Primary Hyperoxaluria Type 1 with Systemic Calcium Oxalate Deposition: Case Report and Literature Review

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Abstract. We present an adult autopsy case of primary hyperoxaluria type 1. Diagnosis was established with skin biopsy and subsequent genetic analysis one month prior to death. At autopsy, calcium oxalate crystals refringent to polarized light were found systemically. Interestingly, however, calcium oxalate crystals were not identified in the bone. Additionally, we have included a review of the literature for previous autopsy cases, presentations, diagnosis, complications, and treatment of this rare genetic systemic process.

Introduction

A deceased 33-year-old African-American female was referred for autopsy after respiratory failure and asystole. She had a past medical history of end stage renal disease (ESRD), congestive heart failure, hypertension, and nephrolithiasis. Her family history was significant for two siblings dying at less than 40-years-old with renal failure. A month prior to her demise, a skin biopsy showed vascular calcium oxalate (CaOx) deposition consistent with cutaneous oxalosis. Genetic analysis showed a single-nucleotide substitution in the gene encoding the enzyme alanine:glyoxylate aminotransferase (AGXT), which is seen in primary hyperoxaluria type 1 (PH1). She was being evaluated for a liver-kidney transplant, but was not a candidate due to small vessel disease complicated by bilateral lower extremity gangrene. A bone scan was negative for bone oxalosis.

Materials and Methods

An autopsy was performed and representative samples from the decedent’s tissue were fixed in 10% buffered formalin, embedded in paraffin, sectioned (at 5 µm), and stained with hematoxylin-eosin. Hematoxylin-eosin slides of small, medium, and large vessels, gastrointestinal tract, liver, pancreas, kidneys, skeletal and cardiac muscle, bone and skin were examined with polarized light.

Results

Bilateral pulmonary emboli and left- and right-sided heart failure (including biventricular myocyte hypertrophy), centrilobular necrosis of the liver with bridging fibrosis, and splenomegaly were identified. CaOx crystals refringent to polarized light were found systemically. The crystals were seen in the media of small, medium, and large vessels including the aorta, basilar, and vertebral arteries, and vessels of subcutaneous skin, liver, pancreas, skeletal muscle, and muscularis propria of the gastrointestinal tract. The crystals filled the tubules of the kidneys and occurred within cardiac myocytes (Figure 1). No crystals were noted in the bone.

Discussion

Primary or secondary acquired disease can lead to hyperoxaluria. Primary hyperoxalurias are characterized by errors in the metabolism of glyoxylate and oxalate, leading to excessive production of oxalate. Primary hyperoxaluria types 1 and 2 (PH2) have the following inherited enzyme defects: alanine:glyoxylate aminotransferase (AGT) and glyoxylate reductase/hydroxypruvate reductase (GRHPR), respectively. AGT is a hepatic, peroxisomal, pyridoxal 5’-phosphate-dependent enzyme which catalyses the transamination of glyoxylate to glycine while pyruvate is converted to alanine. The reduction of glyoxylate to glycocolate is catalyzed by GRHPR, and the GRPHR gene is located on chromosome 9 (9q11); more than 15 mutations have been identified. In PH1 and PH2, glyoxylate cannot be detoxified, so it is converted into oxalate by...
cytosolic lactate dehydrogenase. Primary hyperoxaluria type 3 (PH3) is linked to the gene \textit{DHDPSL}, which codes a mitochondrial enzyme. PH1 is the most common primary hyperoxaluria, which occurs in 0.11 to 0.26 per 100,000 births. All three types are autosomal recessive [1-4].

There are variable presentations of PH1 ranging anywhere from birth to the sixth decade. The infantile form has a rapid progression, and by the age of 3 years, 80% of these patients have developed ESRD. Recurrent urolithiasis and progressive renal failure in childhood or adolescence may lead to the diagnosis. Patients with the late-onset form may have urolithiasis or ESRD as the first symptoms. Sometimes, however, the diagnosis is made with recurrence following kidney transplantation. From the initial symptoms, there is an average 5-year interval to diagnosis of PH1, and by this time 10-40% of patients have ESRD. Early diagnosis is achieved in only 30% of cases. Half of the patients reach ESRD between 24 and 33 years [1-2].

Several methods are useful in diagnosing PH1. 24-hour urine collection oxalate measurement corrected for body surface area can be used. Until genetic analysis allowed for the detection of the \textit{AGXT} gene, liver biopsy to measure AGT catalytic activity was essential for the diagnosis. Liver biopsy is still used in patients with no identified mutation. The normal \textit{AGXT} (AGXT with an ‘X’ and italicized is the change) gene is a single copy gene located on chromosome 2q37.3. This protein contains 392 amino acids, 11 exons, has a molecular mass of 43-kDa, and is vitamin B6(pyridoxine)-dependent. Almost 50% of mutations cosegregate with a so-called minor allele that has a 74-bp duplication in intron 1 with a proline to leucine change in position 11. The most frequent mutation, found in 20 to 40% of patients, is p.Gly170Arg. Except for the p.Ile244Thr

![Figure 1. Calcium oxalate crystals refringent to polarized light (insets) in the media of the left anterior descending artery of heart (A), aorta (B), renal tubules (C) and cardiac myocytes (D).](image)
mutation being more common in patients of North African/Spanish decent, the mutations have few ethnic associations. DNA obtained from crude chorionic villi or amniocytes can be used for prenatal diagnosis. At least 146 genetic mutations of the \( AGXT \) gene have been reported, 75% of which are single-nucleotide substitutions. The other mutations include insertions and deletions as well as missense, nonsense, and splice mutations. More than 99% of PH1 patients have been found to have mutations in the \( AGXT \) gene [1,2,5-7].

PH1 has detrimental effects on the urinary system. In PH1, CaOx has an increased synthesis and urinary excretion. Because CaOx is insoluble in urine, the symptoms usually present as urinary symptoms such as urolithiasis and/or nephrocalcinosis. Once a critical saturation point of plasma oxalate has been reached (> 30-50 μmol/l), and the glomerular filtration rate has fallen below 30-50 mL/min per 1.73 m², oxalate deposition occurs in many organs, bone being the major component. The systemic involvement commonly involves the heart, central nervous system, joints, skin, soft tissues, retina, and other visceral lesions [1,2,8]. With worsening renal function, oxalosis involves the myocardial conducting system, leading to heart failure and fatal arrhythmias. CaOx crystals can deposit in the media of cardiac vessels and form plaques termed “atherosclerotic oxalosis” [9, 10]. Due to CaOx vascular deposition, PH1 has been seen to cause gangrene of the extremities as well as acrocyanosis, livedo reticularis, and Raynaud’s phenomenon [4].

Treatment is initiated with conservative measures aimed at increasing the urinary solubility of CaOx and decreasing oxalate production. High fluid intake (>2 L/m² per day) along with CaOx crystallization inhibitors, such as potassium or sodium citrate and elemental phosphorus, are used to decrease calcium absorption, calciuria, and the growth and agglomeration of CaOx crystals. Calcium and oxalate intake should remain normal, but excessive vitamin C and D intake should be avoided. 10 – 30% of PH1 patients are sensitive to pyridoxine, which chelates the precursors of oxalate and is metabolized to pyridoxal phosphate, the main co-factor of AGT, and should be used once ESRD is reached. Urinary stones may be treated with extra-corporeal shock wave lithotripsy in select patients, and hemodialysis usually has disappointing results unless it is performed daily for greater than 5 hours per session [1,2].

For unresponsive patients and those with glomerular filtration rates between 15 and 40 mL/min per 1.73 m², liver or combined liver-kidney transplantation is the next option and would ideally occur before the onset of ESRD. Isolated kidney transplantation is no longer recommended, due to the high frequency of recurrence, since the biochemical defect is in the liver [11]. Isolated kidney transplantation may, however, benefit PH1 patients with proven pyridoxine responsiveness if this treatment is continued after transplantation. Liver transplantation provides gene and enzyme replacement therapy. Before chronic renal failure occurs, preemptive isolated liver transplantation may be an option in select patients. Combined liver-kidney transplantation is the preferred approach. The United States Renal Data System reports above 80% patient survival at 5 years and kidney graft survival of 76% at 8 years after combined liver-kidney transplantation. Since oxalate can remain elevated for several years post-transplantation, high fluid intake and crystallization inhibitors should be continued to avoid recurrent nephrocalcinosis, renal calculi, and decreased graft function. Gene therapy may be in the future of PH1 treatment [1,2,12-14].

We present possibly (and to our knowledge) the second autopsy case and the first adult autopsy case of PH1 to be reported in recent literature. One pediatric autopsy case of PH1 was reported in 2009 [15]. Ours is a case of PH1 diagnosed with a skin biopsy and subsequent genetic analysis one month prior to death in a young patient with a personal and a family history of ESRD. Although this patient was being treated with pyridoxamine, she developed extensive systemic CaOx deposition. Her bone scan, however, showed no CaOx deposition, and no bone involvement was noted histologically. Promoting earlier diagnosis through increased awareness of this genetic entity will enable treatment and the prevention of ESRD and further systemic sequelae of PH1.
References


