Ochronotic heart disease leading to severe aortic valve and coronary artery stenosis

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Abstract

Cardiac ochronosis is a rare disease, estimated to affect 1 in 250,000 persons. While there is extensive evidence of the musculoskeletal alterations of the disease, cardiac involvement has not been widely studied and most information we currently have derives from case reports and case series. We report the case of a 64-year old patient with a known history of alkaptonuria who presented with dyspnea and weight loss. On evaluation, he was found to have severe aortic stenosis, coronary artery disease, and interventricular septal hypertrophy. Surgery revealed extensive ochronotic pigment deposition affecting the cardiac septum, both internal thoracic arteries, the native coronary arteries, and the aortic valve. Ochronotic heart disease is an often disregarded presentation of alkaptonuria. More information is needed on the course of the disease, as well as long-term outcomes after valve replacement surgery and/or CABG in patients with alkaptonuria.

Introduction

Alkaptonuria is a rare autosomal recessive disorder that is reported to affect 1 in 250,000 individuals. [1] This disorder is due to a deficiency of homogentisate 1,2-dioxygenase which leads to an accumulation of homogentisic acid (HGA) and its derivatives within the blood and urine. Once homogentisic acid is oxidized and polymerized, the derivatives deposit into connective tissue, leading to microscopic yellow discoloration and macroscopic black pigmentation of the tissue, leading to ochronosis.[2]

While the involvement of the connective tissue and genitourinary system have been well documented, and are often regarded as the most common manifestations of alkaptonuria, the cardiovascular system has been shown to be severely affected in many patients with alkaptonuria as well.[3] Most cases of ochronotic heart disease have reported involvement of the aortic valve, but manifestations can be extensive and affect the myocardium, coronary vessels, and internal thoracic arteries as well.[4]

Case report

A 64-year-old male with a known history of hypertension, dyslipidemia, ankylosing spondylitis, alkaptonuria, right bundle branch block, and known mild to moderate aortic valve stenosis presented with progressive dyspnea on exertion and a two-month history of 20-pound weight loss. On physical examination the patient was noted to have bony enlargement of both knees, marked thoracic and cervical kyphosis, and blue-black discoloration of the sclera and pinna (**Figure 1**). A transthoracic echocardiogram (TTE) demonstrated a well-preserved left ventricular function with an ejection fraction of 65%, left ventricular hypertrophy with a maximum septal diameter of 2.20 cm, and severe aortic valve stenosis. Aortic valve stenosis was characterized by diffuse sclerosis and calcification with reduced leaflet excursion. An estimated aortic valve area of 1 cm^2 was noted with a peak aortic valve gradient of 69 mmHg and mean gradient of 41 mmHg.

After CT angiography of the chest demonstrated evidence of diffuse coronary calcification, he underwent cardiac catheterization which revealed severe three vessel coronary artery disease. The patient was referred to the Cardiac Surgery service for surgical evaluation and was recommended three vessel coronary artery bypass grafting (CABG), septal myectomy and aortic valve replacement with a bovine pericardial valve.

During arteriotomy of the native diseased coronary vessels and harvesting of both internal thoracic arteries, a diffuse bluish discoloration of the endothelial layer was noted (**Figure 2**). Upon septal myectomy, blue pigment was noted across the myocardium (**Figure 2**). Similarly, during the transverse aortotomy the tri-leaflet aortic valve had diffuse macular discoloration with bluish and blackish areas, especially in correspondence of the annulus. Transection of the aortic valve leaflets revealed a diffusely calcified aortic valve annulus with deposits of black carbonaceous material (**Figure 3**). The aortic valve was subsequently sent for pathological evaluation, which was remarkable for multiple black calcified lesions up to 0.5 cm in dimension, and involved approximately 15% of the leaflet surface (**Figure 4**).

Due to his pre-existing significant mobility limitation, the patient was discharged to an acute rehabilitation facility on postoperative day 11. The patient returned for routine 1 and 6-month follow-up with no complaints, and echocardiographic assessment revealed adequate contractility and bioprosthetic valve function. Follow-up 20 months after surgery revealed adequate ejection fraction (65%) and normal bioprosthetic valve function and gradients.

Discussion:

Our patient demonstrates many of the classic characteristics of alkaptonuria, including kyphosis, corneal and pinnae pigmentation, as well as cardiac manifestations such as aortic valve stenosis and aortic dilation. The propensity of HGA deposits to manifest in joints, the aorta, and the base of the aortic valve suggests that increased pressure or turbulence leads to microvascular damage that primes the tissue for ochronosis, which subsequently leads to dystrophic calcification.[3] This finding could potentially suggest that the severity of ochronosis in increased pressure environments, such as the joints, may act as an earlier indicator of the more disguised cardiovascular complications associated with alkaptonuria, and may also explain the presence of myocardial septal involvement in this patient with a history of hypertension.

Ather et al. reviewed 66 case reports of ochronotic cardiovascular disease.[4] Until now, there has been only one other case report with a presentation similar to the this case: a patient with severe aortic stenosis and evidence of ochronosis of the aortic valve, coronary arteries, and the internal thoracic artery.[5]Another case series reported that 83% and 100% of patients over 60 years of age had aortic and intracardiac calcification respectively, without correlation to standard cardiac risk factors.[3] This raises the question of whether the cardiovascular complications could potentially be predicted with increasing age in a patient with alkaptonuria, and whether these patients should undergo different cardiovascular screening than the rest of the population.

Previous to this case, the feasibility to successfully utilize ochronotic arterial conduits in a bypass setting and follow the patient outcomes has yet to be reported.[6] Our patient's post-operative care and 20-month follow-up, including TTE, revealed no deterioration to either the aortic valve or the overall ventricular function suggesting compromise of the arterial grafts. This demonstrates, for the first time, the safe utilization of ochronotic arteries in the setting of a CABG along with aortic valve replacement. Larger studies are needed to determine the long-term effects of alkaptonuria in patients with ochronotic heart disease who have undergone cardiac surgery.

References:

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Figure 1: External Manifestations of Alkaptonuria. Cartilaginous blue discoloration of the antihelix of the pinna (left) and sclera discoloration (right) due to deposition of homogentisic acid derivatives.

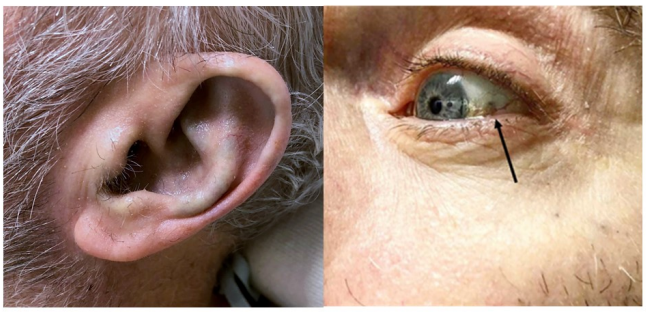

Figure 2: Internal Manifestations of Alkaptonuria. Discoloration of the right coronary artery (left), left internal thoracic artery (middle), and myocardial septum (right) due to deposition of homogentisic acid derivatives.

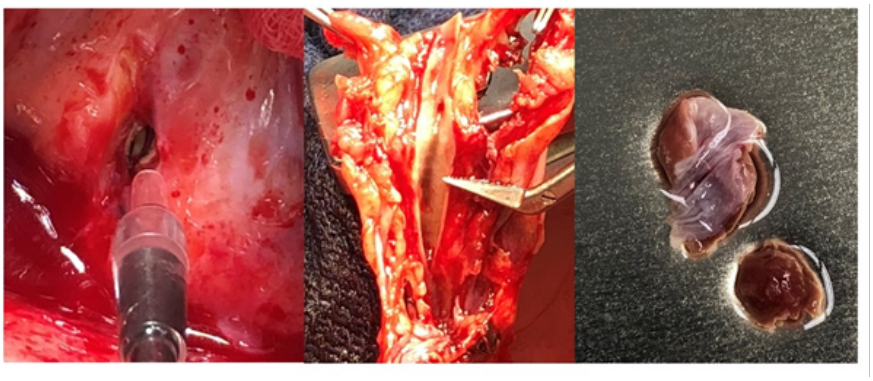

Figure 3: Sclerotic Aortic Valve. Aortic valve with blackened carbonaceous tissue due to homogentisic acid derivative deposits.

Figure 4: Histological Evidence of Alkaptonuria. Aortic Valve Leaflet with myxoid degeneration, calcification and pigment seen at arrow with higher magnification insert