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CASE REPORT
Cardiovascular surgery

Surgical management of calcific valvular and coronary disease in a patient with alkaptonuria: a case report

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Background Alkaptonuria is a rare metabolic disease that causes an increase in homogentisic acid (HGA) due to a lack of enzymatic activity. Commonly, accumulation of HGA presents with dark discoloration of skin and other tissues, also known as ochronosis. Additionally, alkaptonuria can result in other clinical manifestations, including arthritis and cardiac disease. This case highlights alkaptonuria-related cardiac disease and challenges that cardiac surgery teams may face when treating this patient population.

Case summary A 62-year-old male with a history of alkaptonuria, Hodgkin's lymphoma treated with chemoradiation, hypertension, and hyperlipidaemia originally presented with shortness of breath in the setting of known cardiac disease. Cardiac work-up demonstrated aortic stenosis, mitral stenosis, and multivessel coronary artery disease requiring aortic valve replacement, mitral valve replacement, and coronary artery bypass grafting. During the operation, significant discoloration of tissue was observed. This correlated with areas of severe calcification, which was noted throughout both valves. Extensive debridement was required prior to proceeding to valve replacements. Additionally, near-infrared spectroscopy failed to provide accurate measurements of cerebral oxygenation.

Discussion Alkaptonuria is correlated with cardiovascular disease, particularly valvular disease. Intraoperatively, these patients may exhibit noticeable discoloration and severe calcification of various tissues. Additionally, traditional infrared-based methods of cerebral oxygenation monitoring may not be reliable; however, other options of cerebral monitoring may be feasible. With proper pre-operative planning, however, patients with alkaptonuria may safely undergo cardiac surgery.

Keywords Case report • Alkaptonuria • Aortic stenosis • Mitral stenosis • Aortic valve replacement • Coronary artery bypass grafting

ESC curriculum 3.1 Coronary artery disease • 4.2 Aortic stenosis • 4.4 Mitral stenosis • 4.9 Multivalvular disease

Learning points

- Alkaptonuria may lead to notable calcification, making cardiac surgery more difficult. However, cardiac surgery can be safely performed in these patients.
- Traditional forms of cerebral monitoring may not be sufficient in patients with alkaptonuria. Pre-operative planning should take this into account if possible.

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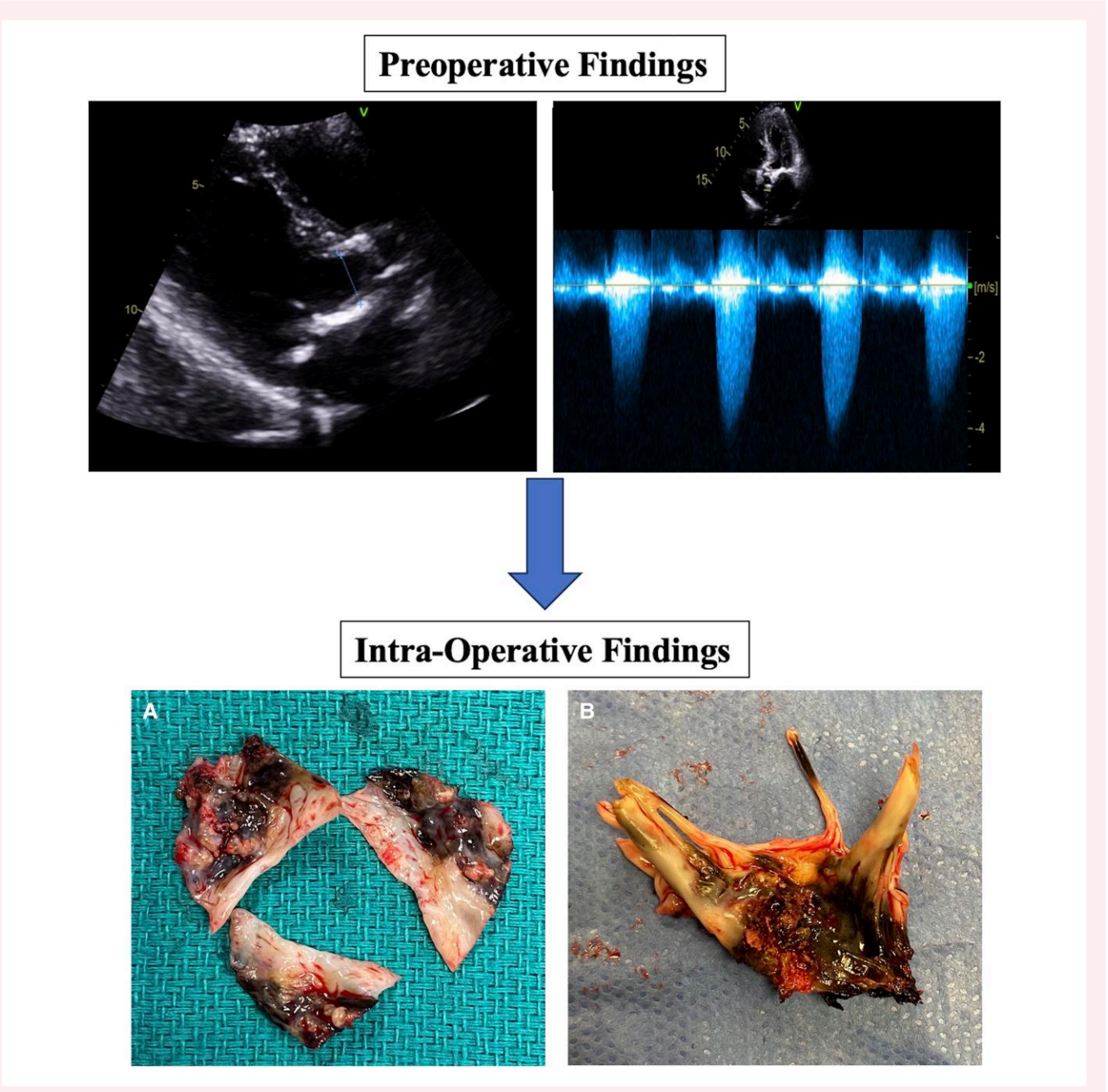
Introduction

Alkaptonuria is a rare genetic disorder that results in homogentisic acid (HGA) accumulation. Clinical effects of HGA include arthritis and discoloration, or ochronosis, of tissue. Alkaptonuria is correlated with cardiovascular disease. One series including 76 patients with alkaptonuria found that 17% of patients had aortic valve disease, a higher rate than would be expected in the general public.[1] Aortic stenosis is the most common complication of alkaptonuria, however mitral valve and coronary involvement can also occur. Herein, we report a case of aortic valve replacement, mitral valve replacement, and coronary artery bypass grafting (CABG). This case highlights the potential findings and challenges that patients with alkaptonuria undergoing cardiac surgery may present with.

Summary figure



Case description

A 62-year-old man with a history of alkaptonuria, Hodgkin's lymphoma treated with radiation and chemotherapy, severe osteoarthritis, hypertension, and hyperlipidaemia was referred to cardiac surgery for progressive shortness of breath on exertion and fatigue in the setting of known valvular heart disease. Prior to presentation, he had been limited in his activities due to severe joint pain and progressive fatigue. He did not endorse chest pain, oedema, palpitations, light-headedness, or syncope. Functionally, he remained able to climb stairs/ambulate

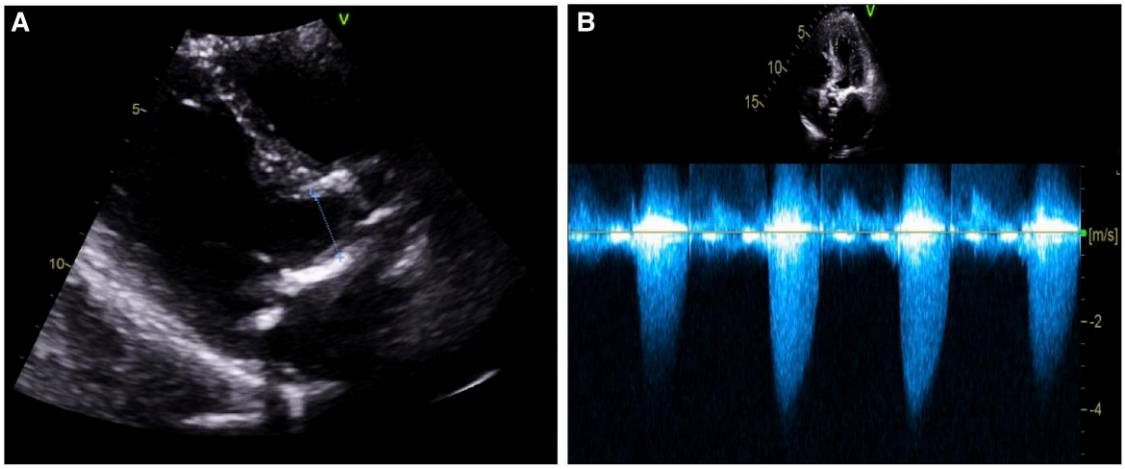


Figure 1 Representative echocardiographic images showing the (*A*) aortic valve diameter and (*B*) velocity through the aortic valve.

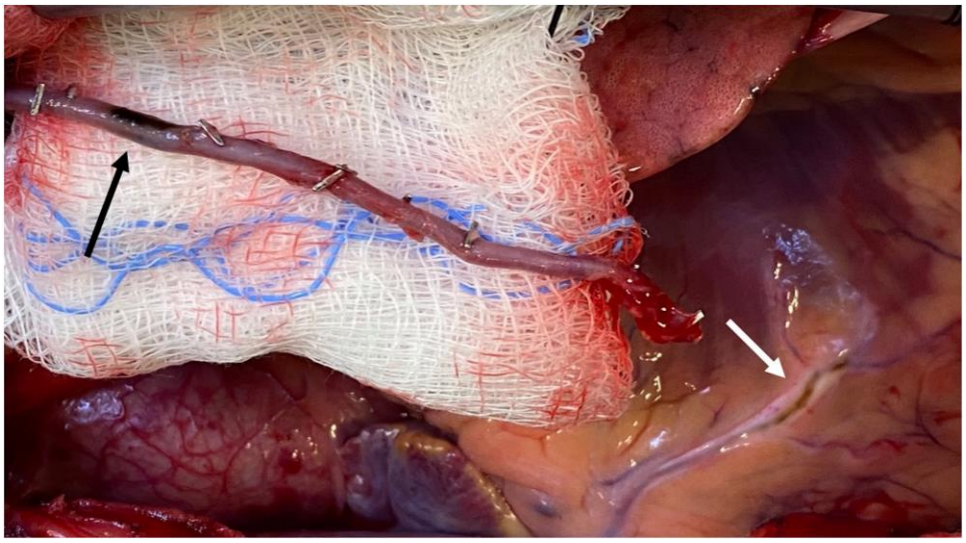


Figure 2 Ochronosis of the left internal mammary artery (black arrow) and coronary arteries (white arrow).

comfortably. Cardiac exam was notable for a single, diminished S2, a late peaking systolic ejection murmur best heard at the base, and an opening snap. The remainder of the physical exam was not notable for typical signs of alkaptonuria, such as discoloration of the eyes or skin.

Pre-operative electrocardiogram demonstrated normal sinus rhythm. Transthoracic echocardiography demonstrated a normal left ventricular ejection fraction with severe aortic stenosis with an aortic valve area of 0.62 cm^2 and mean pressure gradient of 43 mmHg (*Figure 1*). Moderate mitral stenosis, trivial to mild tricuspid valve regurgitation, and trivial pulmonary regurgitation were also present. Coronary angiography demonstrated 80% stenosis of the left anterior descending artery and 70% stenosis of the first diagonal artery.

Given the above findings, elective coronary artery bypass with bioprosthetic aortic and mitral valve replacement was planned. At the time of surgery, near-infrared spectroscopy (NIRS) readings were unobtainable despite extensive device troubleshooting. Of note, there was no visible discoloration of the patient's skin over the temples, suggesting that discoloration of deeper tissues may have inhibited infrared-based oximetry readings.

Intraoperatively, the patient's sternum, aorta, and heart had a bluish-black hue. The left internal mammary artery (LIMA) was skeletonized for grafting of the distal left anterior descending artery. Islands of black discoloration were noted (*Figure 2*) and one area was sent for pathology. Similar discoloration was noted in the coronary arteries (*Figure 2*). The islands of discoloration were not specifically associated

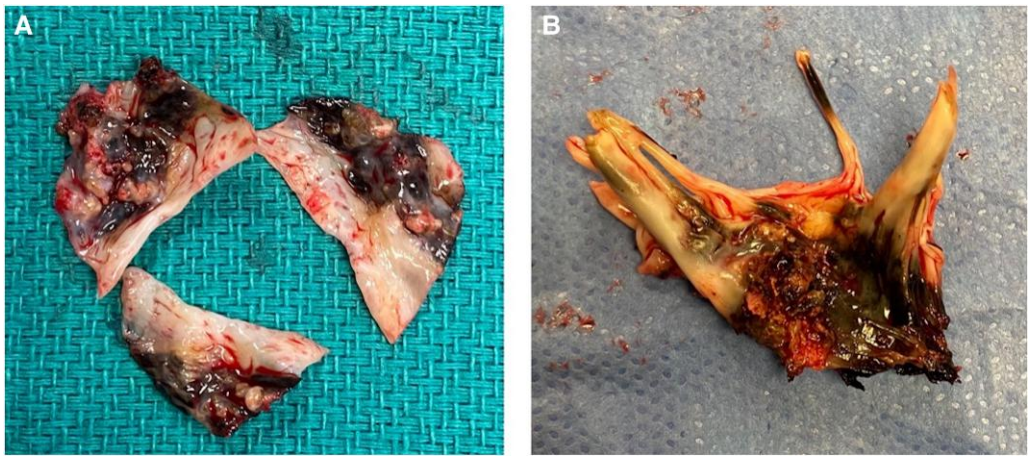


Figure 3 Significant calcification and ochronosis of the (*A*) aortic valve leaflets and (*B*) anterior mitral valve leaflet were present.

with increased adhesions/attachments during LIMA takedown. The aortic valve leaflets, aortomitral curtain, and anterior mitral valve leaflet were also found to be heavily calcified with black discoloration throughout (*Figure 3*). Of note, the discoloration was associated with areas of increased calcific disease. The root and annulus required extensive debridement and subsequent patch reconstruction. Of note, tissue discoloration may increase complexity of tissue debridement as the colour of the tissue planes may not appear as expected. The aortic and mitral valves were replaced with an Edwards Inspiris 23 mm valve and Edwards Mitral Magna Ease 25 mm valve, respectively. The patient was brought to the cardiothoracic intensive care unit in stable condition and extubated on the first post-operative day. Post-operative echocardiogram demonstrated normal biventricular function and normal valve function and gradients. The patient was discharged home on post-operative Day 5 with instructions to remain on warfarin with a goal INR of 2.0–2.5 for 3 months following valve replacements.

At the patient's one month follow-up appointment, he reported that he had increased energy levels and had been ambulating more. The patient will continue regular follow-up with his cardiology team.

Discussion

Alkaptonuria is a rare disease characterized by a lack of homogentisate 1,2 dioxygenase activity, resulting in an accumulation of HGA.[2] Oxidized HGA can polymerize and accumulate in urine or deposit in connective tissue leading to discoloration. Common manifestations of alkaptonuria are homogentisic acidosis, arthritis, and discoloration of tissue, or ochronosis. The heart, kidneys, tendons, and gallbladder can also be involved. Alkaptonuria-related cardiac disease is rare but typically manifests as aortic stenosis when present.[3] Nonetheless, other forms of cardiac disease, including coronary artery disease and other forms of valvular disease, have also been reported.[4–6] The mechanism of alkaptonuria-related cardiovascular disease is unclear; however, it is believed that deposited polymers play a critical role in the development of disease.[7,8]

The aetiology of our patient's coronary artery disease is likely multifactorial, with contributions from alkaptonuria and history of radiation. Previous literature has demonstrated increased coronary calcification in the form of coronary artery disease in alkaptonuria[1,2,4] and increased rates of coronary artery disease following radiation.[9] In this patient, intraoperative visual examination showed that areas of ochronosis largely overlapped with areas of calcification on the coronaries, supporting the hypothesized causal effect of oxidized HGA polymer deposition on calcific cardiovascular disease. Despite discoloration, we found that coronary targets may still be identified using usual techniques, including finger palpation. On the LIMA, ochronosis seemed to be localized to areas in close contact with the ribs. While discoloration may obscure tissue planes during LIMA takedown, no increase in adhesions/attachments of the LIMA was noted during takedown. Further, specimens sent for pathology did not demonstrate any endoluminal abnormalities within the LIMA.

Our case also highlights limitations in cerebral saturation monitoring, as NIRS signals may be reduced or absent in this population due the effect of ochronosis, mirroring the effect darker skin complexion has on infrared light-based oxygenation monitoring.[10] Our experience is consistent with a report from Argiriadou *et al*.,[11] who were likewise unsuccessful in employing NIRS cerebral oxygenation monitoring. It is important to note that a lack of ochronosis of the temples may not exclude discoloration of deeper soft tissue or bone that may inhibit infrared-based oxygenation measurement. Though not necessary, if surgical teams plan to utilize cerebral oxygen monitoring, alternatives include systems that rely on more than two wavelengths to measure cerebral oxygenation.[12] Jugular venous oxygen saturation may also provide more reliable measurements of cerebral oxygenation.[13]

To our knowledge, this is the first reported case of a concomitant aortic and mitral valve replacement with CABG in a patient with alkaptonuria. The extensive calcification of both valves highlights increased difficulty/extent of valve debridement that may be necessary due to the systemic effects of alkaptonuria. This may make valve repair or replacement more challenging in these patients.

Aortic stenosis due to alkaptonuria is thought to present around 50 years of age;[2] as such, most of these patients would likely qualify for a bioprosthetic valve replacement according to current ESC/EACTS guidelines.[14] However, some groups have speculated that the pathogenic process of alkaptonuria-related cardiac disease may negatively impact bioprosthetic valve function.[5,15] To date, there is a paucity of follow-up data to guide the choice of mechanical vs. bioprosthetic valve selection in patients with alkaptonuria, but this is a factor that may impact the lifespan of bioprosthetic valves in this population.

In summary, our report emphasizes the effect of alkaptonuria on cardiac disease while highlighting what to expect while caring for these patients both the peri-operative and operative setting.

Lead author biography

Riley Boyd recently graduated from Northwestern University Feinberg School of Medicine and is now a paediatrics resident at Ann & Robert H. Lurie Children's Hospital of Chicago. He is a former Backer Fellow in the Heart Center at Ann & Robert H. Lurie Children's Hospital of Chicago and intends to pursue a career in paediatric cardiology.

Consent: The authors have received consent in accordance with COPE guidelines for the publication of this case report.

Conflict of interest: None declared.

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Data availability

Data pertaining to this article are provided within the manuscript. Please contact the corresponding author to request further details.

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