympanic eardrum, and the tendons. This condition leads to a severe and crippling arthropathy. We present a case of AKU in a 53 year old woman in Mashhad, Iran.
Case Presentation: In this paper, we report a case of 53-year-old woman who presented with AKU and ochronotic pigment deposited in articular cartilage, sclera, cartilage of the ear, hands and

**Corresponding author: E-mail: khodashahim921@mums.ac.ir, mkhodashahi53@gmail.com;*

degenerative arthropathy in Ghaem Hospital, in Mashhad, Iran. The features include arthritis of the spine and in larger peripheral joints. The problem began about 9 years ago with a history of darkening of urine and discoloration of sclera, ears and hands. In imaging studies, there were degenerative changes in spine. She also underwent hand biopsy which showed Ochronotic pigmentation.

Conclusion: This case report that shows AKU must be considered in the evaluation of low back pain of patients' bluish discoloration, ochronotic pigment deposited in cartilage tissues, sclera and hands. Therapeutic options include protein restriction, administration of high dose vitamin C.

Keywords: Alkaptonuria; ochronosis; skin lesion; degenerative arthropathy.

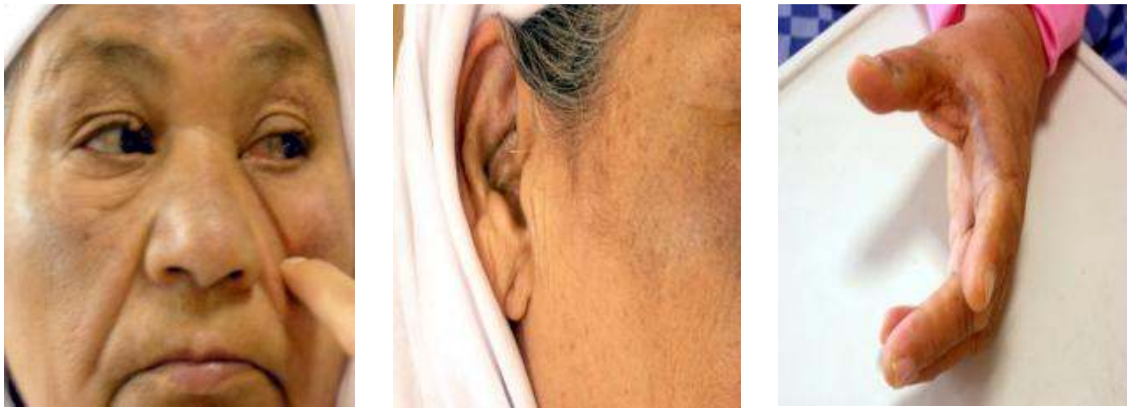
1. INTRODUCTION

Alkaptonuria (AKU) is a rare inherited genetic disorder of tyrosine metabolism that causes the urine to turn black on contact with the air when homogentisic acid is oxidized to form a pigment-like polymer material [1,2]. AKU gene is located on chromosome 3q21-323, arises from total inhibition of homogentisic acid oxidase enzyme [3]. Its prevalence is estimated bout 1:100,000-250,000 in most ethnic group, but this rate is higher in East Europe [4]. Only a few cases have been reported from Iran. The first sign of the disorder is the proclivity for babies' diapers to stain black; later on in childhood and early adulthood, there is an asymptomatic, progressive deposition of the polymer into collagenous tissues [5]. Its excess is deposited mainly in cartilaginous tissue, mucous, skin, bone surface and internal cardiac structures, as well as excreted in biological solutions. The main complications of Alkaptonuria are valvular calcifications and osteoarthritis, more frequent in the cervical spine, also dark pigment deposition in skin, cartilage, sclera and other connective tissues [6]. AKU diagnosis is based on clinical history, histopathological exam and urinary homogentisic acid level [7]. Although AKU is not very rare, most cases have been diagnosed in child hood and adolescence, but our described case was a middle aged woman. In which many manifestation of disease might mimic malignancies.

2. CASE REPORT

A 53 year-old woman presented to our Rheumatologic clinic in Ghaem Hospital, Mashhad, Iran, in March 2015 for low back pain and limitation of motion due to increasingly severe back pain. Physical examination revealed black discoloration of the sclera as well as of the ear. She had bilateral typical bluish black pigmentation of the hands and fingernails (Fig. 1). She had no other constitutional symptoms. Her problems have been began and progressed from 9 years.

She had a history of discoloration of urine that changed to Gray - black after urination. In physical examination, the vital sign was normal. In the head and neck examination, pigmentation was seen in sclera and bluish discoloration of auricle found.



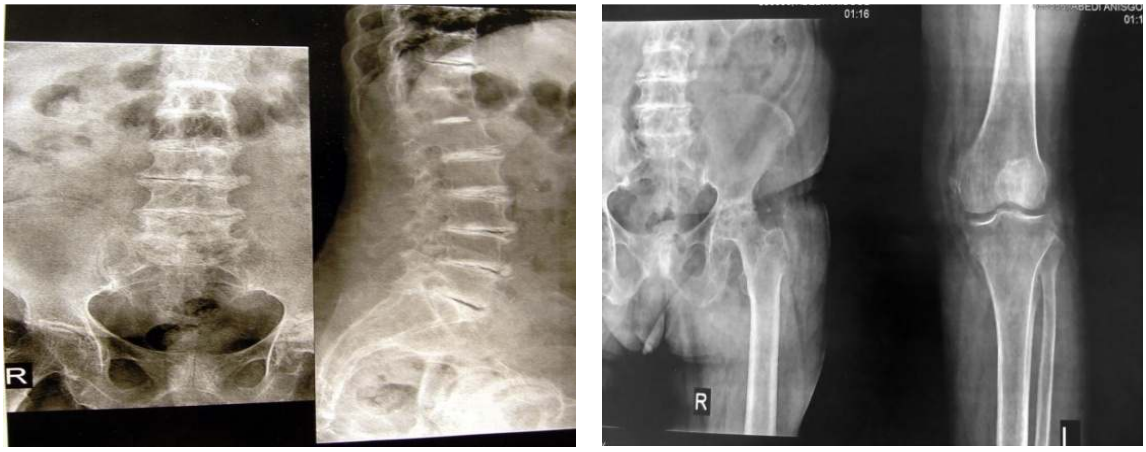
A **B** **C**

Fig. 1. A: Sclera pigmentation, B: Ear pigmentation, C: Hands and fingernails pigmentation

Chest and abdomen examinations were normal. Morning stiffness was less than 15 minutes and back pain had mechanical characteristics. In axial examination, there was tenderness in spine limitation of motion found in all plane of movements. The hip examination was normal. AKU was proposed as a probable diagnosis regards to clinical findings, spine pain and ochronosis. The back pain was insidious in onset and progressive in nature associated with early morning stiffness. The cause of the pain in both knee joints was degenerative changes. In radiological studies, loss of intervertebral disc spaces was prominent, and degenerative changes were found in hip joints (Fig. 2). Other peripheral joints were normal.

There were no abnormal findings in the other examinations. Laboratory examination showed a white blood cell count of 7,600/mm3 with platelets 256,000/mm3, a hemoglobin level of 12.6 g/dL, hematocrit 39%. The results of the blood chemistry were AST 37 IU/L, ALT 33 IU/L, BUN 14.6 mg/dL, creatinine 0.4 mg/dL, PT 10.5 sec (INR : 0.95), PTT 23 sec, and CRP 2.1 mg/L (normal range). Urinary homogentisic acid was not detectable. So, diagnosis was confirmed by histopathologic study and homogentisic acid decomposition in skin tissue.

Fig. 3 showed the histopathologic findings from lateral border of the second finger biopsy.



A **B**

Fig. 2. A: Lumbar spine radiograph showing typical calcification. B: X-ray of the hip and left knee of the patients

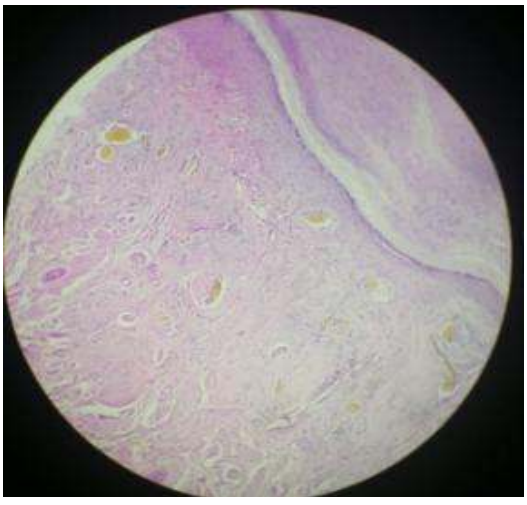


Fig. 3. Punch biopsy sample showed hyperkeratosis and Ochronotic pigmentation

3. DISCUSSION

Alkaptonuria, an autosomal recessive disorder, was first described by Garrod in 1902 [8]. In 1908, Garrod coined the term ′inborn error of metabolism′ and proposed that AKU resulted from the deficiency of an enzyme that normally splits the aromatic ring of homogentisic acid. The deficient enzyme was identified by La Du in 1958 [9]. Sixty-seven mutations of the Alkaptonuria gene have been identified up to date. It was even detected in an Egyptian mummy [10]. AKU patients are usually asymptomatic as children or young adult, pigmentation of the sclera or the cartilage of the ear start to appear later.

There is no pharmacological modality treatment which cures AKU. Vitamin C as an antioxidant can be helpful in AKU with preventing the oxidation of the homogentisic acid. In our patient main treatment attempts have focused on preventing AKU through the reduction of accumulating homogentisic acid. For the articular lesions the use of non-steroidal anti-inflammatory drugs is recommended, associated with the practice of physical exercises and physical therapy. In some cases, a surgery will be necessary for substitution of large articulations. Ochronotic arthropathy in the hips and the knees may be so severe as to require total joint arthroplasty [11]. There must be restricted intake of proteins, mainly phenylalanine and tyrosine aminoacids. Several recent studies have suggested that the herbicide nitisinone (not yet available in Iran), may be effective in the treatment of AKU [12-14].

4. CONCLUSION

Although AKU is not a rare disease, this diagnosis must be considered in middle aged patients with low back pain, ochronotic pigment deposited in cartilage tissues, sclera and hands.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Garrod AE. About alkaptonuria. Lancet. 1901;ii:1484-6.
2. Garrod AE. The incidence of alkaptonuria: A study in chemical individuality. Lancet. 1902;ii:1616-20.
3. Zouheir Habbal M, Bou-Assi T, Zhu J, Owen R, Chehab FF. First report of a deletion encompassing an entire exon in the homogentisate 1,2-dioxygenase gene causing alkaptonuria. 2014;9(9):e106948. DOI:10.1371/journal.pone.0106948. eCollection 2014.
4. Montagutelli X, Lalouette A, Coude M, Kamoun P, Forest M, Guenet JL. Aku, a mutation of the mouse homologous to human, alkaptonuria, maps to chromosome 16. Genomics. 1994;19(1): 9-11. Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, Fitzpatrick DL, et al. Natural History of alkaptonuria. N Engl J Med. Natural History of Alkaptonuria. 2002;347:2111–21.
5. Watts RWE, Watts RA. Alkaptonuria: a 60-yr follow-up+Watts department of medicine. Imperial College, Hammersmith Campus, DuCane Road, London W12 0HS; 2006.
6. Aquaron R. Alkaptonuria: A very rare metabolic disorder. Indian Journal of Biochemistry & Biophysics. 2013;50(5): 339-44.
7. Datta A, Mandal S, Ghosh t. Alkaptonuria diagnosed in a 4-month-old baby girl: A case report. Cases Journal. 2008;1:308.
   DOI: 10.1186/1757-1626-1-308
8. Wile A, Steverding D. Ochronosis as an unusual cause of valvular defect: A case report. Journal of Medical Case Reports. 2009;3:9302.
9. Romero SA, Pereira PM, Mariano AV, Francesconi F, Francesconi VA. Use of dermoscopy for diagnosis of exogenous ochronosis. An Bras Dermatol. 2011;86: S31–S34.
10. Odabas A, Karakuzu A, Selcuk Y, Erdem T, Cetinkaya R. Alkaptonuria: A case report. The Journal of Dermatology. 2001;28(3):158-160.
11. Khatu S, More Y, Vankawala D, Chavan D, Gokhale N. Alkaptonuria: Case report. Maharashtra India. 2015;8(1):84-86.

12. Singh N, Ranjan R, Ramachandran T, Sageev G. Case report – anesthetic management of a case of alkaptonuria; 2008.
13. Haridas V. Alkaptonuria, a rare cause for low back pain. IJRCI. 2013;1(1):CS5.
14. Ummais K, Cornelia W, Eric W. Back pain in a middle-aged man: Alkaptonuria American Journal. 2015;94(5):120-124.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/12941