

Case Report / Olgu Sunumu

Incidental diagnosis of ochronosis by aortic valve replacement

Aort kapak replasmanı ile rastlantısal okronozis tanısı

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ABSTRACT

Alkaptonuria is a rare inherited metabolic disease caused by homogentisic acid oxidase enzyme deficiency. Homogentisic acid formed during phenylalanine and tyrosine metabolism cannot be further metabolized and accumulates due to this enzyme deficiency. Some of the homogentisic acid that cannot be removed by metabolism is excreted with urine, some of it causes this accumulation known as ochronosis, which is characterized by dark pigmented color change in tissues. The classic clinical triad of the disease is darkening of the urine color, degenerative arthritis in the joints and dark colored pigmentation in the connective tissue. Herein, we present a case of ochronosis detected incidentally during aortic valve replacement with the diagnosis of aortic insufficiency.

Keywords: Alkaptonuria, aortic valve, homogentisic acid, ochronosis, pathology.

Ochronosis is caused by an inborn gene defect that causes the absence or deficiency of the homogentisic acid (HGA) oxidase enzyme. The classic description of pathological-anatomical changes in ochronosis was made by Virchow, the famous pathologist in 1866.^[1] Homogentisic acid is an intermediate in the metabolism of the amino acids, phenylalanine and tyrosine. In affected individuals, HGA, which forms a yellow-brown-black pigment, accumulates in connective tissue and various other tissues, particularly cartilage. Polymerized HGA binds strongly to tissue. The most frequently affected areas in external examination are ear cartilage, eyelids, sclera and nails. The most common place ochronosis affects the cardiovascular system is the aortic valve. It usually manifests itself

ÖZ

Alkaptonüri, homojensitik asit oksidaz enzim eksikliği nedeniyle oluşan nadir görülen kalıtsal bir metabolik hastalıktır. Fenialanin ve tirozin metabolizması esnasında oluşan homojensitik asit, bu enzim eksikliği nedeniyle daha fazla metabolize edilemez ve birikir. Metabolizma ile uzaklaştırılmayan homojensitik asidin bir kısmı idrar ile atılırken, bir kısmı da dokularda koyu pigmente renk değişikliği ile karakterize okronozis olarak bilinen bu birikime yol açar. İdrar renginde koyulaşma, eklemlerde dejeneratif artrit ve bağ dokuda koyu renkli pigmentasyon hastalığın klasik klinik tiradıdır. Bu yazıda, aort yetersizliği tanısı ile aort kapak replasmanı sırasında rastlantısal olarak tespit edilen bir okronozis olgusu sunuldu.

Anahtar sözcükler: Alkaptonüri, aort kapak, homojensitik asit, okronozis, patoloji.

as stenosis due to the degeneration it causes and calcifications, as well.

Herein, we present a case of ochronosis detected incidentally during aortic valve replacement (AVR) with the diagnosis of aortic insufficiency.

CASE REPORT

A 46-year-old male patient was referred to our clinic for AVR operation, while he was being diagnosed with advanced aortic regurgitation. Transthoracic echocardiographic evaluation revealed dilated ascending aortic sinus as 46 mm at the level of Valsalva, left ventricle hypertrophy, preserved ejection fraction, and tricuspid aortic valve. No stenotic pathology was

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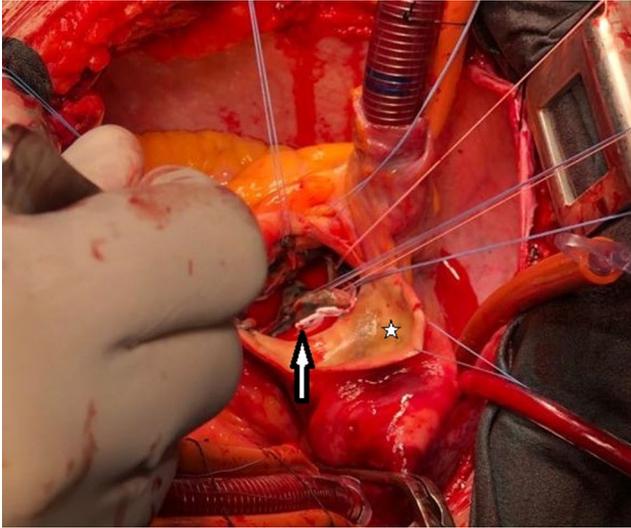


Figure 1. During the operation, black pigmentation extending along the endothelium to the annulus border of aortic valve leaflets (arrow), into the ventricle, the mitral valve and the ascending aortic wall (asterisk).

seen in coronary angiography, except for minimal plaque formations. The patient, who did not have a history of any additional disease, underwent isolated AVR surgery under elective conditions. Since our patient was 110 kg and 182 cm tall and had a body mass index of 33.21 kg/m², when we considered the body surface area value and the calculation of indexed values recommended to account for body size,^[2] only AVR application to the patient was deemed more appropriate intraoperatively according to the current guidelines, and surgical intervention was not preferred in the ascending aorta.^[3] Therefore, AVR alone was performed. During the exploration of the aortic valve, it was observed macroscopically that dark blue-black areas on the aortic valve leaflets, also extending to the left ventricular outflow tract (Figure 1). Samples were taken for pathological examination with suspicion of alkaptonuria. Following aortic valve resection, 27-mm bileaflet mechanical aortic valve replacement (Saint Jude Medical Inc., St. Paul, MN, USA) was

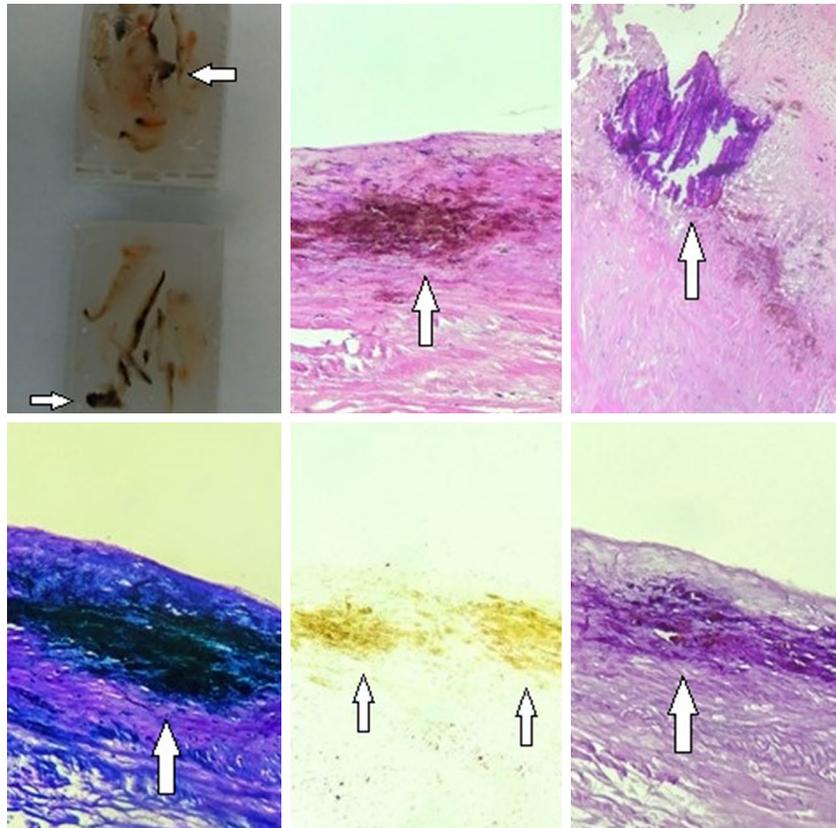


Figure 2. Macroscopic view of the samples taken from the aortic valve in the paraffin block; (a, b) HE dye, at $\times 200$ magnification; yellow-brown pigment deposition and degenerated collagen, dystrophic calcification, positive with (c-e) methylene blue and negative pigmentation with iron (Fe) and melanin withering (arrows).

performed. During the postoperative period, the patient had no previous history of alkaptonuria, but occasionally darkening in the color of the urine. In the histopathological examination of the excised tissues, areas of degenerated collagen, dystrophic calcification with smooth shiny, dense fibrotic, elastic, concave appearance were observed on both surfaces of aortic leaflets (Figure 2). While HGA was found to be high in the urine analysis of the patient, other measurable organic acid values were found to be normal and the patient was diagnosed with alkaptonuria. After the intensive care and service processes went uneventfully, the patient was discharged on Day 6. A written informed consent was obtained from the patient.

DISCUSSION

Alkaptonuria and ochronosis are diseases that have been identified and described in autopsy series since the early 1900s. Although they are more common in some ethnic groups than in other societies, most patients can only be diagnosed incidentally. It progresses with large joint involvement in the musculoskeletal system which is most affected by the disease.^[4] Phornphutkul *et al.*^[5] reported, in their observational study related to the natural course of the disease, that there was joint involvement at the age of 55 years, urinary system stones at the age of 64, and valve involvement at the average age of 54 years. There is no known effective treatment for alkaptonuria, yet. However, the use of high-dose ascorbic acid (vitamin C) is thought to contribute to HGA degradation.^[6]

It should be kept in mind that ochronosis may be due to the use of some drugs, as well as endogenous reasons. Drugs known to cause this non-endogenous secondary form of ochronosis are hydroquinone, phenol or antimalarial drugs. Although the clinic of the disease is well defined, the dark pigmented image, which is very typical, is not one of the first pathologies that come to mind in practice, as it is not a common disease in the society. The situation is similar in the rare ochronotic heart valve involvement. There have been reports of patients who were previously diagnosed with alkaptonuria and followed, as well as many cases that were never diagnosed before and diagnosed during valve operation. While involvement on the aortic valve or in the aortic vessel is observed in almost all of these cases, only mitral valve involvement has been reported very rarely.^[7] Alkaptonuria causes calcific deposits in the aortic valve that typically result in stenosis. There are four aortic insufficiency cases with other

cardiovascular pathologies reported in the literature.^[8,9] As in the other four cases, valvular insufficiency was observed with calcific deposits in our patient. Braconi *et al.*^[10] reported that HGA accumulation triggers oxidative stress and inflammation via serum and chondrocyte proteins, leading to calcium accumulation. The most likely scenario is that this oxidative degeneration and inflammatory processes in the leaflets cause regurgitant flow by disrupting the valve coaptation. Atalay *et al.*^[11] reported that the accumulation in other parts of the cardiovascular system such as the mitral and tricuspid valve has a less pathological course. This can be explained by the relatively higher pressure and flow stress on the aortic valve. Besides, Thakur *et al.*^[12] also argued that the choice of biological valve in patients who are scheduled for replacement due to ochronosis may result in early degeneration due to these high flow dynamics.

In conclusion, although alkaptonuria and related ochronosis are rare, cardiac surgeons should consider ochronosis when confronted with a black pigmented valve structure during the operation of patients scheduled for open heart surgery.

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