CASE REPORT

Ochronosis of the knee with secondary osteoarthritis requiring total knee replacement in a patient with cryptogenic organising pneumonia

Jorrit Jasper, Wieneke Metsaars, Joris Jansen

Department of Orthopedics, Alrijne Ziekenhuis, Leiderdorp, The Netherlands

Correspondence to
Jorrit Jasper,
jorritjasper@hotmail.com

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SUMMARY

Ochronosis is a rare autosomal recessive metabolic disease caused by homogentisic acid oxidase enzyme deficiency. High homogentisic acid levels will eventually result in black deposits in skin, sclerae, connective tissues and urine (alkaptonuria). It can lead to early degeneration of connective tissues and cartilage. Ochronosis can damage normal cartilage, leading to secondary osteoarthritis. The diagnosis is often delayed because of its low prevalence and non-specific early symptoms. In our patient, the secondary osteoarthritis due to ochronosis deposits in the cartilage was treated by total knee arthroplasty, with good clinical outcome. This article reports the first case of ochronosis with secondary osteoarthritis of the knee in a patient previously diagnosed with cryptogenic organising pneumonia (COP).

BACKGROUND

Ochronosis is a rare autosomal recessive metabolic disease that can lead to early degeneration of connective tissues and cartilage.[1] The homogentisic acid oxidase enzyme, which is normally active in the liver and kidneys, is deficient in patients with ochronosis. Elevated serum levels cause oxidation of homogentisic acid excess causing black pigmentation of the skin, sclerae, earwax, joint cartilage and urine (alkaptonuria).[1] Dark discolouration of the ear shells, eyes and facial skin can be seen as early signs of ochronosis. Reports of degenerative cartilage in the spine, shoulder, hip and knee joints are usually more advanced symptoms.[1 2] The diagnosis is often delayed because of its low prevalence and mild early symptoms. When suspicion for the diagnosis is present, a simple test can be performed. Adding caustic soda (NaOH) to urine produces a dark brown discolouration. Elevated homogentisic acid levels in the urine sample confirm the diagnosis.[2 3] A curative therapy has yet to be found for ochronosis as the homogentisic acid oxidase enzyme is not available for therapeutic use. A phenylalanine and tyrosine restricted diet may be effective in children, but benefits in adults have not yet been demonstrated. The effectiveness of high-dose ascorbic acid (vitamin C) treatment is still unproven.[4–6] Symptomatic treatment with adequate analgaesia and physiotherapy is recommended. End-stage osteoarthritis can be treated by joint replacement.

This is the first report of ochronosis with secondary osteoarthritis of the knee in a patient previously diagnosed with cryptogenic organising pneumonia (COP).

CASE PRESENTATION

A 64-year-old woman presented with a problematic left hip. She had a medical history of gallbladder stones and persistent lumbar symptoms for over 6 years. She had also been diagnosed with a lung disease called COP, which had been treated with high-dose steroids. She reported about stiffness in her left hip and pain during the night. After a period of conservative treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, a total hip arthroplasty (THA) was performed in 2012, due to invalidating symptoms. During the surgery, brown-dark cartilage was seen at the femoral head. Owing to the macroscopic aspect, the most likely diagnosis at this stage was secondary osteoarthritis caused by avascular necrosis due to corticosteroid use.

During follow-up of the THA, the patient presented with progressive pain and stiffness of the right knee. Radiographic examination showed osteoarthritis of the right knee (figure 1). Owing to the severity of the symptoms, a total knee arthroplasty (TKA) was performed in 2014. During the surgery, prominent dark pigmentation of the entire knee joint cartilage was seen (figure 2A–C). The histological examination showed the characteristic pattern of dark pigment depositions throughout the cartilage (figure 3A, B), pathognomic for the

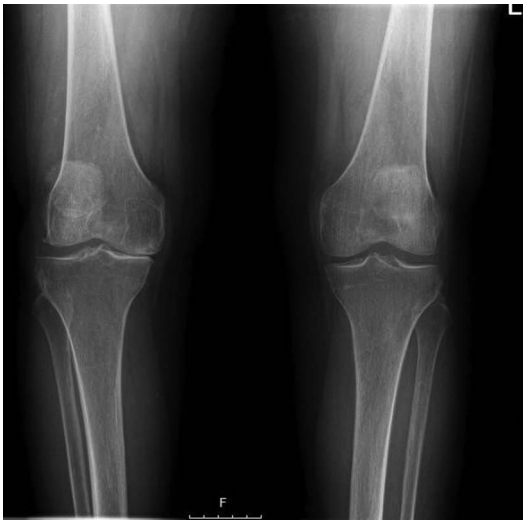

Figure 1 X-ray shows osteoarthritis in the right knee.

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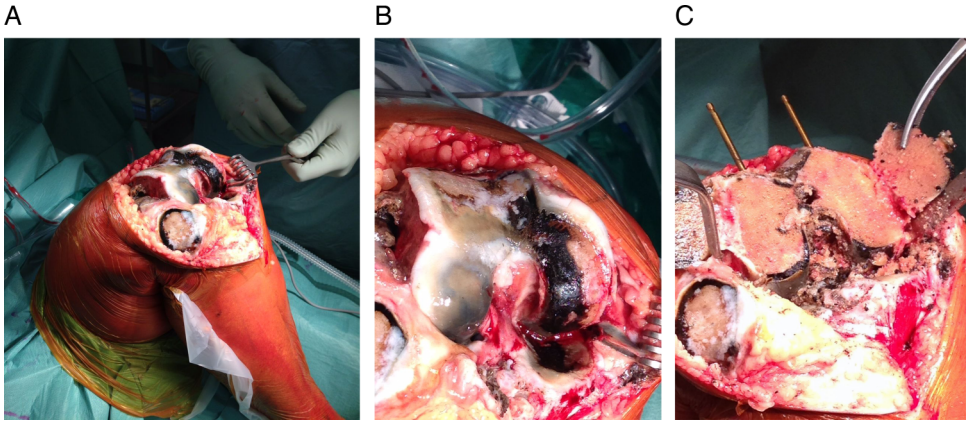

Figure 2 (A–C) Perioperative dark deposition of pigment in the knee cartilage.

diagnosis of ochronosis. The patient's medical history of gallbladder stones, lumbar osteoarthritis, hip and knee osteoarthritis, and dark pigmentation of the sclerae and ear shells, were all symptoms characteristic of ochronosis. The delay in diagnosing the disease in this case is not uncommon. In retrospect, review of the bronchoscopy showed dark pigmentation of the bronchial cartilage, which can be characteristic of ochronosis.

OUTCOME AND FOLLOW-UP

The patient followed the standard postoperative rehabilitation programme for TKA, and the postoperative X-ray showed well positioned femoral and tibial components (figure 4). At the last follow-up 2 years after the TKA, she had good knee function and no symptoms on the hip and knee arthroplasty. She experienced episodes of coughing and shortness of breath on exercise as a result of her chronic lung disease but no hospital admissions were required during the past 2 years.

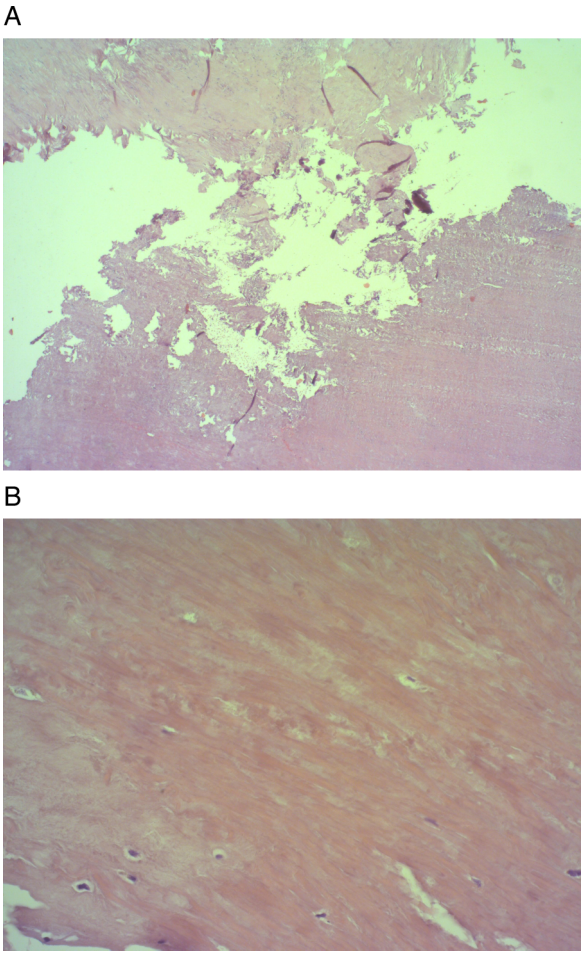

Figure 3 (A and B) Histological findings with deposition of pigment in collagen fibres and cartilage.

DISCUSSION

Ochronosis is a musculoskeletal manifestation of alkaptonuria. Alkaptonuria was first described in 1584 by Scribonius. The incidence of this autosomal recessive disorder is 1:1 000 000 individuals, with a higher incidence in interfamilial marriage. Patients with alkaptonuria have a deficiency of the enzyme homogentisic acid (HA) oxidase, which is active in the liver, kidneys and bowel. Normally, HA oxidase is involved in the reaction of phenylalanine and tyrosine, which results in the metabolic product HA. There is a deficiency of HA oxidase and as a result the HA accumulates in all connective tissue of the body. Consequently, the kidneys will increase the amount of HA excreted in urine.[1 2 6] When the urine with HA is exposed to oxygen it darkens, this dark urine is characteristically seen in ochronosis. Secondary osteoarthritis is a primary symptom that

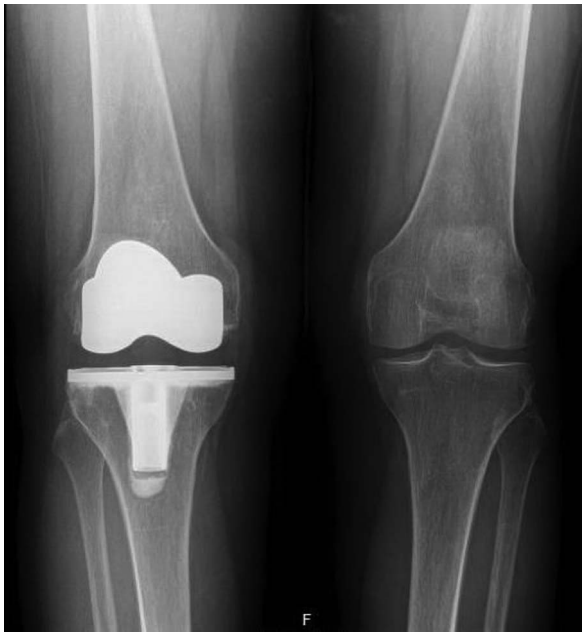

Figure 4 Postoperative X-ray shows right total knee replacement.

typically first presents itself in the lower back. The osteoarthritis is caused by increased accumulation of pigment in the cartilage. This leads to decreased cross-linkage of collagen, which impairs the strength of the articular cartilage.[1 7] Patients are normally asymptomatic until the fourth decade of life. Ocular pigmentation is especially prominent and appears in ~70% of patients. Referred to as the Osler sign, ochronotic pigment deposition is confined to the exposed areas of the sclerae 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.

Symptomatic treatment of the complications of alkaptonuria is the only option. Degenerative joint disease is first treated with analgaesics and physiotherapy, but in case of progressive osteoarthritis, joint replacement is the only option. Progressive cartilage degeneration can cause chronic pain, especially in osteoarthritis of the spine. Research towards preventive treatments by changing the patient's diet has shown some promising results. Diets low in tyrosine and phenylalanine intake may decrease the toxic by-product HA. High phenylalanine foods include soybeans, cheese, nuts, seeds, beef, lamb, chicken, pork, fish, eggs, dairy, beans and whole grains. Increased vitamin C intake may prevent oxidation to benzoquinone acetate and free radical formation. Some studies have shown lower urine HA, but these diets do not prevent the complications of joint degeneration by ochronosis.[1 4 6] Nitisinone has been shown to significantly lower the urinary excretion of HA in both, murine models and humans. Nitisinone is a triketone herbicide that inhibits 4-hydrophenylpyruvate dioxygenase by rapid, reversible binding; this action would cause direct pharmacological reduction of HA production by inhibiting the tyrosine degradation pathway and, theoretically, would prevent HA accumulation. Nitisinone is Food and Drug Administration (FDA) approved for the treatment of tyrosinaemia type I, but further investigations into the efficacy of this treatment are required, as there are several unknowns regarding long-term results.[1 4]

Our case is unique in that the patient had been previously diagnosed as having COP, an autoimmune disease. There are no publications in which the combination of COP and ochronosis has been described.

In this case it is unique that the patient was previously diagnosed with an autoimmune lung disease COP. There are no publications in which the combination of COP and ochronosis have described before. The diagnosis of COP depends on demonstration of the typical histopathological features in a patient with a compatible clinical and radiographic pattern in the absence of another disease process. In our case, it could be that the COP was misdiagnosed as histopathology review of pulmonary biopsies showed pigmented bronchial cartilage, which is part of the later diagnosed ochronosis. In the literature, only one previous article has described lung symptoms in alkaptonuria as part of ochronosis.[8 9]

Learning points

- Ochronosis has a variety of relatively mild symptoms and the diagnosis is therefore frequently delayed.
- If a patient has a combination of symptoms (gallbladder stones, lower back pain, dark urine and osteoarthritis), ochronosis as a possible diagnosis should be considered.
- Urine can be tested for ochronosis simply by adding NaOH to a sample, which, if positive, will show dark discolouration.
- In patients with blackish dark discolouration of the cartilage in joint replacement, ochronosis should strongly be considered.

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Competing interests None declared.

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