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## CLINICAL INFORMATION

# Anesthetic management of two patients with alkaptonuric ochronosis for total knee arthroplasty



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### KEYWORDS

Alkaptonuria;  
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**Abstract** The current case report describes two cases of alkaptonuric ochronosis for anesthetic management. Alkaptonuria is a rare genetic orphan disease of tyrosine metabolism characterized by an accumulation of homogentisic acid in cartilage and connective tissues. Patients present most commonly for orthopedic joint surgery due to progressive arthropathy that can be misdiagnosed many a times. However respiratory, airway, cardiovascular and genitourinary systems complications can occur with age progressing. Restricted range of motion of cervical spine may lead to difficulty with airway management. In addition, degenerative changes and stiffness of lumbar spine due to ochronosis would make neuraxial blockade challenging. Although this inherited condition is extremely rare, anesthesiologists should be aware of its existence and prepare for management of potential challenging problems. This report highlights special care and precautions that need to be taken during anesthetic management.

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### PALAVRAS-CHAVE

Alcaptonúria;  
Ocronose;  
Anestesia

### Manejo anestésico de dois pacientes com ocronose alcaptonúrica para artroplastia total do joelho

**Resumo** Este relato descreve o manejo anestésico em dois casos de ocronose alcaptonúrica. Alcaptonúria é uma doença genética rara do metabolismo de tirosina caracterizada por acúmulo de ácido homogentísico em cartilagem e tecidos conjuntivos. Os pacientes geralmente recorrem à cirurgia ortopédica devido à artropatia progressiva que, muitas vezes, pode ser diagnosticada incorretamente. No entanto, complicações das vias respiratórias, cardiovasculares e geniturinárias podem ocorrer com o avanço da idade. A restrição de mobilidade da

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coluna cervical pode levar ao manejo difícil das vias aéreas. Além disso, as alterações degenerativas e a rigidez da coluna lombar devido à ocrnose podem tornar o bloqueio neuroaxial um desafio. Embora essa condição hereditária seja extremamente rara, os anestesiológicos devem estar cientes de sua existência e se prepararem para o manejo de potenciais problemas desafiadores. Este relato destaca os cuidados e precauções especiais que devem ser tomadas durante o manejo anestésico.

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## Introduction

Alkaptonuria (AKU) is a rare metabolic disorder, with an estimated prevalence between 1 in 250,000 and 1 million live births in most populations.<sup>1</sup> AKU is caused by a deficiency of the Homogentisate 1,2-dioxygenase (HGO) enzyme, which converts homogentisic acid (HGA) to maleylacetoacetic acid in the catabolic pathway of tyrosine. Disease is characterized by the accumulation of HGA and its oxidized products in all connective tissues of the body. Accumulation of HGA may act as a chemical irritant, leading to inflammation and degeneration. As a result, AKU has three major features; (1) homogentisic aciduria (darkening of the urine upon contact with air or after exposure to an alkaline agent); (2) ochronosis (bluish-black pigmentation of connective tissue); and (3) arthritis.<sup>1</sup>

Ochronotic arthropathy is the most common complication of AKU.<sup>1</sup> The deposition of polymer is assumed to cause an inflammatory response that results in calcium deposition in both synovial and intervertebral joints. Clinical manifestations include back and peripheral joint pain, limitation of movement and stiffness. Joint symptoms, typically begin in the large weightbearing joints at third decade of life, and progress, until chronic pain prompts a knee, hip, or shoulder replacement, at an average age of 55 years.<sup>1</sup> Valvular heart diseases,<sup>1,2</sup> renal stones,<sup>1</sup> restrictive pulmonary disease are other important but less common consequences of alkaptonuric ochronosis.<sup>1</sup> There is no definitive cure for AKU and treatment management is usually symptomatic. In this case report we describe the anesthetic management of two patients with AKU for a total knee replacement surgery.

## Case 1

A 59-year-old, body mass index (BMI) = 44.6 kg.m<sup>-2</sup> female patient complained of low back pain with stiffness, bilateral knee pain causing restricted mobility. She was diagnosed with end-stage knee arthritis and scheduled for left knee replacement surgery. A review of her medical history revealed hypertension and diabetes mellitus. She had previously undergone bilateral hip replacement surgery (at ages 49 and 48). Preoperative airway examination showed adequate mouth opening, Mallampati classification MP-III, 5.5 cm of thyromental distance, short, thick neck, with limited cervical spine mobility. The cardiac and respiratory systems were normal on examination. Complete blood count, coagulation profile, biochemical parameters, renal

and liver function were also within normal limits. She was American Society of Anesthesiologists (ASA) physical class III. We initially planned to perform surgery under spinal anesthesia and written informed consent was obtained. In the operating room standard monitors (ECG, pulse oximeter, non-invasive blood pressure) were applied and an intravenous infusion of normal saline solution started at a rate of 15 mL.min<sup>-1</sup>. During positioning we faced with difficulty due to her multiple joint deformities. After premedication (midazolam 2 mg and fentanyl 50 mcg) and taking all aseptic precautions lumbar punctures were attempted at 2 different spinal levels (L3–4 and L4–5) using by median or paramedian approach by two experienced anesthesiologists. But unfortunately flexibility of the lumbar spine was reduced and our attempts failed as the needle was met with bone in all directions. The technique of awake intubation under local anesthesia was explained to the patient and consent was obtained. Our initial plan was to use fiberoptic methods, but the equipment was unavailable, so the videolaryngoscope was used instead. The patient oropharyngeal mucosa was anesthetized by 10% lidocaine topical spray; fentanyl 50 µg and atropine 0.5 mg were administered intravenously. The tracheal intubation was performed at the first attempt using the McGrath videolaryngoscope without any complications. A Grade 3 view (Cormack and Lehane) of the larynx was obtained and 7.0 cuffed endotracheal tube was passed through the larynx over difficult intubation stylet. The surgery lasted 55 min, patient remained hemodynamically stable throughout the procedure. There was minimal blood loss, approximately 1700 mL of normal saline was infused. During surgery, black discoloration was visible on the joint cartilage and a concern was raised that this patient may have ochronosis. The patient was extubated uneventfully upon full awakening from anesthesia and transported to the recovery room. She was discharged home on the third postoperative day without any complications. After the histological diagnosis, the patient was re-examined for alkaptonuria. She reported a history of dark brown discolored urine but she has never complained about it before. There were black ochronotic pigmentations of the sclera and skin.

## Case 2

A 57-year-old, BMI = 24.4 kg.m<sup>-2</sup> male patient, scheduled for left knee replacement surgery with a diagnosis of alkaptonuric ochronosis. A review of his medical history revealed

dyslipidemia, hypertension. He also had a prior history of coronary heart disease and had undergone percutaneous coronary angioplasty for coronary artery disease, with coronary stent placement. Airway examination revealed Mallampatti class II, thyromental distance was 6.5 cm with adequate mouth opening and minimal restricted neck movement. Preoperative blood analysis was within normal range. Echocardiogram showed a left ventricular ejection fraction of 55%, left ventricular dysfunction, without aortic valve involvement. Pulmonary function tests revealed moderate restrictive pulmonary disease (forced vital capacity = 2.14 L, 66% of predicted airway disease). Radiographic examination showed intervertebral disk calcifications and narrowing of the disk spaces. Ultrasound examination of abdomen was normal. An ASA physical status III was assigned and the patient was informed about the high perioperative risk due to multiple comorbid illnesses. Written informed consent was obtained for both general and neuroaxial anesthesia. Difficult airway cart, including a gum elastic bougie, videolaryngoscope and intubating laryngeal mask airway, was kept ready. On the day of surgery right radial artery catheter was placed. Baseline vital signs were a heart rate of 61 bpm, blood pressure 145/86 mmHg, respiratory rate 12 min, SpO<sub>2</sub> 95% on room air. An intravenous infusion of Lactated Ringer's solution started at a rate of 10 mL.min<sup>-1</sup>, and special care was taken with silicone pads to avoid any pressure on the affected joints. After premedication (midazolam 2 mg) he was placed in the lateral position. Lumbar spine was scanned in a longitudinal parasagittal plane, from L2 spinous level to and S1 vertebrae, using a 2–5 MHz curved ultrasound transducer, to assess the possibility of a central neuraxial blockade. The interlaminar spaces were extremely narrowed except at L4–5 level. The location of the neuraxial midline and the L4–5 intervertebral level was marked on the patient's skin. After aseptic preparation spinal anesthesia was performed with a 25 gauge spinal needle on the first pass and bupivacaine 12.5 mg and fentanyl 25 µg were administered intrathecally. The sensory and motor blocks were adequate. During surgery, the joint surfaces and parts of the patella and tibial condyles showed black discoloration (Fig. 1). The patient remained haemodynamically stable intraoperatively and also there were no postoperative complications.

## Discussion

AKU is a very uncommon disorder. Initial manifestations of disease are often ignored by the patients and remain undiagnosed until significant skeletal changes develop.<sup>1</sup> Moreover most of the cases often misdiagnosed as an early form of osteoarthritis due to lack of physician's knowledge and infrequency of disease confrontation. Also there are no well-defined guidelines concerning the care of these patients that makes the disease even more unmanageable. However ochronosis involve multisystem organ impairments. A detailed preoperative assessment in all patients is essential for helping in the preference of the anesthetic technique and deciding about invasive monitoring usage.<sup>3</sup>

Extremely high levels of urinary HGA excretion leads to accumulation of HGA in the renal system predisposing



**Figure 1** General view of the knee; showing ochronosis of the joint surfaces.

to nephrolithiasis, urinary tract infections and obstructive uropathy, usually in later stages of the disease.<sup>1</sup> Preoperative serum urea nitrogen and creatinine tests, renal ultrasound examination are recommended if renal involvement is suspected. Dosages of anesthetics should be modified according to the degree of renal dysfunction. Cardiovascular abnormalities such as generalized atherosclerosis, conduction blocks, aortic valve stenosis and the risk of myocardial infarction may be associated with ochronosis.<sup>1,4</sup> In patients over 40, echocardiography and Computed Tomography scan may be recommended to detect potential cardiac complications such as aortic dilation, calcification, regurgitation of the aortic or mitral valves and coronary artery calcification. The cartilage of the airway and respiratory system may be affected in ochronosis.<sup>3</sup> Decreased rotation and inadequacy to extend the cervical spine may cause a difficult tracheal intubation with a standard laryngoscope.<sup>3</sup> Pigment deposition in the tracheobronchial tree and larynx cartilages can result in hoarseness, dysphagia, a sign of narrowing of the glottic opening, a smaller endotracheal tube may be considered. In these patients, exact preoperative evaluation alongside preparation of a difficult intubation set is necessary. Additionally in patients with progressive kyphoscoliosis and significantly decreased spinal and thoracic mobility lead to poor pulmonary inflation, decreased respiratory reserve and postoperative dyspnea.<sup>3</sup> General anesthesia may not be convenient if there is severe valvular regurgitation, stiffness

of cartilage in the chest wall or reduced cervical spine. Our first case was undiagnosed with AKU but her preoperative assessment suspected as difficult airway. We performed the necessary preparations for difficult airway and intubation, and decided to use local anesthesia with sedation for awake videolaryngoscopy when we failed with neuroaxial block. She tolerated the procedure well and endotracheal intubation was achieved at first attempt. Awake tracheal intubation with videolaryngoscope is one recommended option when there is known or suspected difficulty with mask ventilation or tracheal intubation.<sup>5</sup>

As the disease progresses, cervical, thoracic and lumbosacral degenerative disk disease develops, as widespread arthritic changes in peripheral and weight-bearing joints, resulting in stiffness and pain.<sup>1,3</sup> Position of the patient on the operating room table can be uncomfortable therefore pressure points should be adequately padded to minimize the risk of neurovascular compression and additional joint injury. Narrowing of the disk space, disk calcification, deformity and stiffness of the spine may result in difficulties in spinal and epidural anesthesia.<sup>3</sup> In our first case lumbar puncture had failed despite the several attempts by expert hands. Probably ochronosis of spine make the access of subarachnoid space unsuccessful. However in the second case we prompted to plan a pre-procedural Ultrasound (US) and we reached intrathecal space successfully in a single attempt. When technical difficulty is anticipated; US of the lumbar spine may be a useful preoperative assessment tool for evaluating the feasibility of spinal anesthesia.<sup>6</sup>

## Conclusion

AKU is a rare inherited disorder but both difficult airway access and difficult neuroaxial block are the situations that need a thorough assessment and preparation. Case series are helpful to gain some kind of knowledge about this rare disease however AKU should be added in difficult airway management guidelines in order to alert practitioner to preventing life threatening situations.

## Conflicts of interest

The author declares no conflicts of interest.

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