The case:

A 50-year-old woman with a chronic polyarthropathy was seen by her orthopedist for long-standing back and shoulder and worsening hip pain. A lateral labral tear and chronic trochanteric bursitis were diagnosed on hip magnetic resonance imaging, which was otherwise unremarkable. Hip arthroscopy was performed revealing an unusual bluish-tinged femoral head articular surface. Computed tomography scans of the spine were also obtained.

Figure: Sagittal (A) and coronal (B) reformatted computed tomography scans of the lumbar spine.

Your diagnosis?

For answer, see next page
A 50-year-old woman with a chronic polyarthritis presented with long-standing left shoulder and hip pain currently causing her to be wheelchair bound. Computed tomography scans of the spine showed bone demineralization, multilevel intervertebral disk calcification with disk space narrowing, and syndesmophytes (Figure 1). Magnetic resonance imaging of the hip showed a lateral labral tear with chronic trochanteric bursitis in the left hip, but was otherwise unremarkable (not shown). In addition to the labral tear, hip arthroscopy revealed a black and bluish hue at the femoral head articular cartilage (Figure 2). Physical examination also revealed a bluish tinge to the sclera (Figure 3). A prior computed tomography scan of the shoulder had revealed advanced osteoarthritis (Figure 4). Four years earlier, the patient had knee arthroscopy performed by another orthopedist for the treatment of a lateral meniscal tear. This revealed a speckled “ground pepper” appearance of the synovial fluid that prompted further investigation (Figure 5). Urine chromatography was performed at that time and confirmed the diagnosis of alkaptonuria.

**DISCUSSION**

Alkaptonuria is a rare metabolic disease of autosomal recessive inheritance that is due to a deficiency in the production of homogentisate 1,2-dioxygenase, which is involved in phenylalanine and tyrosine catabolism.\(^1\)\(^^3\) This was first described by Sir Archibald Edward Garrod in 1902, when he linked ochronosis with an accumulation of alkaptons.\(^4\) The incidence rate is 1:250,000 to 1 million,\(^3\) with the highest prevalence among adults older than 30 years in Slovakia, the Dominican Republic, India, and Jordan.\(^5\) The current patient was born in Pennsylvania, having an Amish ancestry and reporting a remote family history of inbreeding. The gene responsible for alkaptonuria is located on chromosome 3q and usually codes for a 445-amino acid protein that forms a functional hexamer, homogentisate 1,2-dioxygenase.\(^2\) Excess alkaptons are mainly deposited in cartilaginous tissue, mu-

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**Disclosure**

The authors have no relevant financial relationships to disclose.

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Figure 2: Arthroscopic view of the femoral head with a bluish tinge and chondromalacia.

Figure 3: Photograph showing blue-tinged sclera.

Figure 4: Coronal computed tomography scan of the shoulder showing severe joint space narrowing, subchondral sclerosis, and geode formation out of proportion to the patient’s age. Also note the inferiorly projecting osteophyte (black arrow) and loose body (white arrow).

Figure 5: Arthroscopic image of the knee showing a speckled “ground pepper” appearance of the synovial fluid.

Cous, skin, bone surface, and internal cardiac structures, as well as excreted in the urine, sweat, and semen.⁵

CLINICAL FINDINGS

Due to its rarity, children are not routinely screened for alkaptonuria in the United States, but screening tests with paper chromatography have been found to be beneficial in other countries.⁶ The earliest indication of the disorder is black staining in a child’s diaper, but this can be absent in 25% of these patients.⁷ The current patient had normal color urine that turned a “tea” color only when left to oxidize for 24 hours. This was probably the main reason why the diagnosis was delayed.

During childhood and most of early adulthood, patients can have asymptomatic bony deformities incidentally identified on imaging studies and subtle bluish hyperpigmented nevi along the skin.⁸ Ochronosis is a term used to describe the deposition of homogentisic acid in collagen-containing tissues in individuals with alkaptonuria.⁸ On physical examination, a bluish hue and pigmentation of the sclera of the eyes and the cartilage of the ears is common. Patients older than 30 years tend to also develop pain and advanced arthrosis in the weight-bearing joints of the spine, hips, and knees. Synovial fluid has been reported to have a speckled “ground pepper” appearance, which was also seen in the current patient.⁹ Joint replacement surgery is common in these patients.⁹ The involvement of the spinal joints is also common, leading to reduced movement of the rib cage, which may affect breathing. The likelihood of bone fractures and rupture of muscles and tendons is also increased due to the alkaptan deposition. The current patient reported noticing a bluish hue in her sclera and had an abundance of joint issues, particularly in the knees, spine, shoulders, and hips, noted with various imaging modalities.

LABORATORY EVALUATION

Several laboratory tests were performed, involving a complete blood count, comprehensive metabolic panel, parathyroid hormone level, and calcitonin levels. The diagnosis was made by collecting urine in a 24-hour period and evaluating it with chromatography for the presence of homogentisic acid.

IMAGING

In some aspects, ochronosis can resemble ankylosing spondylitis and hemochromatosis.¹⁰ The most characteristic abnormality of this disease is the widespread calcification of the intervertebral disks.¹⁰ Generally, the accumulation of the alkaptans within the intervertebral disks can lead to intervertebral disk herniations.¹¹ Alkaptonuria most prominently involves the lumbar region, with eventual stiffness of the lumbar spine, gradual loss of lordosis, syndesmophyte formation, decreased disk space height, and exaggeration of the kyphosis.¹¹ Other joint findings are characterized by early osteoarthrosis, subchondral sclerosis, and chondrocalcinosis.

TREATMENT

No treatment modality has shown an unequivocal effect of reducing the complications associated with alkaptonuria. Most treatment regimens focus on preventing ochronosis through reduction of homogentisic acid via dietary restrictions of the amino acids tyrosine and phenylalanine. Thus, most patients with alkaptonuria are treated supportively.¹² Another treatment modality uses nitrisinone, which inhibits the enzyme responsible for the conversion of tyrosine to homogentisic acid.¹² It has shown a large-scale reduction in the amount of homogentisic acid available; however, detrimental effects of tyrosine have not been well established in the literature.

PROGNOSIS

Alkaptonuria does not appear to adversely affect life expectancy. However, it does greatly impact the quality of life of those afflicted. Most patients generally require major joint surgery in their early years, experience chronic pain, and have difficulty breathing.⁷

REFERENCES


