CASE REPORT

Aortic stenosis in cardiovascular ochronosis

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Alkaptonuria (endogenous ochronosis) is a rare metabolic disorder caused by a deficiency of homogentisic acid oxidase, an enzyme responsible for the metabolic degradation of tyrosine. Patients with alkaptonuria commonly present with joint pain owing to degenerative arthritis. Other affected patients may present with pigmentation of the ear cartilage and sclera. This article reports a case of aortic stenosis associated with ochronosis in a 48-year-old man who presented with severe cardiac failure. He had no previous diagnosis of alkaptonuria, which was confirmed by mass spectrometry analysis of urine. The pathogenesis of cardiovascular ochronosis is unclear, but is probably related to the extensive extracellular deposits of ochronotic pigment in the cardiac tissue.

A 48-year-old Palestinian man was admitted to University College London Hospitals with a 2-month history of gradually increasing shortness of breath on exertion and a 3-week history of exertional chest pain. He had a 9-year history of type 2 diabetes treated with insulin, complicated by peripheral neuropathy. He was diagnosed with severe congestive cardiac failure, and an echocardiogram showed a severely impaired left ventricle. The ejection fraction was 25%. A calcified aortic valve had severe stenosis, with a valve area of 0.65 cm² and a peak gradient of 76 mm Hg. An echocardiogram showed left ventricular hypertrophy, with no acute ischaemic changes. Troponin T was negative. He was put forward for a heart transplant, but was declined in view of end-organ damage as a result of having diabetes. A coronary angiogram showed considerable disease in the left anterior descending artery (LAD) and obtuse marginal vessels. The right coronary artery was dominant and normal.

He underwent replacement of the aortic valve by a mechanical heart valve (St Jude Medical) along with a single coronary artery bypass graft (left internal mammary artery to LAD), 2 months after his initial presentation. At operation, it was noted that the entire inside wall of the aorta was covered in black patches that extended down into the endothelium of the left ventricle and involved the aortic valve. Black patches were also seen on the inside of the LAD, which itself showed marked atherosclerosis. He recovered uneventfully from the operation, and on follow-up had satisfactory exercise tolerance and no angina. His only complaint, which dates back to the time of the operation, was widespread joint pain, particularly affecting the knees and hands. Macroscopic examination of the valves showed calcified valve leaflets covered in black patches (fig 1). Microscopic examination showed the deposition of a brown pigment in the body of the valve, which was associated with nodules of calcium (fig 2). Staining with Masson–Fontana and Von Kossa, histochemical stains, for melanin and calcium respectively, were carried out on the valve section. Masson–Fontana was negative and Von Kossa confirmed the presence of calcium in the body of the valve but did not explain the additional brown pigment deposited in the valve.

A diagnosis of alkaptonuria was suspected. This was confirmed on mass spectrometry analysis of the patient's urine, which showed markedly raised levels of homogentisic acid (fig 3).

DISCUSSION

Ochronosis refers to the deposition of ochre-coloured pigment in the collagen bundles of connective tissue, including the skin. Exogenous ochronosis is limited to the skin and can result from topical application of hydroquinones, phenol, picric acid, resorcinol and antimalarial drugs. Endogenous ochronosis is seen in alkaptonuria, a disease that results from a deficiency of

Figure 1 Aortic valve leaflets covered in black patches (the third aortic valve leaflet was sent for microbiological analysis).

Figure 2 Sections of the valve leaflet examined microscopically show brown pigment deposition in the body of the valve (haematoxylin and eosin, $\times 200$).

Abbreviation: LAD, left anterior descending artery

Figure 3 Mass spectrometry of the patient's urine sample with raised levels of homogentisic acid.

homogentisic acid oxidase, an enzyme responsible for the metabolic degradation of tyrosine, which is normally present in the liver and kidney. This leads to raised levels of homogentisic acid, which, when polymerised, accumulates in many tissues including those of the skeletal, cardiovascular, genitourinary, respiratory and ocular systems, as well as in the skin. Inheritance is autosomal recessive and occurs with an incidence of one per million births.¹ In groups where consanguinity is present, the incidence may be as high as 1 in 25 000 births.² It is more common in certain areas, notably the former Czechoslovakia. The responsible gene is on chromosome 3q, with various mutations in the gene.³ The enzyme deficiency leads to an accumulation of homogentisic acid, with affected people excreting 4–8 g/day in the urine. The acid produces a false positive for glucose in the Clinitest reaction, but the urine darkens rapidly owing to the presence of 2,5-dehydroxyphenylacetic acid derived from the oxidation and polymerisation of homogentisic acid. Polymerisation increases in alkaline urine. Polymerised homogentisic acid binds strongly to connective tissue. Its destructive effects in cartilage and connective tissue may be related to increased cross-linkage of collagen.⁴

Alkaptonuria is usually diagnosed from the triad of degenerative arthritis, ochronotic connective tissue pigmentation and urine that turns dark brown or black on alkalinisation. The disease is not usually detected until adulthood because the only manifestation in childhood is darkening of urine. Externally, ochronosis is manifested by pigmentation of the ear cartilage and sclera. The most common serious effect of alkaptonuric ochronosis is the development of ochronotic arthropathy. Nearly all patients have arthritis of the knees, hips and occasionally the shoulders. The arthritis clinically and radiologically resembles osteoarthritis and may be confused with it. Changes on radiography are typical and almost pathognomonic (calcification of the intervertebral cartilages). The arthritis is thought to be due to the deposition of homogentisic acid causing premature degeneration of articular cartilages. More sophisticated orthopaedic surgery enables patients with alkaptonuria to live a more active life and as a result, the cardiovascular involvement becomes more evident.

There have been increasing reports of cardiovascular ochronosis.^{3–8} It is well accepted that ochronosis is associated with aortic valve stenosis but mitral and pulmonary valves can be affected, and multiple valves may be involved. The pigment is usually most marked at the valve cusp or at the leaflet base extending into the valve annulus. The pathogenesis of aortic valve calcification and aortic stenosis is probably related to the extensive extracellular deposits of ochronotic pigment. Gaines and Pai⁹ suggest that the anatomical derangement of the valves is caused by the degeneration of pigment-laden fibrocytes, which leads to progressive calcification, and by the fibrosis of the valve substance.

The aorta, coronary arteries, aortic valve and the left ventricle were all affected in our patient, who required an aortic valve replacement and coronary artery bypass grafting. The presence of ochronotic pigment in the aorta and coronary arteries in patients with ochronosis has previously been recorded; however, our patient also had a 9-year history of type 2 diabetes that no doubt contributed to his vascular disease. It has previously been suggested that the deposition of ochronotic pigment in vascular endothelium could lead to the initial injury responsible for the genesis of atheroma, because ochronotic pigmentation has been described in macrophages and smooth-muscle cells of the aortic media.¹⁰ The combination of diabetes and ochronosis is likely to have accelerated this patient's cardiovascular disease.

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