We report the case of a 67-year-old woman who underwent aortic valve replacement and mitral valve repair due to ochronotic valvular disease (alkaptonuria), which was diagnosed incidentally during cardiac surgery. (Tex Heart Inst J 2004;31:445-7)

Alkaptonuria is a very rare congenital metabolic disorder that affects about 1 in 1 million births. This disease is transmitted by a single recessive autosomal gene, resulting in an irreversible, progressive, connective tissue disease. Alkaptonuria is associated with homogentisic acid (HGA) oxidase enzyme deficiency (Fig. 1). This deficiency causes the excretion of large quantities of HGA in the urine, which turns dark upon standing. Although the most common clinical feature is severe ochronotic spondylarthropathy, a wide spectrum of clinical manifestations—including ocular and cutaneous pigmentation, genitourinary obstruction by ochronotic calculi, and cardiovascular system involvement—has been described. Deposition of polymerized HGA occurs in the aortic intima, the aortic and mitral valves, the coronary arteries, the subendocardium, and the pericardium. The exact incidence of cardiovascular disease in patients with ochronosis is not clear; a number of reports suggest a high prevalence of aortic valve stenosis in such patients who are more than 50 years old.1 13

We report the case of a patient who was diagnosed intraoperatively with alkaptonuria.

Case Report

In April 2003, a 67-year-old woman who had severe aortic valve stenosis and moderate mitral valve insufficiency presented at our clinic with dyspnea. She had no history of rheumatic fever or endocarditis, but a history of bilateral total hip and knee replacements was noted. She also had lumbar and cervical polyarthrosis, with some kyphoscoliosis. The results of routine laboratory tests were normal. Echocardiographic findings demonstrated severely calcified aortic valve leaflets, with a mean aortic valve gradient of 65 mmHg. The calculated aortic valve area was 0.4 cm². Mitral valve leaflet malcoaptation and grade 3/4 regurgitation were present. The left ventricular function was normal. Cardiac catheterization confirmed the diagnosis and revealed normal coronary arteries.

The patient underwent open heart surgery. We first detected a dark green sternum, during sternotomy. After opening the pericardium, we noted a brown aorta, which was also remarkable. Cardiopulmonary bypass was instituted by ascending aortic and bicaval cannulation, and cold crystalloid cardioplegic solution was administered retrogradely. Oblique aortotomy revealed a tricuspid aortic valve with thickened dark green leaflets. The aortic wall and mitral valve leaflets had a similar appearance (Fig. 2). As a consequence, a diagnosis of endogenous alkaptonuria was strongly suspected. We resected the aortic valve leaflets and implanted a 19-mm Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis (Model 2700, Edwards Lifesciences; Irvine, Calif) by using 2-0 Ticon interrupted simple sutures. Mitral valve annuloplasty with a 26-mm semi-rigid annuloplasty ring (St. Jude Medical, Inc.; St. Paul, Minn) was also performed via a left atriotomy. The postoperative course of the patient was uneventful, and she was discharged from the hospital on day 9. On her 1-year follow-up visit, she was in New York Heart Association functional class I.

A detailed history taken retrospectively after surgery revealed that the patient’s urine turned dark if it stood for several hours. Maculae corneae were prominent.
She was 1 of 2 siblings. None of her relatives had been diagnosed with alkaptonuria; however, her brother (60 years old) had undergone a lumbar hernia operation, and he also had a cervical hernia and maculae corneae. One of the patient’s 2 daughters had polyarthrosis in her back and hip.

Pathologic examination of the aortic leaflets revealed ochronosis (Fig. 3), and high urine HGA levels confirmed alkaptonuria (1,600 mmol/mol creatinine).

Discussion

In 1908, Sir Archibald Garrod found alkaptonuria to be the 1st disorder in human beings to conform to the principles of mendelian autosomal recessive inheritance.2 The most common complications of alkaptonuria are spondylosis and arthropathies, which result in impairment of posture and gait. A diet low in phenylalanine and tyrosine and high doses of ascorbic acid have been recommended, although they have not been proved useful.1, 2 Nitisinone can reduce HGA production, but this treatment has not yet been tested in the long term.2 In fact, there is no cure for the disease, and treatment is based on management of symptoms. Almost all patients need orthopedic surgery, and the mean age for joint replacement is 55 years. Physical therapy and analgesics are the usual conservative therapy. With current modern management, most patients have a normal life span.1, 2

Although several reports have been published in recent years,3, 4 it is difficult to assess the incidence of cardiac ochronosis accurately because of its rarity. Gould and colleagues5 described autopsy findings in a patient who had died of cardiac ochronosis: calcification had thickened the pigmented valvular cusps with ochronotic material, and both coronary arteries were obstructed by black intimal deposits. However, other authors have concluded that the incidence of coronary arteriosclerosis is not increased by alkaptonuria, and that alkaptonuria is not significantly related to an arteriosclerotic process.1, 2 In a recent study that evaluated the natural history of 58 patients with alkapto-
nuria, no patient had coronary artery calcification before the age of 40 years, but 50% had computed tomographic evidence of coronary artery calcification by the age of 59. In affected patients, there was no correlation between coronary artery calcification and an elevated serum cholesterol level.2

It is generally accepted that aortic valvular stenosis is the most frequent cardiac manifestation of the disease. Gaines and Pai6 suggested that the ochronotic pigment in the aortic valve serves as a stimulus for dystrophic calcifications, which eventually lead to aortic valve stenosis.6 The mean age of cardiac valve involvement (aortic or mitral calcification or regurgitation) is around 54 years; several such patients have undergone aortic valve replacement.2

Mitral and tricuspid involvement do not seem to cause increased prevalence of valvular disease;1, 2 however, as in our case, it might be speculated that chronic ochronosis can cause leaflet thickening and eventual mitral valvular dysfunction. We are not aware of any investigations concerning the optimal prosthetic valve for these patients. We used a bioprosthesis because of the patient’s age, but we do not know whether the disease will lead to increased degeneration of the bioprosthesis.

In conclusion, cardiac ochronosis is a very rare disease, but cardiac surgeons should be aware of this condition since they might be confronted with the typical signs during elective cardiac surgery. Good results can be obtained with a standard surgical approach despite extensive pigment deposits and calcifications.

References