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Case Report

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Black heart at surgery - primary diagnosis of alkaptonuria at surgery

Abstract

Alkaptonuria is a rare genetic disorder of tyrosine catabolism in which homogentisic acid accumulates leading to ochronotic deposition in connective tissue. This has widespread effects including degenerative arthritis and, more rarely, cardiovascular manifestations, the most common of which is aortic stenosis. We present a 66-year old patient in whom we diagnosed alkaptonuria during an aortic valve replacement for symptomatic aortic stenosis. We conducted a world literature review to examine the evidence for the prevalence of aortic valve disease and cardiac involvement in alkaptonuria. We discuss the pathogenesis of aortic valve ochronosis.

Keywords: aortic valve, valve stenosis, alkaptonuria, valve replacement, surgery

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Introduction

Alkaptonuria is a very rare autosomal recessive genetic disorder of tyrosine catabolism affecting between 1 in 250,000 and 1 in 1 million births.[1] The highest incidence occurs in Slovakia and the Dominican Republic, where incidence reaches 1 in 19,000 births. It is caused by a discrete mutation in chromosome 3q21-3q23, leading to a deficiency in the homogentisate 1, 2 dioxygenase (HGO).[2] This in turn leads to an accumulation of homogentisic acid (HGA) which is excreted in the urine, accounting for the dark colour which occurs on standing, and the deposition of melanin-like oxidised HGA-derived polymers in connective tissue. The pathological pigmentation that occurs as a result is termed ochronosis.

Alkaptonuria typically presents as a triad of homogentisic aciduria, ochronosis and degenerative arthritis. There is a wide clinical variability in presentation that can be explained by the 84 different mutations found so far. There are also varying differences in rates of renal clearance. The disease usually manifests late in life after the 4th decade due to decline in renal clearance with age. Rarely, alkaptonuria can have cardiovascular manifestations: with ochronosis described in the heart valves, aorta, pericardium, endocardium and coronary arteries.[3-5] Aortic stenosis is the most commonly reported cardiovascular manifestation with a number of case series describing an increase in the prevalence of aortic stenosis compared to the general population.

Case

A 66-year old ex-smoker who presented with gradual deterioration with dyspnoea (NYHA II) that developed over 3-years. Past medical history included hypertension and hypercholesterolaemia. Examination was unremarkable apart from an ejection systolic murmur. A transthoracic echocardiogram confirmed a calcified aortic valve with severe aortic stenosis (EOA 0.7cm^2, MG 53mmHg), mild aortic regurgitation (vena contracta 0.3cm) (Figure 1) and severe three-vessel disease involving the left main stem, the ostial and distal left anterior descending and mid circumflex and distal right coronary artery. His haematological investigations revealed only a minimally raised ESR (43mm/hour). His Logistical Euroscore II was 1.1%. He underwent an elective tissue aortic valve replacement using a 25mm Perimount Magna Ease bioprosthesis and coronary artery bypass grafting. This involved the left internal mammary artery grafted to the left anterior descending and a saphenous venous graft to the intermediate and right coronary artery. On sternotomy he was found to have a completely black aorta, aortic valve and heart (Figure 2). Histological analysis of aortic wall and leaflet tissue diagnosed alkaptonuria (Figure 3). Patient had a good post-operative recovery and on discharge was referred to clinical geneticists for further testing. He remains well on 2-year follow-up.

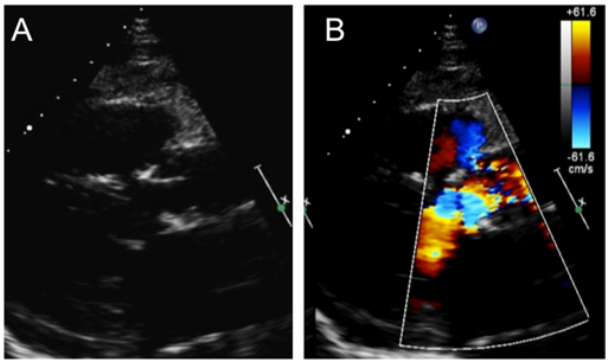

Figure 1 Parasternal long axis transthoracic echocardiogram (A) demonstrating thickened aortic valve leaflets with a stenotic valve on colour flow Doppler (B).

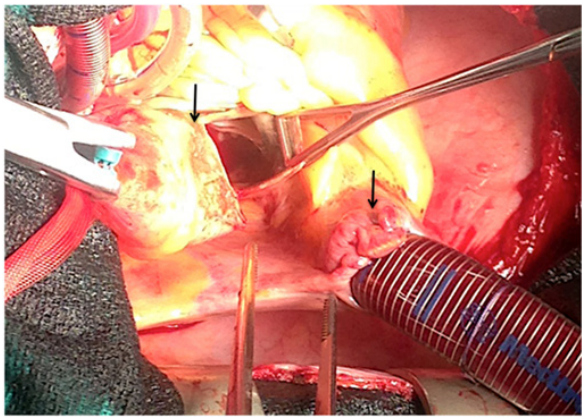

Figure 2 Intraoperative photo demonstrating the opened ascending aorta with the aortic valve exposed. There are pigmented deposits present on the aortic wall and right atrium (arrows) adjacent to the venous drainage line for the cardiopulmonary bypass.

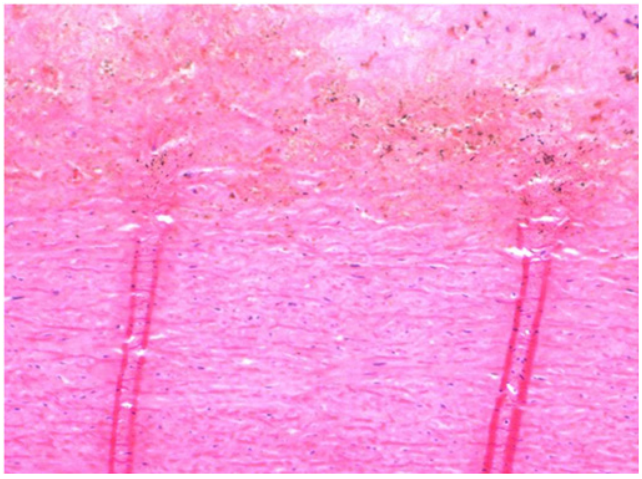

Figure 3 A H&E stained aortic wall histology slide at x20 magnification demonstrating the black pigmentation present in the tunica media and adventia.

Discussion

An increased prevalence of aortic valve disease, and in particular aortic stenosis, is seen in patients with alkaptonuria compared to the general population.[6] In the Cardiovascular Health Study, which looked at 5621 patients aged 65 or older, 1.8% were found to have aortic stenosis.[7] A series of 76 patients with alkaptonuria found aortic stenosis in 25% of patients over 65.[3]. Interestingly, unlike degenerative calcific aortic stenosis, the presence of stenosis was not correlated with the standard cardiovascular risk factors or age related calcification but was moderately correlated with the extent of joint involvement, another manifestation of alkaptonuria where homogenstisate is deposited in the connective tissue within cartilage. Another smaller study of 16 patients found that 50% had aortic valve disease after the 6th decade of life.[8] In our contemporary review of world literature there are 175 patients with alkaptonuria, of whom 35% exhibited aortic valve disease, with 19% stated as aortic stenosis, 11% as aortic regurgitation and 5% as aortic valve disease or aortic valve replacements for unspecified reasons (Table 1).

Table 1

Autopsy studies and case series have also linked alkaptonuria with coronary artery calcification. In particular, an increase in ochronotic deposition in the fibrous caps and lipid cores of atheromatous plaques has been described.[9,10] A large study of 58 patients with alkaptonuria found that 50% of patients over the age of 59 had CT evidence of coronary artery calcification. There is however no independent association of alkaptonuria increased susceptibility to clinically significant atheroma.[1]

The pathogenesis of the cardiac manifestations in alkaptonuria is unclear, however, several theories have been proposed. It is thought that the ochronotic pigment is first deposited in fibrocytes, macrophages, smooth muscle cells and the extracellular matrix. These pigment-laden cells then degenerate, releasing the pigment extracellularly where it acts either as a chemical irritant, producing a pro-inflammatory reaction, or as a direct enzyme inhibitor which alters cartilage metabolism leading to dystrophic calcification and fibrosis of the cardiac valve leaflets.[11,12] Furthermore, ochronotic deposition has been found predominantly in areas of turbulent flow, where there are eddy currents, such as in the sinotublar junction which normally aids diastolic coronary filling. This might explain the deposition of ochronotic pigment in the ostia of the coronary arteries and aortic valve leaflets, whilst there is minimal deposition in venous circulation. Thus vascular flow dynamics dictate the site of pigment deposition leading to the ensuing microvascular damage.[4]

Nitisinone, a potent inhibitor of the second enzyme in tyrosine catabolism, is currently the only treatment effective for reducing HGA levels in alkaptonuria. In a small RCT.[13] 18 patients were treated for 3 years and 4 in-control *versus* 1 in the treated group had an increase in aortic valve velocities (>0.3m/s). The authors concluded that it was difficult to draw conclusions from a small study but postulate the effects might be maximised if treatment is started early before significant pigment deposition has occurred, analogous to statin therapy for calcific aortic stenosis.[13] Other studies have reported a dramatic increase in tyrosine levels with nitisinone. This can lead to corneal irritation, dermatological and neurological side effects, and it remains uncertain whether nitisinone provides any long-term benefits.[1,14] An ongoing study to explore age-related differences in toxicity of nitisinone with a view to optimising therapeutic doses in presymptomatic patients is currently taking place.[15]. Attempts to treat alkaptonuria with high dose vitamin C and dietary restriction of tyrosine and phenylamine intake has failed to produce a decrease in HGA levels.[16] Nevertheless, patients with alkaptonuria have a high morbidity but a low mortality with a relatively normal lifespan.

Cardiovascular disease can have a significant impact on patients and thus if patients are diagnosed there is growing consensus that they require echocardiographic screening after the age of 40 to detect valvular heart disease and cardiac gated CT to assess coronary artery calcification. The choice of valve prosthesis also remains unclear in such patients at surgery. There are no reports of early deterioration of bioprosthetic valves in these patients. We consented the patient for tissue valve replacement and were unsure of the diagnosis till confirmed histologically after surgery. Thus we carried out a tissue valve replacement.[17,18]

Although cardiac ochronosis is a rare clinical presentation, surgeons should be aware of it as they might be confronted with it as in our case during surgery. They must also investigate and follow patients known to have alkaptonuria as they develop cardiovascular disease at a much earlier age. Timely aggressive intervention and medical treatment are of paramount importance.

Conflict of Interests

None.

Disclosures

None.

Acknowledgments

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