Alkaptonuric ochronosis is a rare autosomal recessive metabolic disorder resulting in a deficiency of homogentisic acid oxidase (alkaptonuria). Ultimately, this enzyme deficiency enables homogentisic acid to accumulate, become polymerized, and be systemically deposited within various tissues of the body (ochronosis). As the disease progresses, tissue deposition of polymerized homogentisic acid eventually will lead to the progressive degeneration of all affected body systems. There is no definitive cure for alkaptonuric ochronosis, and treatment is aimed at controlling and ameliorating symptoms.

Multiple systemic complications occur as a result of alkaptonuric ochronosis. In the skeletal system, cervical, thoracic and lumbosacral degenerative disk disease develop, as do widespread arthritic changes in peripheral and weight-bearing joints. In the respiratory system, dyspnea can develop owing to limited chest excursion as a result of stiffening of cartilage in the chest wall. In the cardiovascular system, coronary and valvular calcification frequently occurs. In the genitourinary system, calculi formation and urine discoloration are chief manifestations.

This case report describes a 63-year-old man with alkaptonuric ochronosis who sustained a stress fracture of the left femoral neck, necessitating surgical repair, which was done without complications. An overview of alkaptonuric ochronosis is presented, and anesthetic implications are discussed.

Key words: Alkaptonuria, homogentisic acid, ochronosis.

Ochronosis is the deposition of an ochre-colored pigment within the skin, cartilage, and collagenous tissues of the body. Although this pigment is pale yellow to reddish brown microscopically, it appears blue-black on visual inspection.1,2 This tissue pigment deposition occurs as a result of alkaptonuria. First described in 1866, alkaptonuria is a rare autosomal recessive disorder resulting in a deficiency of homogentisic acid oxidase (HGAO).3 HGAO is an enzyme necessary for the degradation of homogentisic acid (HGA).3 In the absence of HGAO, HGA accumulates and is polymerized into a blue-black pigment that ultimately is deposited in the skin, cartilage, and collagenous tissues. Specifically, pigment deposition can be seen in skin, bones, articular cartilages, synovial membranes, lungs, heart endocardium and valves, and kidneys.4,5 The major clinical manifestations of this disorder are related to deposition of pigment within affected organs. Thus, a patient with alkaptonuric ochronosis has pigmented skin and often has severe arthritis and pain, restrictive lung dysfunction, coronary artery and valvular disease, and nephrolithiasis and other renal complications. There is no known cure for this disorder, and medical treatment is based on symptomatology.

This case study describes the anesthetic management of a patient with alkaptonuric ochronosis. In addition, the disorder is reviewed and the anesthetic implications are discussed. While alkaptonuric ochronosis is extremely rare, it presents the anesthesia provider with numerous anesthetic implications that can be potentially life threatening.

Case report

A 63-year-old man saw his physician because of a 1-week history of severe pain in his left hip. Despite normal radiographic findings, the patient continued to have severe pain and increased difficulty ambulating. Subsequent magnetic resonance imaging scan demonstrated a stress fracture of the left femoral neck. After consultation and medical clearance by his internist, the patient was scheduled to undergo pinning of the left femoral neck fracture.

A review of his medical history revealed coronary artery disease, mild asthma, prostate cancer, generalized severe ochronotic arthritis, back pain, and hypothyroidism. His surgical history was significant for a total replacement of the right hip, bilateral total knee replacements, lumbar laminectomy, bilateral carpal tunnel repairs, umbilical hernia repair, and coronary artery bypass grafting of 3 vessels with aortic valve replacement. There were no anesthesia-related complications noted in association with these procedures. His present medications were finasteride, warfarin (which was discontinued 1 week before surgery), doxazosin, levethyroxine, folic acid, albuterol, ibuprofen, and meperidine for pain. He had no known drug allergies and denied tobacco and alcohol use.

The preoperative physical examination revealed a
well-nourished man in moderately severe pain (7 on a scale of 0 to 10) secondary to the left femoral neck fracture. The patient’s height was 64 in, and he weighed 100 kg. His admission vital signs were as follows: blood pressure, 167/84 mm Hg; pulse rate, 86 beats per minute (regular rate and rhythm); respiratory rate, 20 breaths per minute; room air oxygen saturation, 97%; and tympanic membrane temperature, 98.8°F.

Inspection revealed a blue-black pigmentation on his sclera, ears, face, and hands. He had marked coarse crepitus and restricted range of motion in his shoulders, elbows, and hands. Furthermore, the coarse crepitus was associated with chronic systemic arthralgias and pain. The airway assessment revealed a short, thick neck with limited neck rotation and poor cervical-spine extension. His Mallampati classification was 3 with a thyromental distance of approximately 6 cm. Auscultation revealed that his lung sounds were clear bilaterally, and no murmurs or abnormal heart sounds were detected.

A 12-lead electrocardiogram showed normal sinus rhythm with left atrial enlargement and nonspecific T-wave changes. A dobutamine stress echocardiograph completed 5 months before admission revealed an ejection fraction of 55% and normal ventricular wall motion with normal valve diameters. Laboratory data obtained preoperatively on the day of surgery revealed the following: hematocrit, 37%; hemoglobin concentration, 12.0 g/dL; platelet count, 201 × 10^9/L; partial thromboplastin time, 28 seconds; prothrombin time, 11.4 seconds; international normalized ratio, 1.1; sodium concentration, 137 mEq/L; chloride concentration, 100 mEq/L; potassium concentration, 3.9 mEq/L; glucose level, 96 mg/dL; serum urea nitrogen concentration, 19 mg/dL; and creatinine level, 1.1 mg/dL. Although thyroid function tests were not completed, the patient was clinically euthyroid.

The anesthesia alternatives, including the risks and benefits, were thoroughly reviewed with the patient. The patient verbalized understanding and desired to proceed with a subarachnoid block. On arrival in the operating room, standard monitors were applied, and oxygen at 4 L/min was administered via nasal cannula. In addition, a flexible fiberoptic bronchoscope and emergency airway cart were available in the room.

Initially, the patient was lightly sedated with midazolam, 2 mg, and fentanyl, 100 µg, and placed in the left lateral decubitus position for placement of the subarachnoid block. Following local infiltration with 1% lidocaine, numerous unsuccessful attempts were made to gain access to the subarachnoid space with a 22-gauge Quincke needle by both nurse anesthesia student and staff anesthesiologist. These approaches were both midline and paramedian and consisted of L2-3, L3-4, and L4-5 levels. All attempts were thwarted by the presence of bone. The patient received an additional 2 mg of midazolam and 100 µg of fentanyl to facilitate multiple attempts.

After witnessing the difficulty in placing the subarachnoid block, the surgeon suggested that the procedure could be completed with infiltration of local anesthesia at the surgical site and intravenous sedation. The patient was positioned supine and placed in the sniffing position, and additional padding was placed at all pressure points. Two sprays of oxymetazoline nasal spray were administered in each nostril. Glycopyrrolate, 0.2 mg, was administered intravenously. Before initial infiltration with local anesthetic at the operative site, a propofol infusion of 75 µg/kg per minute was initiated and titrated during the procedure. The patient also received supplemental 10-mg boluses of ketamine and 25-µg boluses of fentanyl. During the procedure, the patient received a total of 300 mg of propofol, 100 µg of fentanyl, and 50 mg of ketamine. Furthermore, a total of 40 mL of 1% lidocaine with epinephrine 1:200,000 was injected throughout the 38-minute procedure.

The patient continually responded to verbal stimuli throughout the procedure, required no airway support, and was taken to the recovery room awake and alert. His vital signs remained stable throughout the perioperative course, and no problems or complications were noted related to anesthesia. Postoperatively, his pain was markedly reduced, and he was able to ambulate with a walker with partial weight bearing of his left leg. The patient was discharged to home on the first postoperative day.

Discussion

Generally, ochronosis refers to the systemic deposition of ochre-colored pigment within the cartilage and collagenous tissues.1 There are, however, two different forms of ochronosis. Exogenous ochronosis is a chemical syndrome that results from prolonged exposure to certain chemicals such as hydroquinone, phenolic compounds, benzene substances, and oral antimalarials. This prolonged exposure can lead to the abnormal deposition of blue-black pigment in the skin only.2,6 Endogenous ochronosis is a result of alkaptonuria. Alkaptonuria is a rare autosomal recessive disorder occurring in 1 in 1,000,000 individuals; however, there is an even higher incidence with interfamilial marriages.7 It is characterized by a lack of the enzyme HGAO.6 Produced in the kidneys and liver, HGAO is necessary for the conversion of HGA to maleylaceto-
Homogentisic acid that is not excreted by the kidneys into the urine is polymerized into a blue-black pigment that is deposited into virtually all collagen-rich organs. This polymerization and auto-oxidation of HGA into pigment is irreversible. After its formation, this pigment aggressively binds to the connective tissues and stimulates their degeneration. The most common clinical manifestations of ochronosis involve the skeletal, respiratory, cardiovascular, genitourinary, cutaneous, and ocular systems. Generally, these clinical manifestations are not evident until around the fourth decade of life because there is insufficient pigment deposition within affected tissues.

In the skeletal system, cartilaginous deposition of pigment results in brittleness and fragmentation of these structures. While the exact mechanism of these pathologic changes is unknown, it is thought to be due to the pigment acting as a chemical irritant that inhibits the cartilage’s metabolic enzyme system. Consequently, arthritis is the most common clinical feature of ochronosis. Ochronotic arthritis can eventually lead to significant chronic pain, crippling, and disability. This patient manifested systemic crepitus and arthralgias in all of the joints of his upper and lower extremities. We allowed the patient to position himself on the operating room table to his position of comfort and provided additional padding under bony prominences. While acute exacerbations of ochronotic arthritis may clinically resemble rheumatoid arthritis, radiologic findings are typical of osteoarthritis.

With ochronosis, degenerative changes may be seen throughout the entirety of the vertebral column, resulting in generalized pain and stiffness. However, the lumbar spine is the most common region affected. The extent of this patient’s lumbar disease had necessitated a lumbar laminectomy in the past. Other than “stiffness” in his lower back, the patient had no signs or symptoms of lumbar disk disease. As the disease progresses, it is not uncommon for postural deformities to resemble those of ankylosing spondylitis. Although this patient did not have ankylosing spondylitis, he demonstrated decreased rotation and inability to extend his cervical spine. Based on the physical examination, oral tracheal intubation with a standard laryngoscope likely would be extremely difficult.

When we decided to proceed with the procedure using local anesthetic infiltration and intravenous sedation, we also thought it was prudent to prepare the patient and optimize conditions for an awake oral or nasal intubation using the fiberoptic bronchoscope. The nasopharyngeal mucosa was prepared with oxymetazoline for decongestion and vasoconstriction. In addition, glycopyrrolate was administered as an antisialagogue to mitigate the salivary effects of ketamine, minimizing secretions that could impede visualization with the fiberoptic bronchoscopy.

Overall, the radiographic manifestations of ochronotic arthritis can be divided into spinal and extraspinal abnormalities. The characteristic manifestations of spinal abnormalities include widespread disk calcification, disk space narrowing, vertebral osteoporosis, and mild osteophytosis. Extraspinal abnormalities occur in the hips, shoulders, and knees, resulting in joint space loss, mild osteophytosis, and tendon abnormalities. The degree of extraspinal involvement in this case was impressive. This patient had already had both knees and his right hip replaced because of the disease. In addition, despite optimum positioning and multiple attempts, the extent of osteophytosis prevented access to the subarachnoid space.

As in the skeletal system, ochronosis results in pigment deposition in the cartilage associated with the respiratory system. Again, this pigment deposition causes the cartilage to fragment and become brittle. These pathologic cartilaginous changes often result in xerostomia and dyspnea. Heavy deposition of pigment in the laryngeal, tracheal, and bronchial cartilages may result in hoarseness and dysphagia. Restrictive pulmonary disease also may result from ochronotic fibrosis of the costal cartilages. This patient did not manifest any of the potential respiratory problems associated with alkaptonuric ochronosis. Despite his history of asthma and our inability to assess his exercise tolerance, we did not believe that preoperative evaluation by pulmonary function tests were warranted. His asthma was optimized with an albuterol inhaler, he had no adventitious breath sounds, he had a negative smoking history, and he did not demonstrate any other signs or symptoms or respiratory involvement.

A variety of cardiovascular abnormalities are associated with the deposition of pigment in the cardiovascular system. A thorough preoperative evaluation of the patient’s cardiovascular status is essential. The cardiovascular lesions of ochronosis include discol-
oration of the heart valves, endocardium, and intima of the aorta. Heart valves also can become calcified and stenotic. These valvular changes are due to accumulation of pigment and do not occur until middle age. The aortic valve has the highest incidence of calcifications and stenosis, followed by the mitral and pulmonary valves. There is also an increased incidence of generalized atherosclerosis, and myocardial infarction is a common cause of death. Because of the systemic manifestations of this disease, it can be very difficult to evaluate exercise tolerance. Despite replacement of the aortic valve and 3-vessel coronary artery bypass grafting, this patient had normal dobutamine stress test results and no electrocardiographic evidence of ischemia or infarction.

The accumulation of HGA predisposes the patient to the formation of renal calculi, which can form anywhere along the genitourinary tract. However, nephrolithiasis is the most common and, in many patients, may be the initial symptom. Renal calculi can cause frequent urinary tract infections, obstruction, and, potentially, renal failure.

The discoloration evident in the skin is due to deposition of ochronotic pigment within the hair follicles and sweat glands. With age, the blue-black discoloration appears, particularly in the external ears, sclera, and air-exposed cutaneous sites. Pigmentation is rarely observed before the age of 20 or 30 years. Ocular pigmentation is especially prominent and appears in approximately 70% of the patients. Referred to as the Osler sign, ochronotic pigment deposition is confined to the exposed areas of the sclera and becomes evident during the third decade of life. Pigmentation is confined to the exposed areas of the sclera and becomes evident during the third decade of life. To date, there is no literature to suggest that scleral pigment deposition is associated with any effects on visual function.

Anesthetic implications

The systemic manifestations of alkaptonuric ochronosis resemble other musculoskeletal disorders such as osteoarthritis, ankylosing spondylitis, and collagen vascular diseases such as rheumatoid arthritis. Anesthetic considerations for these disorders can serve as a useful guide to the management of a patient with alkaptonuric ochronosis. The anesthetic considerations presented address each organ system as they pertain to the anesthetic management of a patient with alkaptonuric ochronosis. A thorough evaluation of the type and severity of systemic dysfunction is essential before providing anesthesia to these patients. Organ and tissue involvement will influence the anesthetic technique to be used.

Abnormalities in the skeletal system necessitate a preoperative evaluation of joint motion to help determine how the extremities should be positioned and how well these positions will be tolerated during surgery or positioning for regional anesthesia techniques. Proper patient positioning and padding of pressure points prevent nerve palsies, skin ulcerations, and further structural damage to the joints. In addition, degenerative changes along the spine, particularly in the lumbar region, may make regional techniques such as epidural and subarachnoid blocks unsuccessful.

Because pigment deposition can cause cartilage to fragment and become brittle, the extent of vertebral spine involvement must be evaluated carefully. This can be done by performing a thorough preoperative neurological assessment. Degenerative changes in the cervical and lumbar spine may be manifested by radicular pain radiating into the extremities with weakness, numbness, and/or paresthesias. In addition, if severe spinal stenosis and cord compression are present, the patient may have the aforementioned symptoms as well as a positive Babinski reflex, hyperreflexia, and spasticity in the extremities. If neurological symptoms are present, additional radiographic evaluation of the affected spine area may be warranted.

Range of motion evaluation of the cervical spine is critically important in patients with alkaptonuric ochronosis. Progression of the disease may alter joint function to the extent that neck motion may diminish with time and make previous documentation of a successful intubation meaningless. Because patients with alkaptonuric ochronosis may undergo repeated anesthetics, the technique of airway management must be clearly documented each time in the patient’s medical record.

Hoarseness or dyspnea may signal a narrowing of the glottic opening, and a smaller endotracheal tube may be warranted. A flexible fiberoptic bronchoscope and difficult airway cart always should be readily available for patients with ochronosis. The potential for heavy pigment deposition in the cartilage of the respiratory system may cause restrictive pulmonary dysfunction, and preoperative pulmonary function testing should be considered. Restrictive dysfunction will be reflected in a proportional decrease in vital capacity, forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV1); however, the FEV1/FVC ratio will remain normal.

A thorough cardiac evaluation is critical in patients with alkaptonuric ochronosis. During the physical examination, auscultation should be done to detect murmurs, clicks, or gallops. More specifically, to detect aortic stenosis, auscultation of the second right inter-
costal space for a systolic murmur should be performed.28 At a minimum, all patients should have a preoperative 12-lead electrocardiogram. This simple diagnostic test can reveal evidence of ischemia, conduction abnormalities, previous infarction, and left ventricular hypertrophy or strain.25 In the cardiovascular system, underlying coronary artery disease may be masked by debilitation and limited joint mobility, which would interfere with the assessment of exercise tolerance.24 If coronary artery disease is suspected and physical limitations impair the ability to evaluate exercise tolerance with a treadmill, pharmacologic stress tests can be completed with dobutamine, dipyridamole-thallium, or Cardiolite (a kit for the preparation of technetium Tc99m sestamibi for injection).

Valvular heart disease is common in patients with ochronosis, and preoperative evaluation should be concerned primarily with determining the location and severity of the lesion and its hemodynamic significance. Preoperative echocardiography would be a prudent course of action because it will provide information regarding valvular function, chamber filling, wall contractility and motion, and regional and global ventricular function.24 However, in patients who are severely debilitated (recent signs and symptoms of ischemic heart disease or history of congestive heart disease), cardiac catheterization may be warranted. Ultimately, the degree of cardiovascular involvement will dictate the need for invasive monitoring during a proposed surgical procedure.29

In the genitourinary system, medical history is the single most important source of information in establishing the presence or absence of renal dysfunction in patients with ochronosis. Patients with suspected or known renal disease should have serum urea nitrogen and creatinine tests done to evaluate glomerular filtration rate and renal tubular function.24 Furthermore, serum electrolyte, hemoglobin, and hematocrit results should be ascertained. Urine discoloration may be present preoperatively and should be documented. Adjusting the dosage of medications based on the degree of renal dysfunction in patients with ochronosis is an important consideration.

A patient’s medication history should be evaluated thoroughly. Patients with ochronosis also deal with chronic arthritic pain and, as a result, may take nonsteroidal anti-inflammatory drugs. Long-term use of aspirin or a nonsteroidal anti-inflammatory drug may result in platelet dysfunction, prolongation of bleeding time, and gastrointestinal bleeding.25 Coagulation tests such as a platelet count, partial thromboplastin time, and prothrombin time should be assessed.

Summary
Alkaptonuria will almost inevitably progress to ochronosis, and ochronosis will progress to ochronotic arthritis.11 Currently there is no cure for this disorder, and treatment is focused on controlling the patient’s symptoms.10 Alkaptonuric ochronosis is very rare, and most affected patients may be treated by physicians who are unaware of the causal relationship between this metabolic disorder and the patient’s arthritic complaints.3 Much of the literature describes the clinical manifestations of this metabolic disorder; however, there is a paucity of information regarding the anesthetic implications of alkaptonuric ochronosis.

Care of the patient with alkaptonuric ochronosis can be complex and challenging. Comprehensive preoperative evaluation and discussion of the risks are essential when caring for these patients. While there are no formal anesthesia guidelines reported in the literature for patients with this disorder, using the anesthesia considerations for musculoskeletal disorders and collagen vascular diseases may be useful tools in the management of these patients during surgery.

REFERENCES

AUTHORS
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