AORTIC VALVE REPLACEMENT IN ALKAPTONURIC OCHRONOSIS

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Abstract

Alkaptonuria is an autosomal recessive inborn error of metabolism of the aromatic amino acids. Deficiency of the homogentisate1,2-dioxygenase leads to an increased blood and urinary concentration of homogentisc acid resulting in a slow accumulation of its oxidation products in the connective tissues (ochronosis). The most common clinical manifestation of ochronosis is arthropathy whereas cardiac involvement is very infrequent. We report the case of a patient with ochronotic involvement of the aortic valve who underwent a valve replacement. Some aspects of pathogenesis, and treatment are discussed.

INTRODUCTION

Akaptonuria is a rare autosomal recessive inborn error of metabolism of aromatic amino acids caused by a deficiency of homogentisate 1,2-dioxygenase (HGO) activity. The deficiency of HGO activity has been linked to chromosome 3q21-q23 with over 80 mutations discovered. The inability to break down the homogentisic acid (HGA) leads to the accumulation of HGA and its oxidized product benzoquinone in various tissues and fluids. Cell damage results from the deposition of a melanin-like pigment - a polymerized form of benzoquinone with high affinity for connective tissues- leading to characteristic bluish-black pigmentation known as ochronosis.[1,2]

The birth prevalence of alkaptonuria is estimated at around 1/250.000 to 1/1000.000 individuals. The condition is more common in the Dominican Republic and Slovakia where it affects up to 1 in 19.000 individuals.[1]

Alkaptonuria causes a triad of HGA aciduria, ochronotic connective tissue pigmentation and degenerative arthritis of axial and peripheral joints. Alkaptonuric ochronosis of the cardiovascular system is rare. The heart valves, aorta, endocardium, pericardium and coronary arteries may be affected, with the aortic valve more frequently involved.[1,2]

We report the case of a patient with alkaptonuric ochronosis of the aortic valve who underwent a bioprosthetic valve replacement.

CASE REPORT

A 71-year old woman with symptomatic severe aortic valve stenosis was referred to our Cardiac Surgery Unit. The previous history included congenital deafness, thyroid adenoma, bilateral hip joint and right knee replacement. She had been diagnosed with alkaptonuria six years before. The urinary excretion rate of HGA was 6098 mg/24h (upper normal limit 10mg/24h).

On admission physical examination revealed a bluish-black pigmentation of the sclerae and ears (figure 1). An electrocardiogram displayed a sinus rhythm and left ventricular hypertrophy. A chest x-ray revealed cardiomegaly and calcification of intervertebral discs. A transthoracic echocardiogram confirmed the presence of calcified aortic valve stenosis with a maximum/mean gradient of 95/60 mmHg respectively. The preoperative coronary angiogram demonstrated the absence of coronary lesions.

She underwent an aortic valve replacement under cardiopulmonary bypass. During the operation a tricuspid aortic valve with bluish-black leaflets could be observed. The intima of the aortic root and ascending aorta were also black pigmented (figure 2). A 21 mm Mitroflow 12A pericardial bioprosthesis (Sorin, Milan, Italy) was implanted in the supra-annular position.

The resected aortic leaflets were calcified, thickened and bluish-black pigmented being these findings more marked in the aortic than in the ventricular face. The edge of the cusps was relatively free of degenerative changes

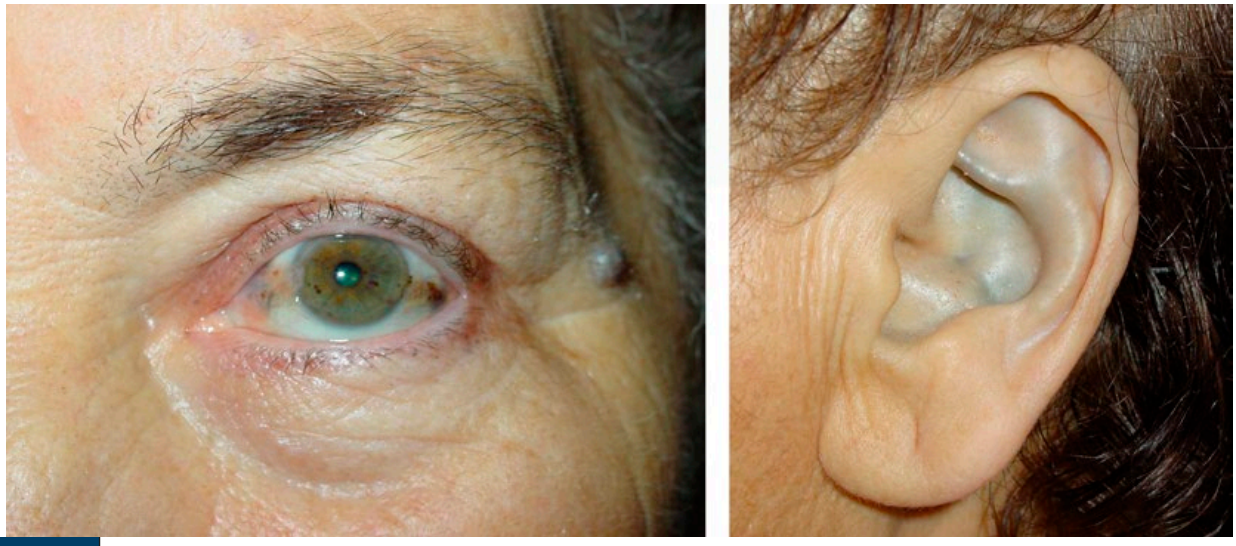

Figure 1 *Ochronotic pigmentation of the ear cartilage and the sclera.*

(figure 3). The microscopic examination revealed nodular calcification, fibrosis, hyalinization and ochronotic dark pigment deposition (figure 4). The patient needed postoperative prolonged mechanical ventilation. Three weeks later she was discharged in good condition. Regular postoperative follow-up visits demonstrated absence of structural valve deterioration until nine years later when the patient died because of a respiratory infection.

DISCUSSION

Cardiac involvement in alkaptonuria is a rare event that not only affects the aortic valve but may also involve the mitral and pulmonary valves, endocardium, pericardium, aorta and coronary arteries.[2,3,4] The life expectancy of patients with alkaptonuria is not significantly reduced although aortic valve involvement may be life-threatening and worsen the prognosis.[1]

It has been suggested that the slow extracellular accumulation of ochronotic pigment in the aortic valve may stimulate an inflammatory response with progressive dystrophic calcification and fibrosis leading to valve stenosis.[2,5] It is important to note that pigment deposition in the aortic valve may be influenced by intravascular pressure and turbulence as we could observe in our case.[4,6]

Alkaptonuria is mostly asymptomatic in early life with arthropathy and heart valve symptoms appearing in the latter decades of life. The prevalence of aortic stenosis in alkaptonuria increases with age affecting around 70% of patients over of 60 years old1. In contrast, the prevalence of coronary artery disease is not increased by alkaptonuria.[2,4]

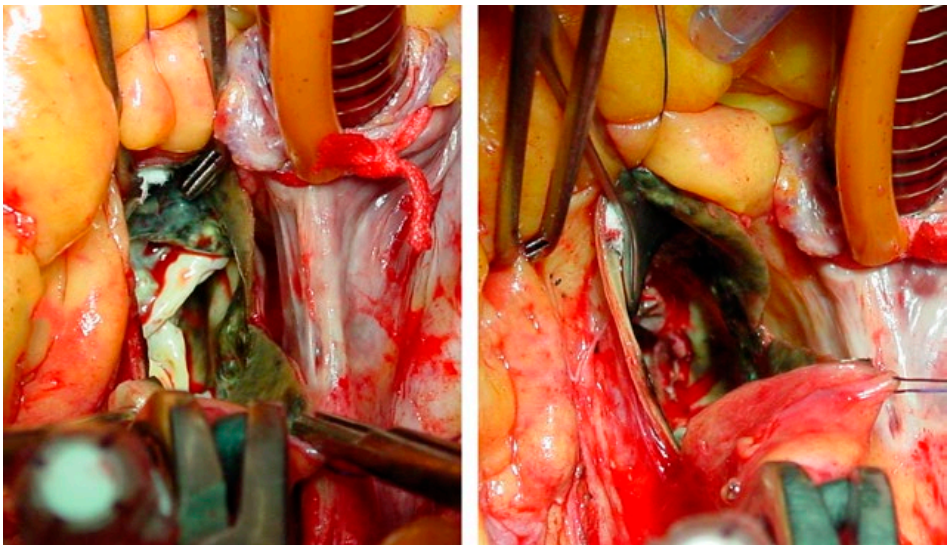

Figure 2 *Black ochronotic pigmentation of the aortic valve (A) and aortic intima after valve resection (B).*

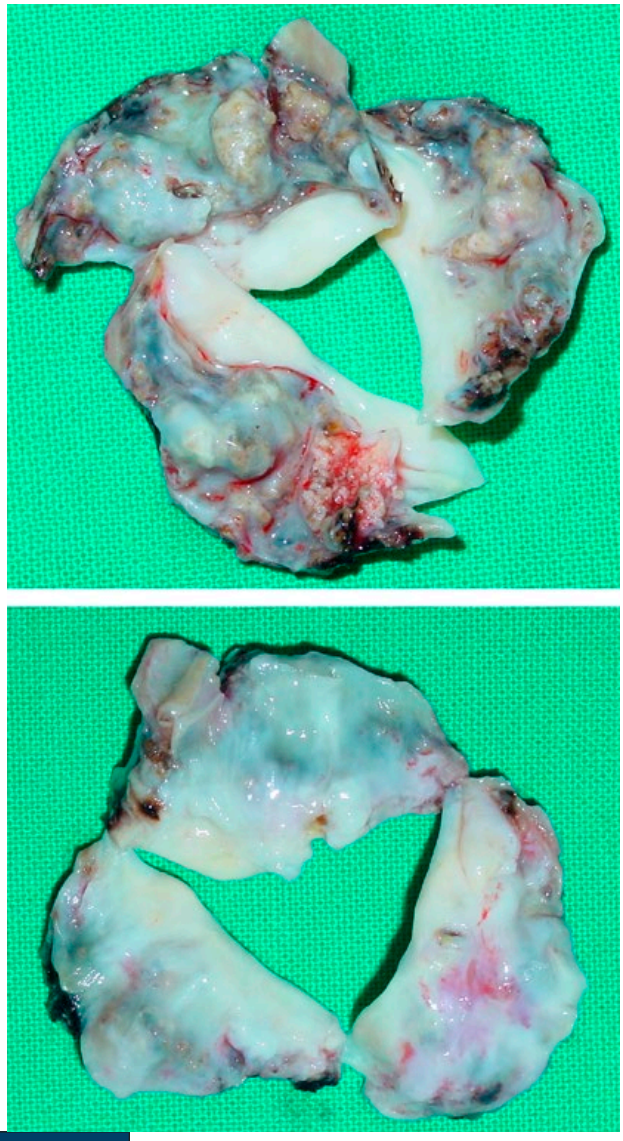

Figure 3 *Massive calcification of the aortic leaflets with ochronotic pigmentation. A) Aortic view. B) Ventricular view.*

The choice of the heart valve prosthesis to use in patients with alkaptonuria is under discussion. It has been suggested that bioprostheses may be exposed to the benzoquinones deposition as in native tissue, thus adversely affecting prosthesis longevity. However the recurrence of ochronosis in bioprosthetic valves has not been reported.[6,7]

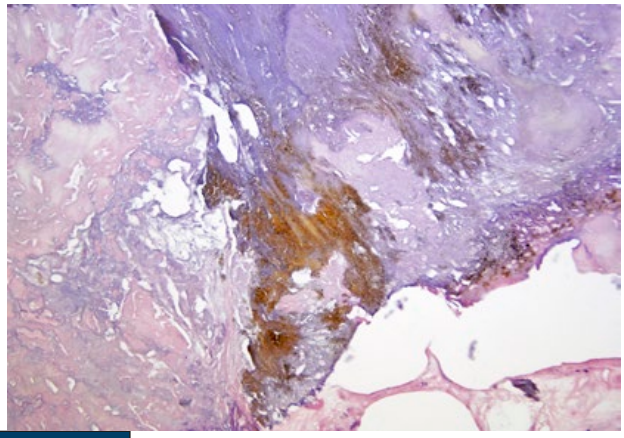

Figure 4 *Histologic examination showing hyalinization, fibrosis and ochre-colored pigment (ochronosis) deposition in the aortic valve leaflets (hematoxylin and eosin x200).*

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