Alkaptonuria - More Than Meets The Eye

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SUMMARY

An elderly gentleman with chronic lower back and bilateral knee pain was found to have clinical and radiographic findings consistent with alkaptonuria. Diagnosis was confirmed by the detection of elevated homogentisic acid level in the urine using gas chromatography-mass spectrometry.

KEY WORDS:
Alkaptonuria, intervertebral disc calcification, aortic stenosis, gas chromatography-mass spectrometry

INTRODUCTION

Alkaptonuria is a rare autosomal recessive metabolic disorder whereby deposition of homogentisic acid in the connective tissues leads to sequelae in the involved organ systems. It affects about one in every 250,000 to 1 million persons. To date, prevalence of alkaptonuria in Malaysia has not been reported. A check with 3 laboratories in Malaysia that offer testing for alkaptonuria using urine organic acid gas chromatography-mass spectrometry (GC-MS) method revealed that between 2005 and 2011, there were 3 other positive cases. Of note, there had been a previous case report of alkaptonuria in Malaysia whereby the patient presented with root canal stenosis [1]. We report this case to highlight to adult physicians that inborn errors of metabolism can present in adulthood and often go undiagnosed. Awareness of the existence of alkaptonuria among doctors of various disciplines including physicians, cardiologists, rheumatologists and orthopaedic surgeons is therefore important, given its multi-organ presentation.

CASE REPORT

A 66 year-old gentleman, a known case of ischaemic heart disease, Type 2 diabetes mellitus and hypertension, presented to the Medical Unit with unstable angina. ECG showed ST depression in the anterolateral leads and cardiac enzymes were not elevated. He was treated accordingly with aspirin, low molecular weight heparin and anti-anginal drugs. Of note, this was the third admission over the past 6 months for unstable angina. Hence he was referred to the cardiology unit for further management.

During this admission, he complained of bilateral knee pain and low back pain which had progressively worsened over the past 10 years, rendering him chair-bound. He had been diagnosed to have osteoarthritis by the orthopaedic surgeons and had tried multiple analgesics. A rheumatology consult was made to see what further treatment options could be offered for a patient with a diagnosis of osteoarthritis.

Clinical examination revealed an overweight gentleman. He was normotensive. Eye examination was remarkable for brownish pigmentation of the sclerae of both eyes. Examination of the hands demonstrated hyperkeratotic linearly arranged blue papules along the apposing surfaces of the thumbs and index fingers bilaterally. There was also bluish discolouration over the thenar eminences of both palms and over the insoles of both feet. The concha and antihelix of both ears did not demonstrate any discolouration. Instead the ears were thickened and stiff.

Cardiovascular examination revealed an aortic stenosis murmur of grade 3/6.

Examination of the spine revealed obliteration of lumbar lordosis and limited spinal excursion. Hip joint movements were not affected. There were clinical features of osteoarthritis in both knees with presence of genu varus, wasting of quadriceps muscles, marked crepitus on active movement and limited range of motion. There was however no sign of active synovitis.

Routine laboratory investigations which included full blood count, renal profile, liver function, fasting serum lipids, HbA1c and erythrocyte sedimentation rate were all within normal limits.

He underwent echocardiography which revealed the following: Severe aortic stenosis with a pressure gradient of 63 mm Hg. Thickened aortic valve and calcification of all cusps. Thickened mitral valve with trivial mitral regurgitation. All cardiac chambers were not dilated. There was left ventricular hypertrophy and left ventricular contraction was impaired with an ejection fraction of 48%.

X-ray of the knees revealed joint space narrowing in the femoro-tibial joints associated with subchondral sclerosis and osteophytes. X-ray of the lumbosacral spine showed intervertebral disc calcification with disc space narrowing. Vertebral bodies were preserved (Figure 1).

Urine specimen was collected and it turned dark on standing. A provisional diagnosis of alkaptonuria was made and urine organic acid analysis using gas chromatography-mass spectrometry (GC-MS) was performed to establish the

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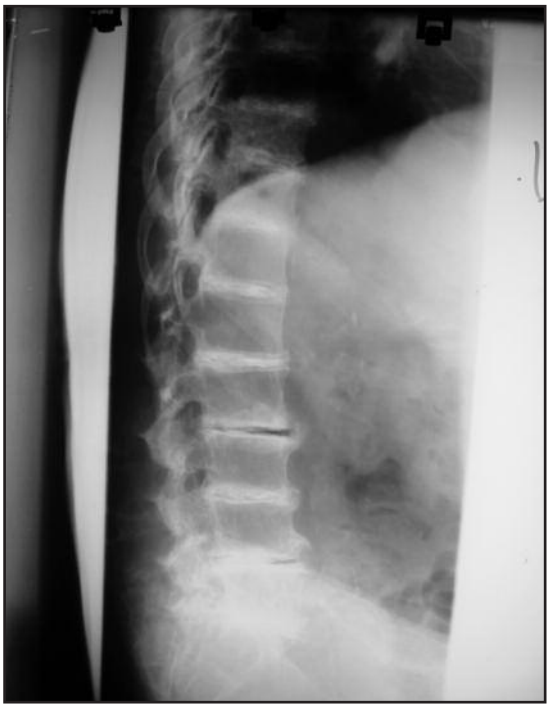

Fig. 1: Lumbosacral spine X-ray

diagnosis. The analysis showed an elevated homogentisic acid level, consistent with a diagnosis of alkaptonuria.

Further history disclosed that his parents were non-consanguineous.

DISCUSSION

Alkaptonuria results from a deficiency in an enzyme ie, homogentisic acid dioxygenase, which is involved in the tyrosine degradation pathway. This leads to a massive accumulation of homogentisic acid (2,5-dihydroxyphenylacetic acid) and its oxidative products which are excreted in the urine and deposited within connective tissues. Deposition of homogentisic acid (HGA) in connective tissue leads to sequelae associated with the disease. The organ systems involved include ocular, cutaneous, cardiovascular, skeletal, genitourinary and respiratory. Alkaptonuria is asymptomatic in childhood hence diagnosis is usually established at a later age when the patients develop ochronosis, which refers to brown-black pigmentation in connective tissues, typically the skin, eyes and cartilage.

Alkaptonuria is characterised by the triad of urinary homogentisic acid, ochronosis and ochronotic arthropathy. Our patient demonstrated findings similar to those described in the literature whereby ochronosis was noted in the sclerae, skin, heart valves and joints. Scleral pigmentation is prominent between the cornea and the outer and inner canthi. Even though there was no pigmentation of the ears, the cartilage of the ears of our patient are thickened and stiff, indicating homogentisic acid deposition. The hyperkeratotic linearly arranged blue papules along the lateral aspects of fingers have been described, albeit a rare presentation[2]. Deposition of HGA in cardiac valves results in calcification of the valves with associated valvular stenosis or insufficiency and may require replacement [3].

Ochronotic arthritis can be disabling whereby the spine and large joints especially the knees, hips and shoulders, are typically affected. As the radiographic findings of the knees show degenerative changes, patients with alkaptonuria can be dismissed as having primary osteoarthritis. However findings on spine radiograph are characteristic with diffuse calcification of the intervertebral discs[4]. Other conditions that give rise to similar radiographic feature have to be considered, which includes haemochromatosis, chondrocalcinosis, hyperparathyroidism and acromegaly.

As alkaptonuria is rare, the likelihood that this disease goes unnoticed is high. Therefore a high index of suspicion and awareness is essential to clinch the diagnosis. This is proven in our patient where the diagnosis of alkaptonuria was not established despite having had repeated admissions over the past 2 years for angina and joint pain.

HGA in the urine of patients with alkaptonuria oxidizes and darkens on exposure to air. This characteristic finding was noted in our patient. As it is unusual practice to leave urine standing, this finding is usually overlooked.

The diagnosis of alkaptonuria relies on the detection of elevated homogentisic acid levels in the urine as determined by gas chromatography-mass spectrometry [5]. This test was performed in our patient which detected a huge peak of homogentisic acid and 4-hydroxyphenyl acetate, confirming a diagnosis of alkaptonuria. Recommendation was made for further confirmation with molecular genetic testing of HGD (homogentisic acid dioxygenase) gene.

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