

Ochronotic Arthropathy: Diagnosis and Management—A Critical Review

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Abstract

Alkaptonuria, a rare hereditary metabolic disorder, is characterized by accumulation of homogentisic acid in the connective tissues resulting from lack of the enzyme homogentisic acid oxidase. Ochronosis, dark pigmentation of connective tissues, is the musculoskeletal manifestation of alkaptonuria.

In this article, we report the case of a 53-year-old man who had ochronotic arthropathy and advanced degenerative changes in the shoulders managed with bilateral total shoulder arthroplasty. Three-year follow-up results were satisfactory: good range of motion, no pain, and no signs of prosthesis loosening. Shoulder function was significantly improved after surgery, as documented by Constant scores.

This case suggests that shoulder prosthesis results are not affected by alkaptonuria.

Alkaptonuria is a hereditary disorder transmitted by an autosomal recessive gene.¹ However, on rare occasion, it is autosomal dominant.² Scribonius, the first to describe alkaptonuria, in 1584, reported the case of a young boy whose urine turned black when exposed to the air. The true name of the disorder is attributed to Boedeger, who in 1859 accelerated this reaction by alkalinizing urine (from the Arab *alqaliy*, “alkaline,” and the Latin *capere*, “take in”).^{3,4}

The term *ochronosis* (from the Greek *okhros*, “significant yellow,” and *nosos*, “disease”) was used for the first time by Virchow in 1866.^{4,5} Albrecht and Zdzienicka, in 1902, interrelated the terms *alkaptonuria* and *ochronosis*.⁴

Homogentisic acid (HA) is the metabolic product of phenylalanine and tyrosine via the enzyme HA oxidase, which is active in the liver, kidneys, small bowel, colon, and prostate.^{4,6} A defect on the long arm of chromosome 3 has been thought responsible for an inborn defi-

ciency of HA oxidase,⁷ leading to accumulation of HA in all connective tissues throughout the body, particularly the cartilage,¹ resulting in pathologic blue-black pigmentation⁷ and various systemic abnormalities.^{3,4}

Increased accumulation of HA leads to decreased cross-linkage of collagen, increased vulnerability of articular cartilage to stress with subsequent cartilage failure, and degenerative changes.³ Clinically, increased HA levels are characterized by presence of dark urine, degenerative joint arthritis, and ochronotic pigmentation.³

The incidence of alkaptonuria is 1 in 250,000 to 1 million persons,⁷ and alkaptonuria occurs more often in Slovenian and Dominican populations. The male–female distribution is equal,⁴ though affected males seem to have more disease manifestations than females do.⁸ The site most commonly affected is the spine, followed by the knee joint. Smaller joints are seldom involved.⁴ Usually, the disorder becomes symptomatic during the fourth decade of life.^{7,8}

In this article, we report the case of a 53-year-old man who had ochronotic arthropathy and advanced degenerative changes in the shoulders managed with bilateral total shoulder arthroplasty (TSA). The patient provided written informed consent for print and electronic publication of this case report.

CASE REPORT

A 53-year-old white man, 165 cm tall and weighing 75 kg, presented to our outpatient clinic with reports of severe pain and swelling in both shoulders (left more than right), restriction in movement, particularly during abduction, external rotation, and overhead activities, and pain

and swelling in the right knee. The patient also reported occasional pain and stiffness in the lumbar spine, especially in the morning. He had no family history of alkaptonuria.



Figure 1. Blue-black pigmentation of external ear.

Clinical Assessment

Physical examination of the shoulders revealed pain around the joint, stiffness, decreased range of motion (ROM),

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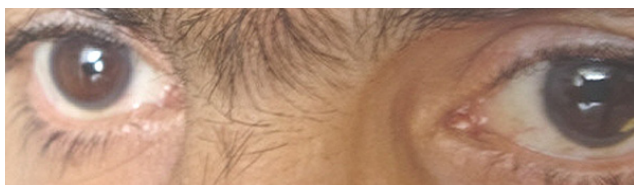


Figure 2. Bilateral grayish black scleral pigmentation.

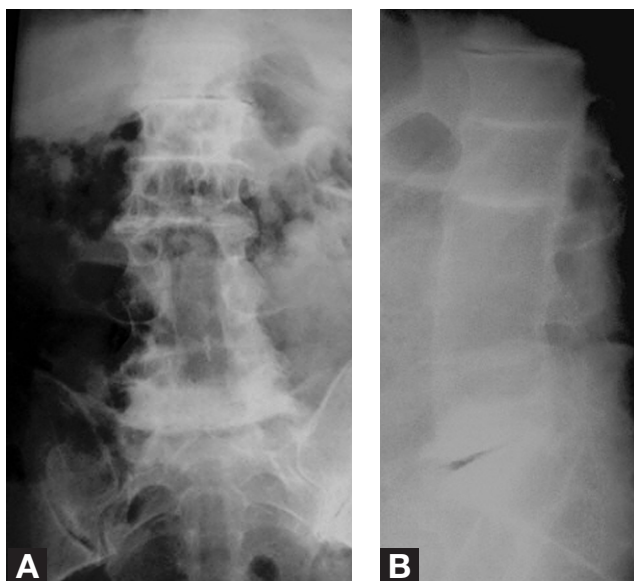


Figure 3. Frontal (A) and lateral (B) radiographs of lumbosacral spine show narrowing and calcification of disk spaces and fusion of vertebral bodies.

diffuse swelling and tenderness over the joints, and characteristic crepitus with movement. Preoperative absolute Constant scores were 18% (left shoulder) and 42% (right shoulder). Physical examination of the right knee revealed synovitis with mild effusion and tenderness over the joint line, plus mild restriction of movements.

Findings included rigidity of lumbar spine, decreased movement along entire length of vertebral column with thoracolumbar kyphosis, and flattened lumbar lordosis. The examination also revealed dark pigmentation of ear cartilage and the characteristic grayish black sclera (Figures 1, 2).

Laboratory Assessment

The patient's urine turned dark when exposed to the air. The diagnosis of alkaptonuria was confirmed by the finding of HA in the urine.

Other laboratory findings were erythrocyte sedimentation rate of 78 mm/h (normal, 0-10 mm/h) and C-reactive protein, white blood cell count, liver enzymes, serum urea nitrogen, serum creatine, calcium, and phosphorus within normal limits. In addition, both rheumatoid factor⁷ and HLA-B27 antigen⁷ were negative. Urine protein was 159.6 mg/24 h (normal, 20-120 mg/24 h).

Ultrasound examination of the kidneys and prostate did not reveal any stones, but cardiac echocardiography showed mild calcification of the mitral valve annulus.



Figure 4. Standing anteroposterior radiograph of right knee shows moderate arthritis.



Figure 5. Anteroposterior radiographs of shoulders show advanced degenerative changes with joint space narrowing and intra-articular calcification.

Radiologic Assessment

Radiographs of the lumbosacral spine showed intervertebral disk narrowing and calcification, fusion of vertebral bodies with osteal bridges between 2 adjacent bodies, diffuse sclerosis of vertebral plates, mild lumbar scoliosis, and osteoporosis of vertebral bodies (Figure 3). Radiographs of the cervical spine were normal.

A radiograph of the right knee showed mild to moderate narrowing of the joint space (medial compartment), subchondral sclerosis, and mild peripheral osteophytosis (Figure 4).

The shoulders were similar in appearance, with degenerative changes of the glenohumeral joint, subchondral sclerosis, intra-articular calcification, and joint space narrowing (Figure 5).

Operative Technique

Arthroscopic examination of the right knee revealed brown pigmentation and hypertrophy of synovium, grayish black discoloration and partial tears of menisci, and characteristic black pigmentation of articular cartilage.

Arthroscopic synovectomy led to symptom improvement. The left shoulder was managed first, with TSA. The right shoulder was managed 5 months later.

During surgery, the cartilage of the humeral head was found to be black (Figure 6). There were also glenoid

Table. Preoperative and Postoperative Absolute Constant Scores for Each Shoulder

	Absolute Constant Score			
	Left Shoulder		Right Shoulder	
	Preoperative	Postoperative	Preoperative	Postoperative
Pain	0	15	10	15
Activities	0	6	4	6
Limb placement	4	8	8	10
Forward flexion	6	8	6	8
Abduction	4	8	6	10
External rotation	2	8	4	10
Internal rotation	2	6	4	4
Abduction strength	0	25	0	25
Results	18	84	42	88

irregularities and a hypertrophic synovium. The long head of the biceps was frayed with many dark intra-articular loose bodies. Synovectomy and debridement of the frayed tissues were performed, along with tenotomy and tenodesis of the long head of the biceps in both shoulders.

The patient started early passive ROM and completed an extensive course of physiotherapy, together with education regarding a home exercise program and strengthening exercises for each shoulder.

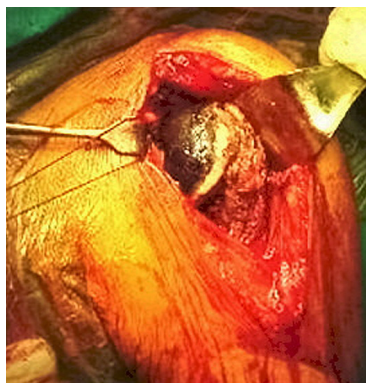


Figure 6. Black discoloration of cartilage of humeral head.

RESULTS

At 3-year follow-up, the prosthesis was stable and seemed unimpaired by ochronosis (Figure 7). There was no late infection



Figure 7. Postoperative anteroposterior radiograph of shoulders shows bilateral total shoulder arthroplasty.



Figure 8. (A) Postoperative external rotation and abduction of both shoulders. (B) Postoperative flexion of both shoulders, after bilateral total shoulder arthroplasty.

or loosening. Pain relief and ROM improvement were significant. Postoperative absolute Constant scores were 84% with 135° flexion and 155° abduction on the left shoulder and 88% with 125° flexion and 160° abduction on the right shoulder (Figures 8A, 8B; Table). The patient returned to normal daily activities. The functional outcomes and lack of complications of TSA in his case showed that TSA could represent the last and inevitable solution in managing progressive ochronotic arthropathy.

DISCUSSION

In alkaptonuria, HA accumulation leads to deposition of blue-black pigment in connective and cartilaginous tissues, which lose their elasticity and develop poor resistance to mechanical strain.⁸

The sites most commonly affected are the earlobes, sclera, nose, axilla, and groin; the cardiovascular, genitourinary, and upper respiratory systems; the skin; the spine; and the articular surfaces of the large peripheral joints (knee, hip, shoulder).²

Specific quantitative determination of HA in urine is available using gas chromatography and mass spectrometry.⁵

Patients are usually asymptomatic until symptomatic arthropathy develops, after the fourth decade of life, with ochronotic pigmentation and urine changes.² A plausible explanation for this delay is renal tubular excretion of HA, which is very effective in the early years, but becomes less so with age. HA accumulation accelerates, resulting in increased pigment deposition on cartilage.⁸ Ochronotic arthropathy must be distinguished from degenerative joint disease (small joints spared; osteophytes and subchondral cysts prominent at peripheral joints) and from ankylosing spondylitis (thin and vertical syndesmophytes, severe involvement of apophyseal facet joints, erosion and fusion of sacroiliac joints).²

There is no specific management option for alkaptonuria.⁵ Physical therapy and rehabilitation can help reduce loss of function and progression of symptoms.⁴ Some authors have referred to the efficacy of using ascorbic acid because of its effect on oxidation and polymerization of HA in vitro, but that efficacy has not been established.⁵

Arthroscopic management involves debridement of destroyed tissues, removal of hypertrophic synovium and loose bodies, and smoothing of articular surfaces—resulting in excellent pain relief, improved ROM, and, in most cases, delayed disease progression. However, the last solution remains arthroplasty.⁶

In our patient's case, bilateral TSA was performed, and there were no complications. Pain relief and ROM outcomes were good and the patient returned to his daily activities. At 3-year follow-up, the prosthesis seemed unimpaired by ochronosis.

AUTHORS' DISCLOSURE STATEMENT

The authors report no actual or potential conflict of interest in relation to this article.

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