

Ochronosis of the Aortic Valve and Aorta

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A 64-year-old male patient with unknown alkaptonuria and severe aortic stenosis and ischemic heart disease was admitted to the authors' institution for elective surgery. The patient underwent aortic valve replacement with a 25-mm aortic valve (ATS Medical, Inc.) and single venous aortocoronary artery bypass grafting for a right coronary artery. Aortotomy

revealed typical ochronotic pigmentation of a severely calcified aortic valve and aortic intima. A diagnosis of alkaptonuria was confirmed by evidence of homogentisic acid in the patient's urine, together with histopathological analysis.

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Alkaptonuria is an extremely rare disease of tyrosine catabolism. The condition is caused by a deficiency of the enzyme homogentisic acid oxidase in the liver and kidney, which in turn leads to the excretion of homogentisic acid in the urine, and an accumulation of oxidized homogentisic acid pigment in connective tissue. In many patients the condition may remain undiagnosed until middle age, at which time presentation is with degenerative arthritis in mid-life, a gray-brown ochronotic pigmentation of the ears (typically on the antihelix, helix, and concha), and sclerae. Some patients may also develop pigmented renal or prostatic calculi. On rare occasions, degenerative cardiovascular diseases - especially aortic stenosis - may be caused by an accumulation of homogentisic acid pigment in the aortic valve (1-6).

Case report

A 64-year-old male patient with unknown alkaptonuria was admitted to the authors' institution for elective aortic valve replacement to treat severe aortic stenosis. Single-vessel aortocoronary artery bypass grafting was also required for a significant stenosis of the right coronary artery. The patient had a medical history of hypertension, hyperlipoproteinemia and left nephrectomy as a result of tuberculosis contracted

some 40 years previously. During the past two years, he had suffered from dyspnea and typical anginosus chest pain. The electrocardiogram showed negative T-waves in the inferior leads, while transthoracic echocardiography and cardiac catheterization revealed severe aortic stenosis with a systolic pressure gradient >100 mmHg, and 80% stenosis of the proximal region of the right coronary artery. The other cardiac valves were not involved, and no signs could be verified of stenosis or regurgitation on the mitral, pulmonary or tricuspid valves. A preoperative pulmonary function test revealed obstructive lung disease.

At surgery, cardiopulmonary bypass was performed using aortic and bicaval cannulation and moderate hypothermia. Cold antegrade crystalloid (Brettschneider HTK) cardioplegia was used. Aortotomy revealed massive calcification of the aortic valve with gray-black ochronotic pigmentation (Fig. 1), in addition to intensive ochronotic pigmentation of the aortic intima. An aortic valve replacement was performed, using a 25-mm aortic valve (ATS Medical, Inc.). Coronary artery bypass grafting was performed on the right coronary artery using a saphenous vein graft. The patient's recovery was prolonged because of respiratory complications due to the obstructive lung disease, but he was extubated after 72 h. Atrial fibrillation occurred on the third postoperative day, but conversion to sinus rhythm was achieved with amiodarone. The patient was subsequently maintained in sinus rhythm with low doses of beta-adrenergic blockers. He was discharged from hospital on day 17 after surgery, with no further complications.

A diagnosis of alkaptonuria was confirmed by the

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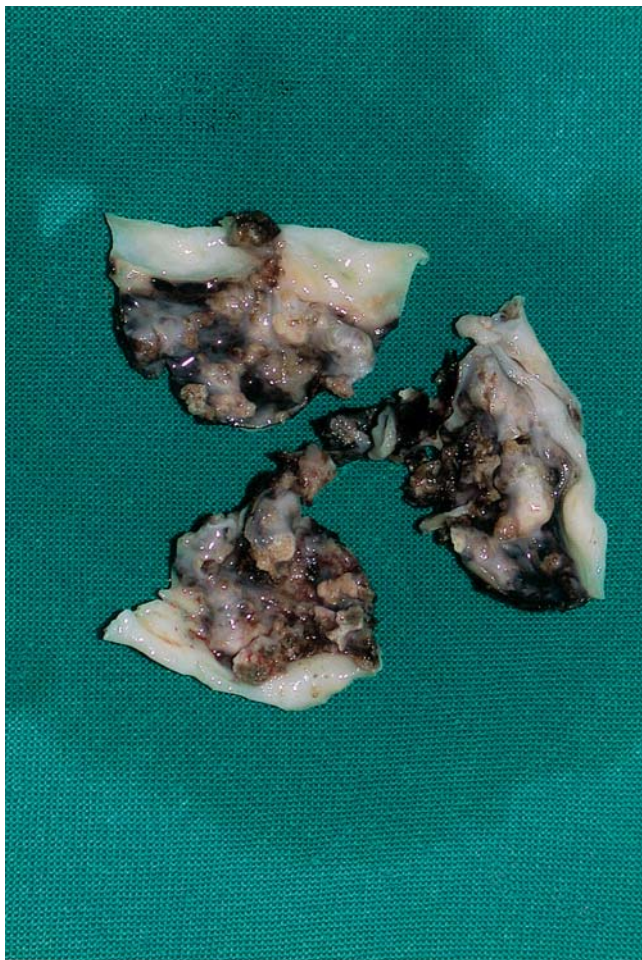


Figure 1: Massive calcification of the aortic cusps with ochronotic pigmentation.

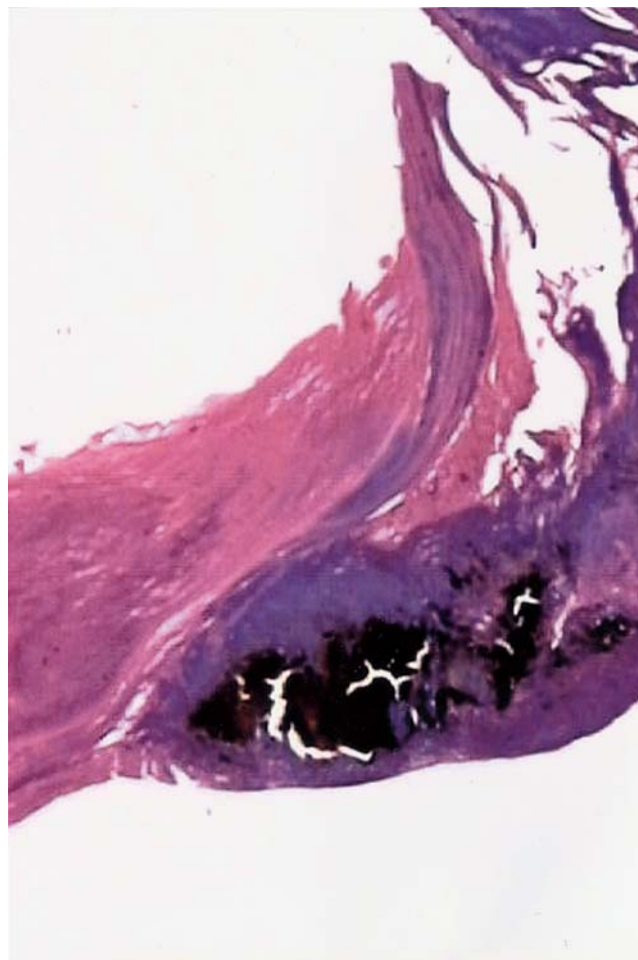


Figure 2: Light microscopic appearance of the aortic cusp in a patient with ochronosis. The cusp is fibrosed and thickened by calcified masses distorting the cuspal architecture.

presence of homogentisic acid in the patient's urine, while histopathological analysis confirmed the diagnosis of ochronosis (Fig. 2).

Microscopically, the cusps were thickened by dense fibrous tissue and calcified masses distorting the cuspal architecture. An extensive deposition of dark brown granular pigment was found in the fibrosal layer, mainly in the areas of calcification. This pigment did not stain with Berlin blue (for iron), and was consistent with the appearance of ochronotic pigment. No relevant family history could be confirmed following the establishment of a diagnosis.

Discussion

Alkaptonuria is extremely rare disease which may not be recognized until middle age, or later. The diagnosis is usually confirmed by a triad of symptoms, including degenerative arthritis, ochronotic pigmentation (typically on the eyes and ears), and urine which

turns black upon alkalization. Rarely, ochronosis may cause degenerative cardiovascular diseases, with ochronotic pigment accumulating in the connective tissue of the aortic, mitral and pulmonary valves, and also in the endocardium of the coronary arteries. In the cardiovascular system the most significant clinical manifestation of ochronosis is aortic stenosis (1-9), though on extremely rare occasions ochronosis may lead to aortic regurgitation (10). The treatment of patients with verified alkaptonuria is usually symptomatic, as therapy with vitamin C and a low-protein diet is ineffective. A proposed alternative treatment with nitisinone (an inhibitor of 4-hydroxyphenylpyruvic acid dioxygenase in the tyrosine catabolic pathway) requires further evaluation (7).

In conclusion, ochronosis is a rare, inherited disease which predominantly involves the aortic valve in the cardiovascular system. The condition should be considered in the differential diagnosis of aortic stenosis.

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