

# Aortic Valve in Black: A Case of Aortic Valve Ochronosis

Ahmed Elagamy Musa<sup>1</sup>, Oliver Grimmig<sup>2</sup>, Jenny Sonke<sup>2</sup>

<sup>1</sup>Sana Cardiac Center, Cottbus, Germany

<sup>2</sup>Carl Thiem Hospital, Cottbus, Germany

Email: aelagamy22@yahoo.com

**How to cite this paper:** Musa, A.E., Grimmig, O. and Sonke, J. (2022) Aortic Valve in Black: A Case of Aortic Valve Ochronosis. *World Journal of Cardiovascular Surgery*, 12, 128-134.  
<https://doi.org/10.4236/wjcs.2022.126010>

**Received:** May 16, 2022

**Accepted:** June 26, 2022

**Published:** June 29, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

## Abstract

Alkaptonuria is a rare inherited tyrosine metabolism disorder, resulting in homogentisic acid deposition in the connective tissues. The condition is commonly referred to as ochronosis and manifests as skin pigmentation, degenerative arthropathy, and black urine. Among the rare complications of this disease is the involvement of the cardiovascular system. We report a case of a 63-year-old woman with alkaptonuric ochronosis who had already undergone three joint replacements. She was referred to our center for aortic valve replacement after accidentally discovering severe aortic valve stenosis in the preoperative assessment prior to her fourth joint replacement. Intraoperative findings included ochronosis of a severely calcified black-pigmented aortic valve and black pigmentation of the aortic intima. Histopathological analysis and elevated homogentisic acid levels in the patient's urine confirmed the diagnosis of alkaptonuria. However, alkaptonuria was not diagnosed until aortic valve replacement despite the previous symptoms and signs. This report aims to outline the history, etiology, pathogenesis, clinical presentation, and treatment of aortic valve ochronosis in addition to presenting the case.

## Keywords

Alkaptonuria, Aortic Valve Ochronosis, Black Aortic Valve, Black Aortic Intima

## 1. Introduction

Alkaptonuria is an autosomal recessive rare genetic disorder of amino acid metabolism, affecting phenylalanine and tyrosine. The condition is caused by insufficient homogentisate 1,2-dioxygenase activity in the liver and is manifested by the accumulation of homogentisic acid in extracellular tissues [1]. The responsi-

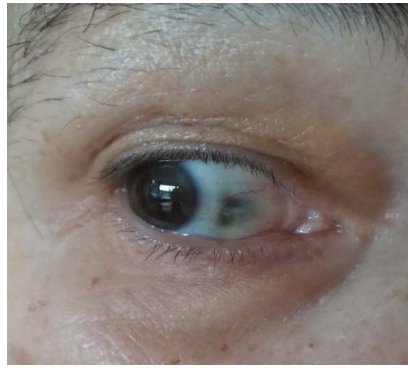
ble gene is on chromosome 3q, with a variety of mutations [2]. Homogenetic acid deposits as oxidized and polymerized pigments (ochronotic pigments) in various tissues and organs, bound irreversibly to collagen, resulting in bluish-black pigmentation [1]. Usually, the diagnosis is based on a triad of degenerative arthritis, ochronotic connective tissue pigmentation, and black urine on alkalinization [3]. Among the most common clinical features is a pigmentation of the skin, sclerae, and ear cartilage; and ochronotic arthropathy affecting mainly the vertebral discs and large joints. Some less common manifestations include urethral and renal calculi and cardiovascular abnormalities, especially valvular disease.

Alkaptonuria affects roughly 1 in 250,000 to 1 in 1,000,000 people, although the incidence in some areas, like Slovakia and the Dominican Republic, is much higher (e.g., 1 in 19,000 in Slovakia) [4]. An Egyptian mummy from 1500 BC was the first specimen verified to have suffered from ochronosis [5]. In 1859, Boedeker used the term alkaptonuria to describe urine discoloration caused by a reducing compound. Wolkow and Baumann identified the compound as homogentisic acid in 1891. In 1866, Virchow named this condition ochronosis (literally “yellow disease” in Greek) since accumulated pigment in the connective tissues appeared yellow under a microscope. In 1908, Garrod proposed that alkaptonuria was an inborn metabolic error, and Neubauer mapped the complete tyrosine-degradation pathway by 1909 [6].

## 2. Case Presentation

We report a case of aortic valve ochronosis encountered during an aortic valve replacement surgery. A 63-year-old woman was referred from a district hospital to our center after severe aortic valve stenosis was discovered in the preoperative evaluation before total right hip replacement. She suffered from intractable chronic right hip pain and restricted mobility not improving despite taking non-steroidal anti-inflammatory drugs and physiotherapy. The patient had a remarkable medical history of progressive degenerative arthritis, which began in her late 40s and affected her hips, knees, shoulders, and spine. Having already undergone a total joint replacement on both knees and the left hip, the right hip should also be replaced. There was no family history of alkaptonuria or other genetic disorders. Her parents were not related. Despite severe aortic stenosis, the patient was asymptomatic until it was discovered accidentally during a preoperative assessment before a right hip replacement. The lack of symptoms may be due to physical limitations resulting from severe arthritis.

General physical examination revealed a well-nourished woman weighing 73 kg with a body mass index of 26.8 and a body surface area of 1.88 m<sup>2</sup>. There was dark blue pigmentation in the sclera of both eyes and the ear cartilages (**Figure 1** & **Figure 2**). Examination of the respiratory, neurological, and abdominal systems was normal. A systolic murmur of Levine grade III/VI was detected in the right intercostal border during auscultation, which implies aortic valve stenosis.



**Figure 1.** Ochronotic pigmentation of the sclera.



**Figure 2.** Ochronotic pigmentation of the ear cartilage.

Electrocardiography revealed sinus rhythm and left ventricular hypertrophy. Echocardiography revealed severely calcified aortic valve leaflets, with a mean aortic valve pressure gradient of 58 mmHg and a maximum pressure gradient of 82 mmHg. The calculated aortic valve area was 0.5 cm<sup>2</sup>. Moreover, both mitral valve leaflets were calcified without significant stenosis (mean pressure gradient: 3 mm Hg with heart rate: 74/min). In addition, there was moderately reduced left ventricular systolic function due to global hypokinesia (left ventricular ejection fraction 40%) accompanied by severe concentric left ventricular hypertrophy. The right ventricular function was normal with a TAPSE of 22 mm. Coronary angiography demonstrated mild coronary artery disease. Routine laboratory tests were unremarkable.

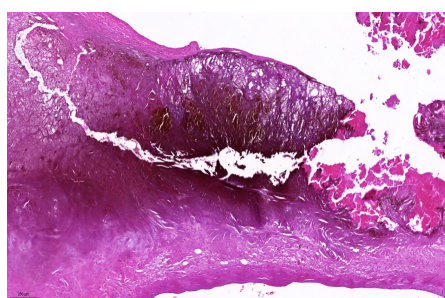
The aortic valve was replaced using cardiopulmonary bypass in January 2022. The intraoperative findings showed a severely calcified tricuspid aortic valve with nodular calcified dark black leaflets (**Figure 3**), severe annular calcification extending into the left ventricle outflow tract, and black pigmentation of the intima extending up the entire luminal surface of ascending aorta. The calcification reached the anterior leaflet of the mitral valve. Neither commissural fusion nor evidence of infective endocarditis was observed. The aortic valve leaflets were resected, the annulus was decalcified, and a portion of the aortic root was resected. Aortic valve replacement (AVR) was performed using a 23 mm Medtronic Hancock II aortic valve prosthesis with a reconstruction of the partially

resected aortic root with a pericardial patch.

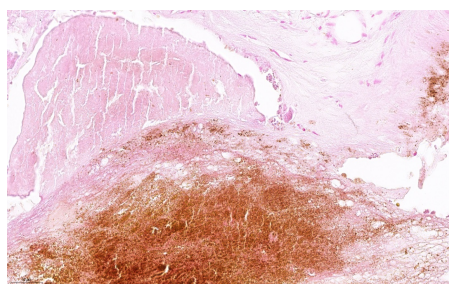
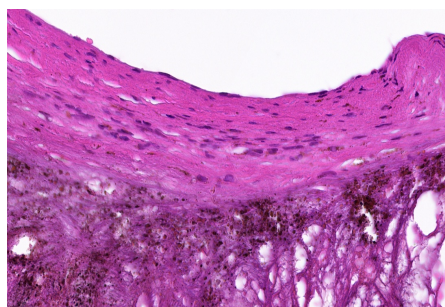
As shown in (Figures 4-6), sections of the aortic valve leaflets show nodular



**Figure 3.** Section of resected aortic valve showing ochronotic black pigmentation.



**Figure 4.** Microscopic view of an aortic valve section showing dark brown to black ochronotic pigment deposition (Hematoxylin and Eosin, original magnification  $\times 5.5$ ).



**Figure 6.** Microscopic view of an aortic valve section showing dark brown pigment deposition (Prussian Blue stain, original magnification  $\times 27$ ). The pigment is not hemosiderin by negative contrast.

calcification and ochronotic dark pigment within the calcified areas and focally in the noncalcified valvular tissue. Both intracellular and extracellular pigment deposition was present, and the granularity was variable, with some areas being coarser and granular like haemosiderin and others being finer.

Alkaptonuria was confirmed by a high level of Homogentisic acid in the urine: 312 mmol/L (reference range: <200 mmol/L). After prolonged exposure to air, the urine color did not change. A urine alkalization test was not performed.

The pathological examination confirmed the diagnosis of aortic valve ochronosis. However, despite the apparent signs and symptoms, our patient had reached 63 years of age without being properly diagnosed with alkaptonuria. The diagnosis of ochronosis was not made until after the aortic valve replacement procedure.

It was an uneventful postoperative course. One week following the surgery, an echocardiogram revealed well-functioning aortic valve prosthesis with a mean aortic valve pressure gradient value of 12 mm Hg and a left ventricular ejection fraction of 40%. The patient was discharged without any complications eight days after surgery.

### **Outcome and Follow-Up**

At present, the patient has not experienced any symptoms related to the cardiovascular system for three months following aortic valve replacement, and a right hip replacement is planned for the near future.

### **3. Discussion**

Alkaptonuria is a rare metabolic disorder which typically manifests as a triad of homogentisic aciduria, ochronotic pigmentation in connective tissues, and degenerative ochronotic arthropathies [3]. Typically, homogentisic aciduria is the first sign, which manifests as blackened urine upon oxidation or alkalization at birth [7]. Secondly, ochronotic connective tissue pigmentation usually appears between the third and fourth decade of life, where dark blue, brown, or black pigmentation appears on the skin, sclera, and cartilages. Finally, in the fourth decade of life, severe degenerative ochronotic arthropathies usually become evident in large joints, such as the hips and knees [8]. Our patient has never noticed abnormal urine discoloration; however, she had a typical presentation of severe ochronotic arthropathy, which began in her late forties. She also noticed the bluish pigmentation of the eye sclera and ear cartilage; however, she did not seek medical attention due to the lack of symptoms.

Cardiovascular involvement is a serious consequence of alkaptonuric ochronosis. Despite several reports being published in recent years [9] [10], it remains challenging to determine the exact incidence of cardiac ochronosis. It has been reported that approximately 40% of alkaptonuric patients will develop cardiovascular disease by their fifth decade [11]. Our patient was 63 years old when severe aortic stenosis was discovered. The ochronotic pigment has been detected

on cardiac valves, aortic intima, coronary arteries, endocardium, and pericardium. The ochronosis-associated valvular disease occurs due to pigment accumulation in valvular tissue, leading to dystrophic calcification and fibrosis, resulting in valvular dysfunction, mainly stenosis [9]. Aortic valve stenosis is the most common cardiac manifestation of the disease, but multiple valvular involvements have also been described [12]. In most cases, the pigment is most prominent at the cusp of the valve or the base of the leaflet extending into the valve annulus. Our patient had a multivalvular disease, including severe aortic valve stenosis and marked calcification of the mitral valve without significant stenosis.

Though alkaptonuria has no effective treatment, its prognosis is relatively good. Management is focused on dealing with the complications associated with the disease. The consumption of high doses of ascorbic acid combined with a dietary restriction in protein (mainly phenylalanine and tyrosine) is often recommended to reduce homogentisic acid levels, but this does not change the course of the disease and is not a long-term treatment for most patients [13]. A high dose of ascorbic acid, approximately 1000 mg per day, has been suggested to reduce homogentisic acid deposition and, therefore, delay or prevent subsequent symptoms. Alkaptonuria-associated arthropathy is typically managed with non-steroidal anti-inflammatory drugs, physical therapy, or total joint replacement.

The 4-hydroxyphenylpyruvate dioxygenase inhibitor Nitisinone reduces the production of homogentisic acid and its excretion in the urine. The initial data showed that Nitisinone slowed down the clinical progression of alkaptonuria, but further studies are still needed to determine its long-term effectiveness and side effects [14]. Due to the minor effect these treatments have on disease progression, the ochronotic valvular disease is most often treated with surgical valve replacement, resulting in a favorable outcome. However, there is still debate about the valve prosthesis of choice for patients with ochronosis. An in-depth understanding of aortic valve ochronosis and its recurrence in heart valve prostheses will require further research. Though cardiac ochronosis is a rare disease, cardiac surgeons need to be aware of its symptoms since they might encounter them during elective cardiac surgery. It is also essential to consider aspergillosis and long-term minocycline therapy as alternate causes of black pigmentation on the aortic valve and walls.

#### **4. Conclusion**

Cardiovascular ochronosis is an extremely rare disease. The diagnosis and management of patients with alkaptonuric ochronosis are complex. Patients have been able to overcome progressive disabilities due to advances in orthopedic and cardiac surgery. Physicians and surgeons should be aware that multiple systems are involved in this disorder; an early diagnosis and proper treatment may significantly improve the quality of life for these patients.

#### **Consent**

Patient consent obtained.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

- [1] Ranganath, L.R., Jarvis, J.C. and Gallagher, J.A. (2013) Recent Advances in Management of Alkaptonuria (Invited Review; Best Practice Article). *Journal of Clinical Pathology*, **66**, 367-373. <https://doi.org/10.1136/jclinpath-2012-200877>
- [2] Janocha, S., Wolz, W., Srsen, S., Srsnova, K., Montagutelli, X., Guénet, J.L., Grimm, T., Kress, W. and Müller, C.R. (1994) The Human Gene for Alkaptonuria (AKU) Maps to Chromosome 3q. *Genomics*, **19**, 5-8. <https://doi.org/10.1006/geno.1994.1003>
- [3] Groseanu, L., Marinescu, R., Laptoiu, D., Botezatu, I., Staniceanu, F., Zurac, S., *et al.* (2010) A Late and Difficult Diagnosis of Ochronosis. *Journal of Medicine and Life*, **3**, 437-443.
- [4] Kottinen, Y.T., Hoikka, V., Landtman, M., Saari, H., Santavirta, S., Metsarinne, K. and Seegmiller, J.E. (1989) Ochronosis: A Report of a Case and a Review of Literature. *Clinical and Experimental Rheumatology*, **7**, 435-444.
- [5] Stenn, F.F., Milgram, J.W., Lee, S.L., Weigand, R.J. and Veis, A. (1977) Biochemical Identification of Homogentisic Acid Pigment in an Ochronotic Egyptian Mummy. *Science*, **197**, 566-568. <https://doi.org/10.1126/science.327549>
- [6] Fernández-Cañón, J.M., Granadino, B., Beltrán-Valero de Bernabé, D., Renedo, M., Fernández-Ruiz, E. and Peñalva, M.A. and Rodríguez de Córdoba, S. (1996) The Molecular Basis of Alkaptonuria. *Nature Genetic*, **14**, 19-24. <https://doi.org/10.1038/ng0996-19>
- [7] Peker, E., Yonden, Z. and Sogut, S. (2008) From Darkening Urine to Early Diagnosis of Alkaptonuria. *Indian Journal of Dermatology, Venereology and Leprology*, **74**, Article No. 700. <https://doi.org/10.4103/0378-6323.45142>
- [8] Keller, J.M., Macaulay, W., Nercessian, O.A. and Jaffe, I.A. (2005) New Developments in Ochronosis: Review of the Literature. *Rheumatology International*, **25**, 81-85. <https://doi.org/10.1007/s00296-004-0498-1>
- [9] Gaines Jr, J.J. and Pai, G.M. (1987) Cardiovascular Ochronosis. *Archives of Pathology & Laboratory Medicine*, **111**, 991-994.
- [10] Cercek, M., Prokselj, K. and Kozelj, M. (2002) Aortic Valve Stenosis in Alkaptonuric Ochronosis. *The Journal of Heart Valve Disease*, **11**, 386-388.
- [11] Pettit, S.J., Fisher, M., Gallagher, J.A. and Ranganath, L.R. (2011) Cardiovascular Manifestations of Alkaptonuria. *Journal of Inherited Metabolic Disease*, **34**, 1177-1181. <https://doi.org/10.1007/s10545-011-9339-z>
- [12] Mori, S., Kawaguchi, T., Kakinuma, H., *et al.* (1994) Alcaptonuria: A Case Complicated with Valvular Heart Disease and Immunodeficiency. *Internal Medicine*, **33**, 512-516. <https://doi.org/10.2169/internalmedicine.33.512>
- [13] Mayatepek, E., Kallas, K., Anninos, A., *et al.* (1998) Effects of Ascorbic Acid and Lowprotein Diet in Alkaptonuria. *European Journal of Pediatrics*, **157**, 867-868. <https://doi.org/10.1007/s004310050956>
- [14] Ranganath, L.R., Khedr, M. and Milan, A.M. (2018) Nitisinone Arrests Ochronosis and Decreases Rate of Progression of Alkaptonuria: Evaluation of the Effect of nItisinone in the United Kingdom National Alkaptonuria Centre. *Molecular Genetics and Metabolism*, **125**, 127-134. <https://doi.org/10.1016/j.ymgme.2018.07.011>