

Lower urinary tract symptoms and prostatic calculi: A rare presentation of alkaptonuria

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ABSTRACT

Alkaptonuria is a rare tyrosine metabolic disorder. A deficiency of homogentisic acid oxidase leads to accumulation of homogentisic acid in the body. Dark-colored urine, cutaneous pigmentations and musculoskeletal deformities are characteristic features. Storage and voiding lower urinary tract symptoms due to prostatic calculi is a rare presentation.

Key words: Alkaptonuria, lower urinary tract symptoms, prostatic calculi

INTRODUCTION

Alkaptonuria is a rare metabolic disorder with an incidence of 1 in 250,000 to 10,00,000 of general population.^[1] Deficiency in homogentisic acid oxidase (homogentisate 1,2-dioxygenase), leads to deposition of oxidized homogentisic acid in the fibrous and cartilaginous tissues (ochronosis), excretion of large amounts of homogentisic acid in the urine (homogentisic aciduria) and disabling musculoskeletal deformities.^[2] We discuss a case of an adult presenting with lower urinary tract symptoms who was diagnosed to have alkaptonuria.

CASE REPORT

A 50-year-old hypertensive, had bothersome voiding and storage lower urinary tract symptoms (poor flow, straining to void, increased frequency - D/N: 6-8/4-5, urgency and urge incontinence) for 10 years. He also had blackish discoloration of his urine. He was diagnosed to have a vesical calculus and underwent a cystolithotomy

10 years ago. He had gradual worsening of his symptoms. He developed a low backache with spinal deformity over the past 3 years. On examination, he was short statured with a kyphotic spine. He had blackish discoloration of his sclera and ear cartilages. On digital rectal examination, the sphincter tone was normal with a hard enlarged prostate and a normal rectal mucosa.

On evaluation, he had a normal hemogram and renal function (serum creatinine 0.8 mg%). Serum PSA was 0.377 ng/ml. Urine examination revealed multiple WBC's and RBC's with a positive urine culture. His flow was a Q max of 6.2 ml/sex for a voided volume of 250 ml and PVR - 60 ml. Pelvic X-ray showed extensive calcification of the prostate and ejaculatory duct with multiple prostatic calculi [Figure 1]. Spinal X-ray revealed features of ochronosis with intervertebral disc calcifications, osteophytes at ligamentous insertions and degenerative changes of the spine [Figure 2]. The ultrasound of the kidneys was negative for any calculi. A transrectal ultrasound [Figure 3] revealed an enlarged prostate with extensive intra prostatic calcifications. On further evaluation for the metabolic and bone disorder, serum calcium, phosphorus and uric acid levels were normal. Vitamin D levels were 14.4 n/ml and parathyroid hormone levels were normal. The 24-hr urine metabolic workup for urolithiasis was normal. Urinary homogentisic acid was positive.

Cystoscopy revealed a rigid prostatic urethra with specks of black pigmentation over the prostatic urethra and a bilobar occlusive prostate. Transurethral resection of prostate unroofed two large cavities in the midprostatic fossa. Both the cavities were filled with multiple brownish calculi [Figure 4], with black inner core, approximately 30-40 in number, and the largest measuring ~3x3 cm in size. Postoperatively, he voided well after catheter removal and

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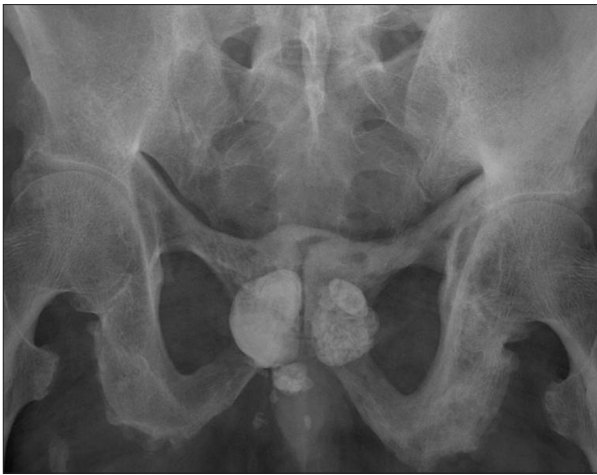


Figure 1: A radiograph of the pelvis showing calcification of the prostate and ejaculatory duct with multiple prostatic calculi

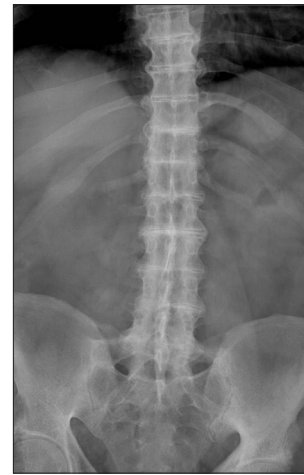


Figure 2: Radiograph of the spine showing ochronosis with inter vertebral disc calcifications, osteophytes at ligamentous insertions and degenerative changes of the spine

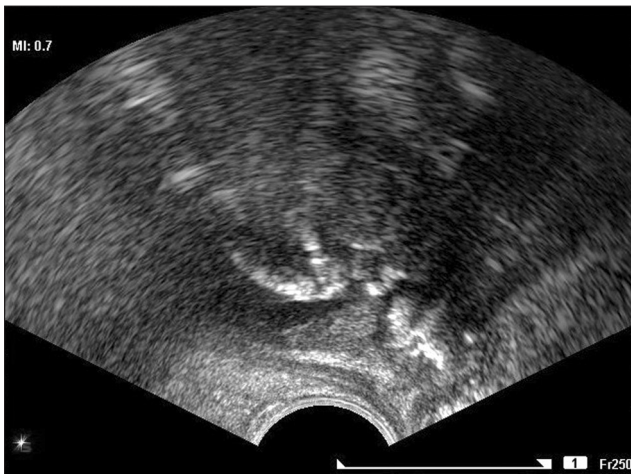


Figure 3: A transrectal ultrasound with extensive intraprostatic calcifications



Figure 4: A postoperative image showing the multiple brownish black calculi in the resected prostate

a repeat X-ray pelvis [Figure 5] showed complete clearance of all the calcification in the prostatic region. The weight of the prostatic tissue resected was 5 gm and the intraprostatic calculi weighed 42 gm. Histopathology of the prostatic specimen was benign hyperplasia of prostate with squamous metaplasia [Figure 6], with no features of malignancy. The chemical analysis of the calculi showed calcium oxalate and carbonate calculi.

DISCUSSION

Alkaptonuria is a rare metabolic disorder first described by Sir Archibald Edward Garrod. He first used the expression, 'inborn errors of metabolism', to describe four rare disorders - alkaptonuria, albinism, cystinuria and pentosuria. He discovered that such disorders resulted from enzymatic defects in the catabolic pathways of aminoacids and sugars.^[1,2] Autosomal recessive mutations of the homogentisic acid oxidase gene, located on human chromosome 3q 21-q 23, results in a defect in the metabolism of homogentisic acid.^[2] Homogentisic acid is a metabolic product of phenylalanine and tyrosine. It accumulates in

patients with alkaptonuria. Oxidation of this acid leads to formation of a blackish melanin like pigment which is selectively deposited in the connective tissue and cartilage.

Symptoms become apparent only around third to fourth decade, but pediatric alkaptonuria, though rare, has been reported. Most common symptoms include, 1) pigmentation of the pinna, sclera and nasal ala, 2) musculoskeletal abnormalities like narrowing of the joint spaces, cartilage degeneration and the calcifications of the disc leading to loss of lumbar lordosis, exaggerated thoracic kyphosis, ankylosis and loss of height, 3) change of the color of the urine to black on exposure to air, 4) cardiac valve calcification and stenosis, 5) renal and prostatic calculi.^[3]

Urine excretion of homogentisic acid (alkapton) is very high. The oxidation and the polymerization of this alkapton turn the color of the urine black.^[1,2] The alkapton urine has a high propensity for stone formation.^[2,3] Very rarely alkaptonuria patients end up into renal failure and the renal biopsy reveals



Figure 5: A postoperative pelvic radiograph showing clearance of the prostatic calculi

a diffuse chronic tubulo-interstitial disease characterized by extensive tubular atrophy, interstitial fibrosis, inflammation and the deposition of the melanin like pigment in the tubular cells and the interstitium.^[4]

There have been similar reports of prostatic calculi and alkaptonuria in the past^[5,6] with the detection of majority of the prostatic calculi being incidental and asymptomatic. There is, however, one case report^[7] where the patient presented with cutaneous manifestations of alkaptonuria with a hard prostate clinically mimicking a carcinoma, secondary to the diffuse deposition of calculi. Prostatolithiasis in alkaptonuria is of two types - true prostatolithiasis with deposition of calculi in the prostatic gland and false prostatolithiasis with the location of calculi being in pars prostatica urethrae.^[6] The formation of calculi is secondary to the accumulation of homogentisic acid in the body which precipitates the deposition of crystals and formation of calculi. The composition of the prostatic and renal calculi is usually the standard calculus constituents such as calcium oxalate monohydrate and dehydrate, hydroxyapatite, β -calcium phosphate and octacalcium phosphate. The prostatic calculi may have substituted calcite $\text{Ca}(\text{Mg}, \text{Mn})\text{CO}_3$.^[6] The incidence of symptomatic prostatic calculi in alkaptonuria is limited to a similar case report where the patient presented with features of chronic prostatitis^[8] and was managed conservatively. To our knowledge this is the first report of symptomatic alkaptonuric prostatolithiasis treated surgically.

Several therapeutic options are proposed to treat patients with alkaptonuria. Dietary protein restriction and high doses of ascorbic acid to reduce urinary homogentisic acid levels did not prove effective.^[1,3] Nitisinone, a triketone herbicide, inhibits 4-hydroxyphenylpyruvate dioxygenase, an enzyme which produces homogentisic acid in the tyrosine metabolism. This is the only drug that has a proven efficacy in reducing the urinary levels of homogentisic acid but the long term safety profile needs to be studied.^[1,3] Symptomatic management in the early stages of the disease and surveillance

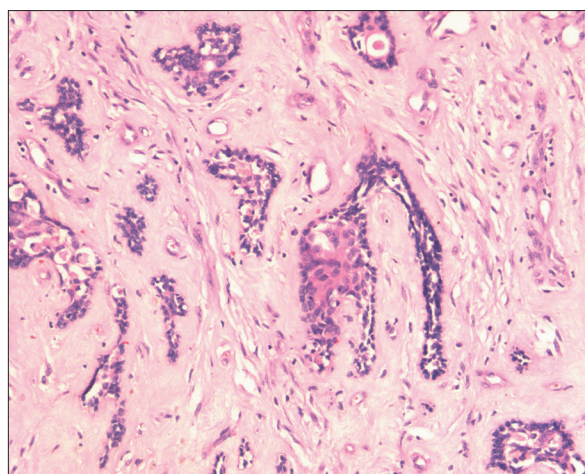


Figure 6: A photomicrograph of the resected prostate showing features of benign prostatic hyperplasia with squamous metaplasia

for cardiac, renal, and prostate complications after the fourth decade of life is advisable.^[3]

CONCLUSIONS

The patient discussed had cutaneous manifestations and musculoskeletal deformities which were asymptomatic. He had bothersome lower urinary tract symptoms due to prostatic calculi. Homogentisic acid in urine was positive to confirm the diagnosis. He was relieved of his symptoms after the removal of the prostatic calculi. This case highlights the role for surgical management in cases of alkaptonuria and prostatolithiasis.

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