Ochronosis of the Hip Joint: Differential Diagnosis of Inflammatory Arthropathy with Lytic Lesion

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Received: 25 March 2013 / Accepted: 11 May 2013 / Published online: 25 May 2013
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Abstract Alkaptonuria or ochronosis is a rare inborn disorder of metabolism which is characterized by deficiency of homogentisic acid oxidase. There is accumulation of homogentisic acid in the connective tissues causing brownish black pigmentation and skeletal damage. The most serious complication of this disease is crippling degenerative arthropathy which presents in late years of life. There is no definitive treatment for the condition. Symptomatic management is the main stay. Surgical management such as arthroplasty is done for severe cases of ochronosis. We report a case of ochronosis of the hip joint presenting with inflammation and lytic lesion which can create confusion and lead to error in diagnosis.

Keywords Alkaptonuria · Ochronosis · Hip joint · Lytic lesion

Introduction

Alkaptonuria (AKU) is a rare autosomal recessive disorder with prevalence lower than 1:250,000. It is a defect in the metabolism of homogentisic acid (HGA). In 1859, Boedeker discovered the reducing properties of a substance present in the urine of an affected patient which darkened on addition of alkali, for which he coined the term alcapton (from the Arabic word-alkali). Virchow named the condition ochronosis after observing the pigmented cartilage, menisci and

sclera. In 1909, Garrod hypothesized that a specific enzyme was missing in AKU, which was later confirmed by La Du who showed the absence of HGA oxidase (homogentisate 1,2-dioxygenase) in the liver of the patient [1]. Neubauer, later described the complete tyrosine degradation pathway [2]. Patients excrete HGA in the urine causing a characteristic dark colour when the urine is alkalinized or oxidized. Deposition of brown black pigment occurs in connective tissues (bone, cartilage, skin and sclerae) leading to skeletal changes which cause degenerative arthropathy. To our knowledge there are no literature reports on ochronosis presenting as inflammatory arthropathy with lytic lesion which can present with considerable confusion in diagnosis.

Case Report

A 65 year old female presented to the hospital with complaints of severe pain in the left hip since 2 months which had aggravated in the last 2 weeks. She also had a history of chronic non-specific back pain for 2 years. There was history of cough with sputum since 2 months. Family history was unremarkable. On examination, her left hip was tender at the anterior joint line with restricted global hip movements. She had dorsal kyphosis and lumbar stiffness. The other peripheral joints were normal. Lab investigations revealed that total leucocyte count was mildly elevated (14,000 cells/mm³) with ESR 24 mm/hour. Hematocrit, serum urea, creatinine, uric acid were within normal limits. Sputum AFB was negative. Radiography of the pelvis and bilateral hip was suggestive of decreased joint space with mild osteophytes. There was a lytic lesion on the neck of the left femur. Spinal radiography showed diffuse narrowing of the lumbar intervertebral spaces with calcification of intervertebral discs. She had no skin or sclera pigmentation. Taking into consideration

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the general, local and radiological investigations, a provisional diagnosis of inflammatory arthropathy with erosion was done and patient was taken up for surgery. On exploration, the joint cartilage of the head of femur appeared darkly pigmented with erosion in the left neck. Pigmented shards of cartilage were noted within the joint space. To rule out malignancy, biopsy was taken from the site and found to be negative. AKU was suspected and ferric chloride test and ammoniacal silver nitrate test were performed in urine sample and diagnosis was confirmed (Figs. 1,2). Urine on standing and exposure to air turned black. On retrospective questioning, she gave history of blackening of underclothes due to wetting with urine. Because of the destructive effect of the disease on the bone and cartilage, a total hip arthroplasty of the left hip was done.

Discussion

In AKU, there is accumulation of HGA in various tissues. HGA polyphenol oxidase catalyzes the formation of benzoquinone acetate (BQA). BQA polymerizes and binds to connective tissue macromolecules altering the cross-linking structure of the tissue [3]. Pigmentation of sclera and ear cartilage occurs mostly after the age of 30 years. Lesser known manifestations include renal, urethral and prostate calculi and cardiovascular abnormalities like aortic dilation and mitral valve calcification [2, 4]. In this case there were signs of inflammation. It could be due to phagocytes, in close proximity to the ochronotic shards, strongly expressing Human leucocyte antigen-D related (DR) [5] or HGA in itself acting as an irritant causing rapid inflammation of joints. Lytic lesions could be confused with malignancy which will require radical resection and/or chemotherapy as AKU presenting with lytic lesions is rare. This occurs probably on an already weakened osteoporotic bone. There are simple biochemical tests available for screening of AKU like ferric chloride test, ammoniacal silver nitrate test, Benedicts test, *N*-butanol test followed by enzymatic spectrophotometry, gas liquid chromatography or high pressure liquid chromatography [6]. The responsible gene is on

Fig. 1 Ferric chloride test

Fig. 2 Ammoniacal silver nitrate test

chromosome 3q [7]. Molecular analysis have identified 67 mutations till date which reflect the disorder's varied clinical presentations [4]. Symptomatic management is the main stay of treatment. Vitamin C, an antioxidant is given to decrease the rate of polymerization of HGA but no proven effect has been seen. Nitisinone (2-(2-nitro-4-trifluoromethyl benzoyl)-1,3-cyclohexanedione) is a therapeutic agent which acts by inhibiting the enzyme 4-hydroxy phenyl pyruvate dioxygenase but it has the side effect of corneal irritation due to increased plasma tyrosine [8]. Its long term effect is also not known. Surgical management like arthroplasty needs to be done whenever required. In conclusion, a clinician needs to be aware of the fact that AKU can present with lytic lesions, before taking up the patient for surgery.

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