Alkaptonuric aortic stenosis: A case report

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Alkaptonuria is a rare disease of phenylalanine, aromatic amino acids, and tyrosine metabolism. Because of a genetic deficiency of the enzyme homogentisic acid oxidase, an accumulation of homogentisic acid causes ochronotic pigment deposition. The most common clinical manifestations are arthropathy, urinary calculi and discoloration, cutaneous and cartilaginous pigmentation, and cardiac valvular disease. Arthropathy and aortic stenosis are the most debilitating manifestations of the disease. A case of alkaptonuric aortic stenosis is described.

A 75-year-old woman with a history of alkaptonuria presented in the emergency department with complaints of progressive dyspnea. Upon examination, the patient was hypertensive, tachypneic, and tachycardic with premature ventricular contractions. She had pitting edema of the lower extremities and complaints of generalized weakness. Chest x-rays revealed congestive heart failure and pulmonary edema. Diuretics were administered, and a continuous nitroglycerin infusion was initiated in the emergency department. The patient was admitted for further evaluation.

The patient's respiratory status continued to decline. She was intubated endotracheally 1 day after admission. Subsequent cardiac evaluation revealed an ejection fraction of 35%, severe aortic stenosis, mild coronary artery disease, ischemic cardiomyopathy, and anteroapical akinesis. A dobutamine infusion was instituted for persistent hypotension, and renal dose dopamine was initiated for oliguric renal failure. The patient underwent an emergency operation for an aortic valve replacement with a Dacron patch 10 days after admission. Cardiopulmonary bypass and mild hypothermia were used during the procedure. The patient's hemodynamic status remained tenuous throughout the procedure. Although the first attempt to wean off cardiopulmonary bypass failed, the second attempt was successful with the aid of an intra-aortic balloon pump, inotropic support, and atrioventricular pacing. These measures were maintained during transport to the surgical intensive care unit. In the intensive care unit, the patient did not have an audible blood pressure or a palpable pulse without the support of the intra-aortic balloon pump and atrioventricular pacing. Coarse atrial fibrillation was the underlying electrocardiogram rhythm in the absence of atrioventricular pacing. Sodium bicarbonate was given without improvement. After discussion with the family, all life support measures were discontinued. The patient died 10 minutes after her arrival in the intensive care unit.

Alkaptonuria's pathogenesis is manifested as both local and systemic in nature. Collagen vascular diseases share a similar pattern of multisystem involvement.
Despite the negative outcome for the patient described, valuable insight can be obtained by studying this case and noting the anesthetic considerations specific to collagen vascular diseases in general.

Key words: Alkaptonuria, aortic stenosis, ochronosis.

Introduction
Alkaptonuria is a rare autosomal recessive disease. An error of metabolism causes a deficiency of homogentisic acid oxidase enzyme in phenylalanine and tyrosine catabolism. An abnormal accumulation of homogentisic acid (HGA) is exclusive to this disorder. Urine left standing gradually darkens as the HGA oxidizes. Alkaline conditions enhance the reaction, which gives rise to the name alkaptonuria. The incidence of this disorder is estimated to be 1:1,000,000 live births. Consanguineous marriages have resulted in an even higher prevalence in certain areas of Eastern Europe.

The accumulated HGA is either excreted through the renal tubules or polymerized into a melanin-like pigment. The pigment has an affinity for fibrillar collagen, especially cartilage. Pigment deposition occurs in the skeletal, synovial, cardiovascular, genitourinary, respiratory, ocular, and cutaneous tissues. The resulting characteristic bluish black discoloration is termed endogenous ochronosis.

Signs and symptoms of this disease vary considerably and include spondylosis, arthropathy, hoarseness, dysphasia, rib-cage stiffness, pulmonary scarring, urinary calculi and obstruction, frequent urinary tract infections, and cardiac valvular calcification and stenosis. Bluish black discoloration of the ears, dorsum of the hands, nail beds, and skin also occurs. The most frequently occurring manifestations are spondylosis, arthropathy, urinary discoloration, and ocular and cutaneous pigmentation. Arthropathy and cardiac valvular disease are the most debilitating symptoms.

The homogentisic acid oxidase enzyme deficiency is present at birth, but HGA is efficiently secreted by the renal tubular system until the third or fourth decade of life, when clinical signs of the disease emerge due to the accumulation of HGA. Any aggregate of clinical signs should suggest the diagnosis, which is confirmed by the presence of HGA in the urine. There is no known cure for the disease, and treatment is based on symptomatology.

This article describes and discusses the relationship between the pathogenesis of alkaptonuria and its subsequent anesthetic implications. The case report describes a profound case of alkaptonuria with severe ochronotic aortic stenosis necessitating emergency aortic valve replacement.

Case report
- **Admission.** A 75-year-old woman was admitted to William Beaumont Hospital via the emergency department with a 5-day history of dyspnea. The patient's medical history included alkaptonuria, obesity, depression, anxiety-related insomnia, shortness of breath, lower extremity edema, and 4 years of weakness-based wheelchair use. The patient was allergic to penicillin and denied smoking or chronic alcoholism. Prior to this admission, the patient stated that she had not seen a doctor in 35 years and had been taking diazepam to relieve her anxiety-related shortness of breath. The patient denied prior hospital admissions or surgeries.

- **Preoperative.** Upon examination in the emergency department, the patient was noted to have a temperature of 35.6°C, blood pressure of 220/110 mm Hg, tachypneic respiratory rate of 40, systolic murmur, sinus tachycardia at a rate of 107 with multiple premature ventricular contractions per 12-lead electrocardiogram (ECG), lethargy, blue scleral deposits, bilateral ochronosis of the ears, and an ulcerated lesion on her back. Coarse bilateral rales were auscultated, and the chest x-ray indicated congestive heart failure and pulmonary edema. Bilateral lower extremities were cyanotic, with cellulitis and 3+ pitting edema. She denied chest pain, pressure, or palpitations. Furosemide, morphine, potassium, and a nitroglycerin infusion were administered in the emergency department. The patient was admitted to a nursing unit for further evaluation.

Subsequent progression to respiratory failure necessitated intubation and transfer to the coronary care unit within 24 hours of admission. Antibiotic therapy was instituted. An echocardiogram revealed severe aortic stenosis, ischemic cardiomyopathy, and significantly impaired left ventricular function. A dopamine infusion was initiated for diuresis and as treatment for oliguric renal failure. A dobutamine infusion also was initiated to treat persistent hypotension. Cardiac catheterization results demonstrated an ejection fraction of 35%, a critical aortic stenosis of 0.6 cm², cardiomyopathy with anteropapical akinesis, and mild coronary artery disease. The patient was noted to be febrile and septic 1 day after catheterization and 6 days after admission, although blood, urine, and wound cultures later were inconclusive.

- **Perioperative.** The patient was ASA physical status VE when taken to the operating room for an aortic valve replacement 10 days after admission. The patient exhibited a decreased level of con-
consciousness, dusky complexion, brown urine, ochronotic ears and sclera, hypotension (80/40 mm Hg), and was intubated and breathing 100% oxygen. During transport to the operating room, a dopamine infusion was infusing rapidly at an undetermined rate, and dobutamine was infusing at 5 µg/kg per minute.

The patient was placed on the ventilator after tube placement was confirmed, and 100% oxygen was maintained throughout the case. A noninvasive blood pressure cuff, 5-lead ECG, and pulse oximetry were used in addition to invasive monitoring. General anesthesia was induced with vecuronium 6 mg intravenously. Vercuronium was used throughout the case to maintain 0 out of 4 train-of-4 twitches on the peripheral nerve stimulator. A nasogastric tube was inserted and placed to low intermittent suction, then removed prior to bypass. An arterial line was placed femorally due to an inability to palpate a radial pulse. A right internal jugular double lumen central line and right internal jugular pulmonary artery catheter were inserted. Her baseline hemodynamic values were heart rate, 100; temperature, 38.3°C; cardiac output, 2.4 L/min; cardiac index, 1.41 L/min per square meter; systemic vascular resistance, 666 dynes; pulmonary artery diastolic pressure, 50 mm Hg; and central venous pressure, 30 mm Hg. Sinus tachycardia was noted per lead II and V5 ECG monitoring. Initial arterial blood gas results were pH, 7.11; PaO2, 48; PaCO2, 103; base excess, -14; O2 saturation, 100%. A total of 150 mEq of sodium bicarbonate was given prior to the initiation of cardiopulmonary bypass (CPB), and the patient was hyperventilated. Hemodynamics prior to CPB were blood pressure, 70/40 mm Hg; central venous pressure, 25 mm Hg; pulmonary artery diastolic pressure, 32 mm Hg; and heart rate, 105, with dobutamine infusing at 5 µg/kg per minute. Aminocaproic acid, 5 g and a total of 5mg of midazolam, titrated in divided doses, were administered intravenously before CPB. No inhalation agents were administered due to the patient's hemodynamic instability.

Prior to cannulation, heparin, 500 U/kg, was administered via a central line. Cardiopulmonary bypass commenced, and the patient was cooled to 32°C. The heart was arrested with antegrade and retrograde cold blood cardioplegia coupled with topical hypothermia and retrograde infusions of cardioplegic agents. The native valve was excised following a transverse aortotomy, and the annulus was debrided of calcium. Intraoperative findings showed the heart had calcification of the lateral wall of the ascending aorta and 4+ concentric hypertrophy. The tricuspid valve was densely calcified, and black pigmentation was noted in the aortic intima and valve leaflets. A 19-mm Carpentier Edwards valve was sutured in place, and the aortotomy was closed with the aid of a Dacron patch. Mean arterial pressures were maintained from 42 to 57 mm Hg during CPB.

The aortic arch and heart were deaired. Initial sinus rhythm was noted after defibrillation with inotropic support; however, weaning from CPB failed. The patient was initially on CPB for 99 minutes. Full CPB was re instituted for another 20 minutes. Before the patient was weaned from the CPB, magnesium sulfate, 1 g; calcium chloride, 1 g; sodium bicarbonate, 50 mEq; and 100 mg of hydrocortisone sodium succinate were administered. An intra-aortic balloon pump (IABP) was inserted via a femoral access site, and the patient was weaned off CPB with the IABP 1:1, DDD atrioventricular pacing at 80 beats per minute, and maximal doses of inotropic intravenous medications. The post-CPB hemodynamic values were cardiac output, 2.8 L/min; cardiac index, 11.6 L/min per square meter; systemic vascular resistance, 857 dynes; and pulmonary artery diastolic pressure 30 mm Hg. Propramine, 500 mg; calcium chloride, 1 g; and midazolam, 1 mg were given intravenously following CPB. A total of 3,500 mL of crystalloid and 1,000 mL of "cell saver" blood was given during the case. The urine output was noted to be 0.3 mL/kg per hour. The sternum was left open due to tenuous hemodynamics and cardiac edema. An occlusive dressing was applied. The patient was transported to the surgical intensive care unit in critical condition with the IABP 1:1, atrioventricular pacing and epinephrine and norepinephrine infusing at high doses.

Postoperative. In the surgical intensive care unit, the underlying ECG rhythm without atrioventricular pacing was a coarse ventricular fibrillation. The patient had no palpable pulse, and the blood pressure was inaudible without the IABP augmentation. A total of 50 mEq of sodium bicarbonate was given intravenously. The underlying ECG rhythm remained coarse ventricular fibrillation. After discussion with the family, the IABP, pacemaker, and ventilator were discontinued. The patient died 10 minutes after her arrival in the surgical intensive care unit.

Pathologic findings. Although a postmortem examination was not performed, the pathologic report of the native aortic valve revealed 3 cardiac valve cusps noted to be markedly thickened and nodular and opaque due to firm, granular, tan-yellow-to-black pigment deposition consistent with ochronosis.

Discussion

Alkaptonuria is caused by a rare autosomal
A recessive metabolic disorder causing a deficiency in homogentisic acid oxidase. Incidence is estimated to be 1 in 1,000,000 individuals. This enzyme deficiency is localized in the liver and kidneys and results in the accumulation of HGA in the phenylalanine and tyrosine metabolic pathway (Figure). The accumulation of HGA results in the deposition of HGA polymer in connective tissue, which causes a constellation of clinical manifestations specific to this disease. The clinical manifestations usually do not appear until after the third or fourth decade of life, due to efficient renal excretion of excess HGA earlier in life. Multisystem involvement typically occurs. Specific signs and symptoms include cutaneous ochronosis, arthropathy, cardiac valvular disease, spondylosis, and renal and prostatic calculi. The patient in this case report was diagnosed with alkaptonuria in her fourth decade of life and had displayed many of the characteristic manifestations of the disease. Her life span was significantly compromised, however, due to her severe aortic stenosis.

Endogenous ochronosis is the term used to describe the bluish black pigment deposition and discoloration in connective tissues caused by alkaptonuria. Exogenous ochronosis is the term used to describe cutaneous ochronosis caused by the topical applications of hydroquinones, phenols, resorcinol, and antimalarial medications. The cutaneous tissues most affected by alkaptonuria are the hands, sclera, and ears. The patient in this case report had scleral and bilateral auricular ochronosis. Other areas that may be affected are the laryngeal, tracheal, bronchial, and costal cartilage. The enzyme HGA polyphenol oxidase, which oxidizes and polymerizes HGA, is most active in the skin and cartilaginous tissues. Although cutaneous involvement is generally asymptomatic, hoarseness, dryness, and dysphasia have been reported.

Alkaptonuria is named primarily for the renal manifestations most prominent to the disease. Urine left standing usually gradually darkens over time due to the oxidation of HGA, which is enhanced by alkaline conditions. This is the most prominent sign of the disease due to the large amount of HGA produced and excreted by the kidneys. Ochronotic deposits can form renal, prostatic, bladder, ureteral, and urethral calculi. Due to the alkaline prostatic environment, calculi are found most commonly in the prostate. Prostatic obstruction may cause uremia and lead to death. Renal calculi also are common, which can cause obstruction and frequent urinary tract infections. The diagnosis of alkaptonuria often results from observed urine discoloration.

The patient in this case report exhibited a dis-
coloration of her urine with a progression to oliguric renal failure. A strong causative factor may have been the patient's persistent hypotensive state prior to surgery. Sepsis, hypovolemic shock, hypoperfusion secondary to valvular disease, or volume depletion may have compromised her renal perfusion by contributing to the formation of calculi. Antibiotics also can affect renal function and cause nephrotoxic acute tubular necrosis. Renal failure in this individual proved to be detrimental to her respiratory status and contributed to ongoing congestive heart failure.

Involvement of the large joints, such as the hip and knee, may result in severe disability. The deposition of the ochronotic pigments results in brittleness and fragmentation of the cartilage. Large joints most frequently involved are the spine, pelvis, shoulders, and knees. Spinal involvement includes disk herniation, spondylitis, and osteophyte formation. The pelvis and knees tend to have tendinous calcification, while the shoulders may exhibit extreme joint space narrowing and bony spurs. Pain, stiffness, crepitation, flexion contractures, and limitation of motion are commonly reported symptoms. The patient in this case had suffered severe disability necessitating wheelchair use; however, the patient denied having arthritis. She had attributed her wheelchair use to the onset of generalized weakness. It is unclear whether arthropathy or aortic stenosis contributed to her generalized weakness and resulting disability.

Pigment deposition may result in aortic stenosis, a functionally significant valvular lesion. Aortic and mitral valves are most commonly affected. Pigment deposition also occurs in the aortic intima and in atherosclerotic plaques. Valvular pigment deposition often leads to rigidity and calcification. Coronary artery disease and peripheral vascular disease have been associated with ochronosis. The association of arteriosclerosis and ochronosis still remains controversial. Kenny et al postulated that ochronotic pigments in vascular endothelium could lead to the initial injury responsible for atheroma genesis, supported by the presence of ochronotic pigmentation in macrophages and smooth muscle cells of the aortic media. It also has been suggested that the anatomical changes in valvular tissue are caused by the degeneration of pigment-laden fibrocytes, leading to progressive fibrosis and calcification of the valve. Cardiac involvement in this case was the primary cause of the patient's disability and mortality. She did not seek early treatment for symptoms related to her aortic stenosis. Her orthopnea and edema persisted for a prolonged period of time. Perhaps early diagnosis and medical intervention would have optimized her cardiovascular status and prevented the cardiomyopathy. An aortic valve replacement earlier in the pathogenesis of her disease also might have provided her with an improved outcome. This case clearly illustrates the importance of prompt medical interventions for symptomatic manifestations of this disease, especially in the face of significant cardiovascular compromise. Although an association with coronary artery disease has been discussed, coronary artery disease was not a major contributor to this patient's pathology. Cardiac evaluation revealed only mild coronary artery disease. Conversely, a critical aortic stenosis, coupled with delayed intervention, led to her poor prognosis and outcome.

Sepsis also contributed to this patient's hemodynamic instability. Although blood and urine cultures did not isolate a specific organism, the patient had a septic profile 6 days after admission and 1 day after cardiac catheterization. Sources of infection may have been a preexisting ulcerative lesion in the lumbar area, cardiac catheterization, intubation, or urosepsis. Urosepsis may have resulted from a urinary tract infection, which often is associated with alkaptonuria. Urine cultures, however, were inconclusive in this case. Immunodeficiency is not a known copathologic feature, but Mori et al reported the first incidence of immunodeficiency in an alkaptonuric patient with valvular disease in 1994. The authors proposed that lymphocytes might be affected by high concentrations of HGA in serum and/or disturbances of its catabolism in the cells. The patient in this case report may have been immunodeficient as Mori et al had described; however, the patient's immune status was never evaluated during this hospitalization.

Anesthetic management. Due to the rarity of this disease, anesthetic management has not been examined in this population. Symptoms will dictate the surgical procedure and the anesthetic technique. The multisystem manifestations of alkaptonuria resemble those seen in other collagen vascular diseases. The most common collagen vascular diseases are rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and polymyositis/dermatomyositis. Although their origin still remains unknown, the immune system is thought to play a major role in the pathogenesis of these diseases. Alkaptonuria and the collagen diseases both involve diffuse localized joint involvement as well as generalized systemic effects. Specific organ system involvement associated with each disease is summarized in Table 1. Anesthetic considerations for collagen diseases serve as a useful guide to the management of the alkaptonuric patient.

Alkaptonuria shares many of the same anes-
The collagen vascular diseases (Table 2). Organ and tissue involvement often dictates the anesthetic technique to be used. Preoperative assessment is very important for these patients. The anesthetist must be familiar with the pathogenesis of this disease in order to manage the anesthetic properly. Early recognition, diagnosis, and intervention may facilitate the prospects for a normal life span in this population.

Preoperative assessment should include renal and hepatic function tests. The blood urea nitrogen and serum creatinine levels should be noted. Urine discoloration should be documented preoperatively. Cardiac and pulmonary function tests should be performed if the patient has a history of dysfunction or complains of related symptoms. Cardiopulmonary involvement will dictate the need for invasive monitoring during long and tenuous surgical procedures. Restrictive pulmonary disease may stem from ochronotic fibrosis of the costal cartilage. Pulmonary assessment may include pulmonary function tests, chest x-rays, or arterial blood gases. Preoperative musculoskeletal limitations should be assessed and documented. Limitations in mobility will necessitate careful positioning. Proper positioning will minimize the risk of neurovascular compression and additional joint injury. Evaluation of head and neck mobility is very important because of the spondylosis associated with the disease. Each patient's airway should be assessed to determine the potential for difficulty associated with laryngoscopy and intubation. The airway management and induction plan should be based on this assessment.

If the patient presents with renal failure, it will be important to assess the blood urea nitrogen, plasma creatinine, and plasma potassium levels. Potassium-containing intravenous solutions, such as lactated Ringer's solution, should be avoided. Normal saline intravenous solutions, titrated sparingly, are preferred. The renal failure patient also should be evaluated for the presence of atrioventricular shunts for dialysis, which will limit intravenous access. Monitoring the patient's volume status is very important and aids in determining the adequacy of renal perfusion. Central venous pressure monitoring often is indicated as a means of assessing and monitoring volume status. Succinylcholine administration should be avoided because of the potential for hyperkalemia. Renal failure reduces protein binding and decreases albumin's affinity for organic acids. For highly protein-bound drugs, such as barbiturates, the volume of distribution increases secondary to a larger free fraction of unbound drug, while the clearance and elimination half-lives remain unchanged. Although the same total dose may be given, it is recommended that initial doses be decreased and additional doses be titrated to effect. To a lesser extent, the same holds true for ketamine and benzodiazepines.

In contrast, opioid metabolism takes place primarily in the liver, with metabolite excretion taking place in the kidneys. Meperidine and morphine active metabolites may accumulate in plasma and cause prolonged respiratory depression and, in
the case of normeperidine, convulsions may ensue. Meperidine should be avoided for these reasons. Fentanyl and its derivatives are metabolized in a similar manner, although fentanyl metabolite accumulation has not been linked to prolonged narcosis. Except for the nephrotoxicity of some inhalation agents, inhalation agents in general are not of major concern because they do not rely on renal elimination.

In regard to muscle relaxants, renally metabolized muscle relaxants exhibit prolonged elimination half-lives. Atracurium and cisatracurium half-lives are not prolonged due to renally independent ester hydrolysis and Hoffmann elimination. The elimination of single-dose vecuronium is not altered. However, cumulative effects of subsequent vecuronium dosing suggests the use of lower maintenance doses in renal failure patients. The anticholinergic agents, neostigmine, pyridostigmine, and edrophonium, are eliminated primarily through the kidneys. Renal failure prolongs their duration and enhances their reversal properties. Due to the potential variability of muscle relaxant and anticholinergic effects in this population, a peripheral nerve stimulator should be utilized to adequately assess the level of neuromuscular blockade.

In the presence of aortic stenosis, cardiopulmonary function must be assessed preoperatively. Ideally, a cardiac catheterization or echocardiogram report should be reviewed. A 12-lead ECG also should be evaluated. The degree of cardiac dysfunction must be known. Dobutamine, dopamine, and nitroglycerin should be readily available. Invasive monitors, such as an arterial line, pulmonary artery catheter, and central venous pressure, should be anticipated depending on the invasiveness and length of the surgical procedure. Five-lead ECG monitoring in leads II and V5 should be utilized intraoperatively. The maintenance of sinus rhythm, adequate ventricular volume, and coronary perfusion is crucial to this population. These patients are dependent on their atrial "kick" for adequate ventricular filling and tend to be sensitive to volume depletion. Bradycardia commonly causes hypotension by inducing a fall in cardiac output. Tachycardia decreases left ventricular filling time and may cause ischemia. Elevated left ventricular filling pressure should be treated with nitroglycerin because of reduced coronary perfusion pressure. Low doses are used in order to minimize any reductions in ventricular volume; forward flow must be maintained.

Summary

In short, early recognition and diagnosis of alkaptonuria is a vital aspect in optimizing outcomes in patients afflicted with this condition. Anesthetic management includes a careful and thorough physical assessment in order to delineate the level of organ and tissue involvement caused by ochronotic pigment deposition. Anesthetic management should be geared toward identifying specific organ system involvement and optimizing organ tissue function through the selection of appropriate anesthetic techniques and monitoring modalities.

REFERENCES


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