

A case of alkaptonuria – ultrasonographic findings

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Abstract

Alkaptonuria is a rare disease with autosomal recessive inheritance and variable expression. The weight-bearing joint involvement and spondylitis-like vertebral changes occur only after the 3rd decade. Musculoskeletal ultrasonographic findings in alkaptonuria were only rarely described, consisting mainly into enthesopathy and non-synovial tendon degeneration. We present the case of a 50 years old man with alkaptonuria and discuss the ultrasonographic findings and the relationship of the disease with chondrocalcinosis. The tendinous and synovial aspect may be peculiar and it could therefore allow recognition and screening for alkaptonuria, along with clinical and radiologic data.

Keywords: alkaptonuria, chondrocalcinosis, cartilage, ultrasonographic findings

Introduction

Alkaptonuria (AKU) or ochronosis is a rare genetic disorder of tyrosine metabolism, resulting into deposition of a dark “ochronotic” pigment or alkapton, a polymer of homogentisinic acid (HGA), in the tissues. AKU is due to the lack of a specific enzyme, homogentisate 1,2 dioxygenase (HDO), leading to accumulation of HGA and its deposition in collagenous structures. The disease is clinically characterized by homogentisinic aciduria, bluish-black discoloration of connective tissues (ochronosis) and vertebral and large joints arthropathy. Less common manifestations are cardiovascular abnormalities, renal, urethral and prostate calculi and scleral and ear involvement [1,2]. The disease may be recognized during childhood, but the musculoskeletal involvement is usually present only after the age of 30 [2]

While the radiological aspect of ochronotic spondylarthropathy is known, there are only few data regarding the musculoskeletal ultrasonography (US) in AKU.

Case report

A 50-year-old man with a history of renal lithiasis presented to the Rheumatology department for recurrent episodes of knee pain, also complaining of mechanic low back pain, with movement restriction. The physical examination revealed a stiff back, a Schober's test of 10/12 cm, mild bilateral knee effusion and painful limitation of hip movements. He also had a bilaterally enlarged Achilles' tendon, with a previous right Achilles' tendon rupture after a minor trauma. No signs of psoriasis were noted. The eye examination revealed a grey-bluish pigmentation of the sclerae (fig 1a) and of the ear cartilage (fig 1b).

The X-ray of the lumbosacral spine showed calcification of multiple intervertebral discs, vacuum phenomenon L1-L2, no sacroiliitis and only minimal enthesopathy in the knees (fig 2). A suspicion of alkaptonuria with associated ochronotic spondylarthropathy was formulated. A urine screening test using sodium hydroxide revealed the presence of the dark pigmentation (fig 1c). The same test was applied to the synovial fluid aspirated from knees,

Received 02.09.2013 Accepted 24.09.2013

Med Ultrason

2013, Vol. 15, No 4, 321-325

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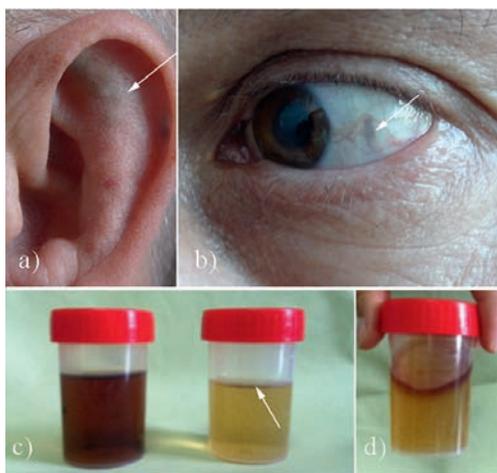


Fig 1. Clinical examination of the pigment deposition and the macroscopic aspect of the body fluids: a) ochronotic pigment deposition in the external ear cartilage (arrow); b) pigmented corneal arch (arrow); c) urine after addition of sodium hydroxide (left) and after emission (right). Note the small superficial ring due to spontaneous oxidation after contact with the air (arrow); d) synovial fluid pigmentation after addition of sodium hydroxide.

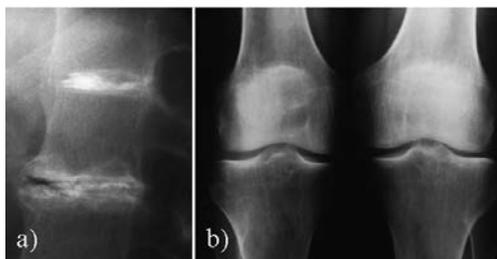


Fig 2. Radiographic aspect: a) disc calcifications, end plate osteosclerosis, L1-L2 vacuum phenomenon. Bony outgrowth may mimic parasindesmophytes; b) knee radiograph shows only mild irregularities at the insertion of crossing ligaments.

revealing a thin dark band (fig 1d). Urinary homogentisinic acid value was 10.3 g/day (normal 1-8g/day).

US examination of knees depicted a large amount of fluid in the suprapatellar bursa and both medial and lateral recesses, with synovial proliferation, no power Doppler signal and enthesopathy-like at the modifications at the quadriceps insertion (fig 3). Interestingly, the femoral cartilage evaluation did not reveal any known sign of chondrocalcinosis as expected (fig 4). The most important aspect shown by US examination was tendon involvement. The tendons appeared thick

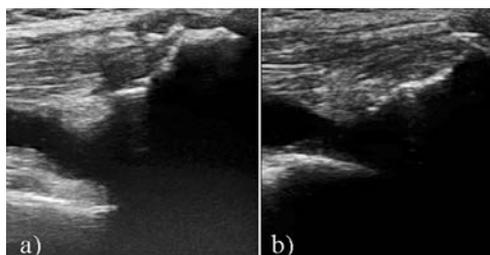


Fig 3. Ultrasonographic aspect of the knees a) left, b) right: Suprapatellar bursa showing large amount of fluid, synovial proliferation, and enthesopathy at patellar tendon insertion.



Fig 4. Ultrasonographic examination of the hypoechoic and homogenous femoral cartilage, without chondrocalcinosis signs.

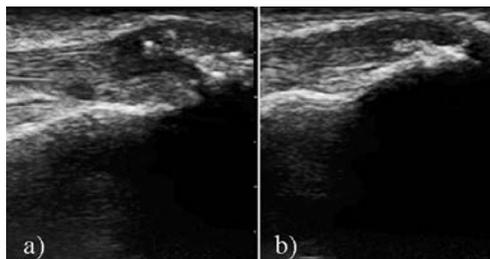


Fig 5. Ultrasonographic examination of the patellar tendons a) left, b) right): the tendons are thick and hypoechoic along its terminal portions with a coarse hyperechoic mass at its bone insertion.

and hypoechoic along its length, with a coarse hyperechoic mass at its bone insertion (fig 5). The aspect resembled a degenerative enthesopathy, but without posterior shadow, as Fillipou has previously shown [3]. No sign of activity (Power Doppler signal) at tendon's insertion was found.

No cardiac involvement could be proved. The patient was treated with NSAIDs, joint aspiration and corticoid injections and high-dose vitamin C. After one year the articular disease evolution was stationary, with remission of acute arthritis but persistent tendinous involvement.

Discussions

Alkaptonuria is a rare disease, with a prevalence of 1/250 000-1/1000000, larger in Slovakia and Dominican Republic [1]. Transmission is autosomal recessive with variable expression. The human HGD locus is on the chromosome 3, on the 3q21-q23 arm. More than 115 mutations impairing the HGD enzyme have been described to date [1].

The diagnosis is confirmed through simple tests. Patients' urine turns black when oxidized (left overnight) or alkalinized (for instance with sodium hydroxide or silver nitrate). The same test can be used for synovial fluid [1]. HGA accumulation and a product of its oxidation, benzoquinone, induce tissue injury. Macrophages are carrying alkapton pigment granules, moving it throughout the body [2].

Ochronotic arthropathy, the most common complication of AKU, usually occurs in the 4th decade of life, affecting large weight-bearing joints and later the shoulders. Costal cartilages and costo-vertebral joints may also be involved [3]. Early changes include diffuse cartilage pigmentation and chondrocyte necrosis, while in advanced disease degenerative changes in synovial and intervertebral joints are noted [4].

Vertebral involvement, initially lumbar, usually precedes the peripheral joint disease, stiffness and pain being the main symptoms. Thoracic and lumbar spine is involved with relative sparing of cervical spine. The AKU spondylopathy is characterized by extensive disc calcifications and "vacuum phenomenon", i.e. splitting of the calcified intervertebral disc. Secondary intervertebral space narrowing and multilevel calcification of annulus fibrosus, but with minimal calcification of the intervertebral ligaments and little osteophyte formation are noted [5]. Longstanding disease may result into severe kyphosis, obliteration of intervertebral spaces and marginal osteophytes that can mimic syndesmophytes [6]. Apart from ankylosing spondylitis, sacroiliac joints are not a main site of disease, although mild narrowing and subchondral sclerosis can be seen [6]. Differential diagnosis of disc calcifications in AKU, besides ankylosing spondylitis, is made with degenerative disease, calcium pyrophosphate arthropathy, hemochromatosis, hyperparathyroidism, acromegaly, and amyloidosis. However, cases of AKU co-existing with ankylosing spondylitis and rheumatoid arthritis have been described [2].

The cartilage of the weight-bearing joints is damaged by chondrocyte accumulation of HGA polymers and benzoquinone [7]. Collagen cross-linkage of cartilage fibers is reduced, leading to cartilage degeneration. Pigmentation initially manifests at the boundary of the subchon-

dral bone and calcified cartilage, then proceeding to the articular surface [8]. Histopathology shows extensive degenerative changes with swollen, rigid, and fragmented collagen fibers, with jagged edges and ochronotic deposition [6]. Intact cartilage seems to be resistant to pigmentation, but focal changes in calcified cartilage render it brittle, prone to fragmentation and loose body formation [8]. Cartilage detached fragments may adhere to synovium leading to chondromatosis. In advanced AKU, aggressive osteoclastic resorption of the underlying calcified plate may progress to complete loss of subchondral plate, like in osteoarthritis (OA). However in AKU less osteophyte production and marked intraarticular osteochondral fragments are seen [6].

Bone involvement seems to be less important, probably due to some protective effect of the mineral substance in which the collagen fibrils are disposed, or to the short time in which the newly formed osteoid matrix remain uncalcified [5]. The ochronotic pigment was not found in osteoblasts, but in the cytoplasmic vacuoles of osteoclasts, osteocytes and calcified matrix [2]. However, while the bone formation markers are normal in AKU, the resorption markers (urinary secretion of cross-linked N -telopeptides of type 1 collagen) are elevated, thus leading to osteoporosis [9]. Vertebral and femoral fractures were described in AKU [2].

Synovial involvement in AKU is also the result of deposition of black pigment resulting in thickening and inflammation [10,11]. Ochrotonic pigment may be seen in the synovial membrane and the disease can sometimes be recognized from the synovial fluid while puncturing a joint ("the ground pepper sign" due to tiny pigmented cartilage fragments and tissue debris) [12]. Histology shows thickened inflamed synovium with multiple pigmented areas and reactive giant cells [11]. The arthropathy is similar to OA with a small inflammatory component. It is not a simple acceleration of OA, as non-weight-bearing joints like shoulders and chondrocostal joints are involved. Nevertheless, general OA mechanisms may participate. Synovitis and joint effusions are secondary phenomena in OA, related to chondrolysis [13]. Inflammation and synthesis of matrix degrading enzymes subsequently aggravate cartilage breakdown in late OA [14]. Structural progression of OA has been linked to synovial inflammation [13]. Our patient had episodes of synovitis with non-inflammatory fluid that may have contributed to the loop of OA amplification. However, at US the cartilage height seemed to be preserved. The lack of signal even in the presence of synovitis seems not to be necessary related to AKU, since ultrasound inflammation was not detected in half of the subjects with chronic, symptomatic OA [13] and

clinical and synovial ultrasound features are not related in knee OA [13].

Calcium pyrophosphate dihydrate (CPPD) seem to participate in the pathogenesis of AKU arthritis [15]. In acute synovitis CPPD crystals were identified in half of cases [16]. However, CPPD crystals were detected in the synovium but not in the cartilage [17]. An arthropathy resembling OA located at the metacarpophalangeal joints of the index and middle fingers, wrist and knees (and therefore similar to CPPD-associated disease) is seen in about half of AKU patients [18]. In our patient no chondrocalcinosis signs were seen in the knees. However, the spine showed signs of disc calcification. Since in most AKU patients the vertebral involvement precedes the peripheral one, it may be argued that chondrocalcinosis could be related to the age of the disease in a certain inflicted site and may be a late finding in peripheral disease.

Tendons and ligaments are heavily pigmented due to their collagen content, resulting in inflammation, calcification and rupture [10]. Initial pigmentation is associated with the periodicity of fibrillar collagen, probably a preferential binding site for the ochronotic pigment [19]. In a 7-cases AKU study, Fillipou described ultrasonographic characteristics of tendinous involvement [3]. The tendons with synovial sheath were not involved, but the enthesopathy at the insertion site was associated with hyperechoic deposits without posterior shadowing (in contrast to the hydroxyapatite deposition disease). Acute enthesitis signs were also observed. The tendons are symmetrically involved and may rupture, like in our case, after minimal trauma. The same type of involvement was found in our patient, consistent with Fillipou's findings. We could only speculate that hypoechoic masses seen in our case by ultrasound near tendon insertions may represent detached cartilage fragments, possibly from the fibrocartilaginous enthesis, or pigmented tissue debris aggregations [8]. Entheses are the regions in which tendons or ligaments insert into bone and the collagen fibers are mineralized and integrated into bone tissue [20]. Fibrocartilaginous entheses could be predilect sites of involvement, as traction and other types of microtrauma may predispose the deep cartilage to pigmentation, starting the degradation process [8].

Our case was previously interpreted as OA of the spine and knees. However, the relatively early onset, without apparent risk factors, as well as the Achille's tendon rupture after a minimal trauma, pointed to a secondary OA. The clinical signs are very suggestive for AKU and the tests employed readily available, even if the disease is rare. Besides radiology, US could add to the diagnosis, especially in the presence of hypoechoic masses near traction tendons' insertion. US also helps in

joint aspiration and ochronotic pigment detection in the articular fluid. Moreover, in an already diagnosed patient, it may contribute in sequential joint cartilage assessment and articular disease monitoring. Even the asymptomatic joints could be evaluated for the presence of involvement, as well as the tendons.

Therapy of AKU consists into analgesics, NSAIDS, colchicine, physical therapy and rehabilitation and joint prosthesis when needed [11]. Dietary restrictions of tyrosine and phenylalanine-containing food, ascorbic acid, N-acetylcysteine, vitamin E and nitisone were employed [7], but the efficacy and drug side effects in humans are currently under study.

In summary, ultrasonographic findings in AKU were enthesopathy mainly close to insertion, hypoechoic masses without shadowing (possibly representing non-calcified cartilage fragments detached and embedded into synovium), joint collections, small osteophytes and degenerative changes. Articular chondrocalcinosis, at least in early cases, however seems not to be a prominent finding. Ultrasonography could prove itself a valuable method for diagnosis and disease monitoring.

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