

Aortic Valve Regurgitation in Alkaptonuria

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Aortic valve lesions associated with alkaptonuria tend mostly to be due to aortic valve stenosis, while aortic valve regurgitation is only rarely observed. Herein, a case is reported of severe aortic valve regurgitation and a fibrous strand in a patient with alkaptonuria. A 65-year-old male, with a history of inferior myocardial infarction, presented with symptoms of congestive heart failure. Alkaptonuria was diagnosed based on urine coloration, skin pigmentation and ochronotic arthropathy in the vertebrae and hip. Grade IV aortic valve regurgitation with mild aortic valve stenosis and occlusive disease in the right coronary artery indicated a need for aortic valve replace-

Alkaptonuria is a rare autosomal genetic disorder of tyrosine metabolism which results from a deficiency in the enzyme, homogentisic acid oxidase (1). As a consequence, homogentisic acid becomes the end-product of tyrosine and phenylalanine metabolism. An elevated level of homogentisic acid, when polymerized, accumulates in the connective tissues of the body, leading to the characteristic gray-green pigmentation known as ochronosis. Ochronosis also affects the cardiovascular system, including the aorta, the aortic, mitral and pulmonary valves, the endocardium, and the coronary arteries (2). The accumulated pigment causes degenerative changes of the valve, resulting in valve calcification and stenosis. The most significant clinical cardiovascular manifestation is aortic valve stenosis (2,3), and to date only one case of aortic valve regurgitation associated with alkaptonuria has been reported (4). A fibrous strand of the aortic valve has been reported with either a tricuspid aortic valve (5) or a bicuspid aortic valve (6,7). The functional role of this fibrous strand is not clear, though its rupture may cause aortic

ment and coronary artery bypass grafting. Sclerotic change in the cusps, and shrinkage of the non-coronary cusp, impeded normal coaptation of the aortic valve, and the left-coronary cusp also had a fibrous strand suspending the free margin of the cusp from the aortic wall just above the commissure. The sclerotic change in the cusps, and shrinkage of the non-coronary cusp, appeared to be the causative lesion of aortic valve regurgitation, implying that cardiovascular ochronosis may cause aortic valve regurgitation.

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valve regurgitation (5,6). Herein, atypical cardiovascular findings in a patient with alkaptonuria, in whom the tricuspid aortic valve demonstrated aortic valve regurgitation, are described.

Case report

A 65-year-old male with a history of an inferior myocardial infarction presented with symptoms of congestive heart failure. He had a gray-green pigmentation on the skin of both hands, and also of the conjunctiva. Alkaptonuria was diagnosed based on the pigmentation, urine coloration and ochronotic arthropathy in the vertebrae and hip. An electrocardiogram showed an abnormal Q-wave, in addition to T-wave inversion in leads II, III and aVF. Echocardiography demonstrated the presence of severe aortic valve regurgitation and akinesis in the inferior wall of the left ventricle, with left ventricular dilatation. Congestive heart failure subsided after medical treatment using diuretics and vasodilators. Cardiac catheterization revealed grade IV aortic valve regurgitation and mild aortic valve stenosis with a transvalvular pressure gradient of 20 mmHg. The right coronary artery also showed signs of occlusive disease.

At surgery, the ascending aorta and aortic valve showed gray-green pigmentation (Fig. 1). Three cusps

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Figure 1: The aortic cusps had gray-green pigmentation and were involved in sclerotic change. Shrinkage of the non-coronary cusp was also recognized. The arrow indicates a fibrous strand. LCC: Left coronary cusp; RCC: Right coronary cusp; NCC: Non-coronary cusp.

were slightly calcified and thickened, and the annulus was also calcified. Sclerotic changes in the cusps, and shrinkage of the non-coronary cusp, impeded normal coaptation of the valve. The left coronary cusp had a fibrous strand (Fig. 1), which tethered the free margin of the cusp to the aortic wall just above the commissure.

Aortic valve replacement using a mechanical valve and coronary artery bypass grafting to the right coronary artery were successfully performed. The intima of the right coronary artery had the same pigmentation as that seen in the aorta and the aortic valve. A pathological study of the resected aortic valve showed a marked hyalinization and calcification of each cusp revealing the sclerotic change (Fig. 2). Gray-green pigmentation was seen in the leaflets, but no signs of infective endocarditis were observed.

The patient made an uneventful recovery and was discharged from hospital without any complications. He was free from any symptoms related to the cardiovascular system after surgery, but subsequently died from complications associated with orthopedic surgery that he underwent five years after the aortic valve replacement.

Discussion

Alkaptonuria is a rare autosomal recessive genetic disorder of tyrosine metabolism in which an accumulation of homogentisic acid occurs in the extracellular tissues. Although this metabolic defect is asymptomatic, it causes a triad of homogentisic acid aciduria, ochronotic connective tissue pigmentation, and degenerative arthritis. Although the major disabling compli-

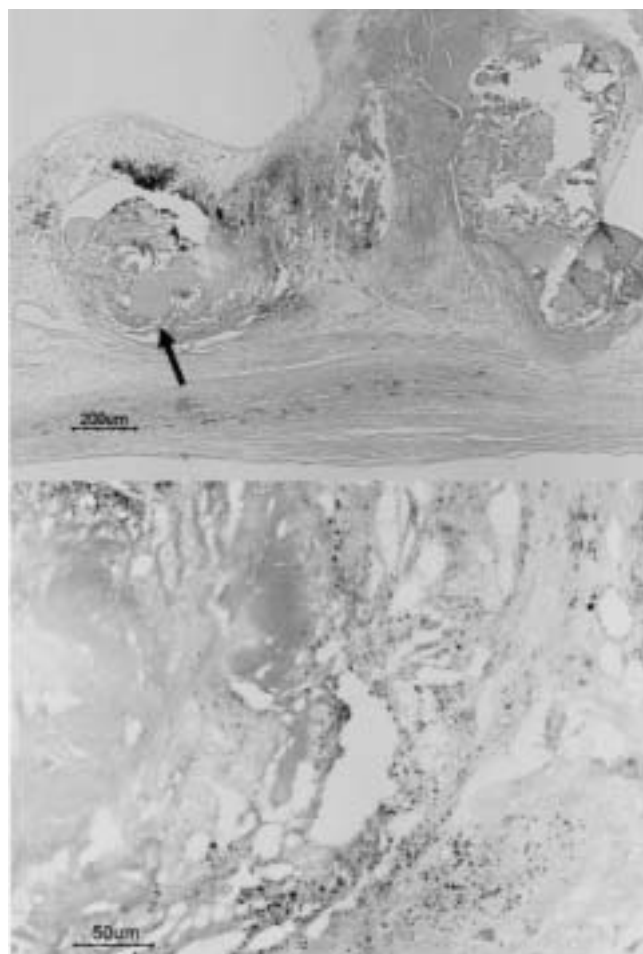


Figure 2: Histopathological examination of the aortic cusp, showing the sclerotic change with hyalinization (arrow) and calcification. Deposits of ochronotic pigment were also observed. (Hematoxylin and eosin staining.)

cations of ochronosis are spondylosis and arthropathy (8,9), recent advances in the orthopedic reconstruction of joints - including total joint replacement - allows for a more active lifestyle in patients with this condition (10). Unfortunately, this active lifestyle tends to unmask clinical cardiovascular symptoms. Cardiovascular ochronosis occurs in the aortic intima, the aortic and mitral valves, coronary arteries and endocardium (2). Gaines and Pai (11), using both transmission electron microscopy and light microscopy, examined the aortic valve of patients with alkaptonuria, and identified extensive extracellular deposits of ochronotic pigment in the aortic valve. These authors postulated that the extracellular pigment resulted from cell death of the pigment-laden cells, and that this was followed by dystrophic calcification with subsequent stenosis of the valve. Therefore, aortic valve calcification and aortic valve stenosis was found predominantly in patients with cardiovascular disease, and to date only one case with aortic valve regurgita-

tion has been reported (4). That case - a 28-year-old male reported by Tsunashima et al. (4) - presented with severe aortic valve regurgitation associated with alkaptonuria, and the patient died from congestive heart failure. The pathogenesis of aortic valve regurgitation in that patient was uncertain, because autopsy had not been performed. In the present case, the aortic valve had gray-green pigmentation, three cusps were slightly calcified and thickened, and the annulus was also calcified. Sclerotic changes in the cusps, and shrinkage of the non-coronary cusp, impeded normal coaptation of the valve, with subsequent valve regurgitation. To the best of the present authors' knowledge, this is the first case of aortic valve regurgitation with alkaptonuria in which the pathogenesis of valve regurgitation has been clarified.

A fibrous strand occurs as a rare abnormal structure attached to the aortic valve, and has been seen in association with either a tricuspid aortic valve (5) or a bicuspid aortic valve (6,7). The functional role of the strand is unclear, though in some cases it appeared to function as a supporting structure of the leaflet (similar to a chorda tendinea in the mitral valve), as its rupture has been reported to cause acute aortic valve regurgitation (5,6). In the present patient, a fibrous strand tethered the left-coronary cusp to the aortic wall, and therefore did not seem to be related to the cause of aortic valve regurgitation.

The present patient was free from any symptoms related to the cardiovascular system for five years following aortic valve replacement. These findings suggest that surgical intervention is appropriate for aortic valve disease with alkaptonuria when the valve lesion fulfills the indicated criteria for valve replacement.

In conclusion, aortic valve regurgitation is a rare lesion observed in patients with cardiovascular ochronosis. It is believed that, if indicated, aortic valve replacement should be performed in patients with alkaptonuria in order to provide a more active lifestyle.

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