G8 Primary Hyperoxaluria: A Case Report and Review of the Literature

Julia M. Braza, MD and Karoly Balogh, MD, Beth Israel Deaconess Medical Center, Pathology Department, 330 Brookline Avenue, Boston, MA 02215

The goal of this presentation is to discuss a case of the rare metabolic syndrome primary hyperoxaluria (PH), with a literature review. The attendees will learn about the inherited form of the disease, its systemic manifestations, genetic alterations and the potential mechanisms of death. PH is relevant and important to the medico-legal and public health fields to identify such cases, especially because it can lead to sudden death in affected patients, who are mostly children and young adults.

The presentation will impact the forensic community and/or humanity by identifying and discussing the etiologies of the disease, its renal and extra-renal manifestations, current therapeutic approaches, i.e. combined liver-kidney transplantation, and the common causes of death in these individuals. The entity is a surgical and anatomic/forensic curiosity, with remarkable gross and histological findings.

Primary hyperoxaluria is a rare autosomal recessive metabolic disorder, caused by the deficiency of the liver-specific peroxisomal enzyme, alanine: glyoxalate aminotransferase (AGT). AGT normally converts glyoxalate to glycine, but when absent, results in an increase of the glyoxalate pool, which is converted to oxalate.

This presentation will discuss the clinico-pathologic features, postmortem gross and microscopic findings of a fatal case of primary hyperoxaluria.

Case Report: The patient MS, a 24-year-old female with end-stage renal disease, presented to *Beth Israel* Deaconess Medical Center institution with gross hematuria of one month duration. She was eight months old when diagnosed with a rare metabolic disorder, Primary Hyperoxaluria (PH). The patient had two failed renal transplants (one in 1981 at eight months of age, and another in 1991). She began hemodialysis in 2000 and continued the treatment until presenting in January 2005, with gross hematuria. A CT scan also revealed a mass in the left renal allograft. Therefore, a nephrectomy was performed, and pathology ruled out post-transplant lymphoproliferative disorder, and revealed chronic allograft nephropathy, with extensive deposition of calcium oxalate crystals. The patient was discharged, with no complications, and returned to the institution one month later for a combined left kidney/liver transplant. Shortly after the procedure, the patient suffered thrombosis of the hepatic artery-aorta conduit, which was repaired the following day. During repair, it was noted that the liver allograft was necrotic in vivo, and a liver biopsy showed massive necrosis consistent with ischemictype injury (left lobe). The patient quickly became hemodynamically unstable, developed supra-ventricular tachycardia, and after attempts at resuscitation had failed, was pronounced dead.

At autopsy, the body was that of a jaundiced female of small build with kyphosis, and a large abdominal surgical wound, covered by mesh. There were many adhesions throughout the peritoneum. The transplanted liver was partially necrotic (40%), and a hemorrhagic infarct was found in the left lower lobe of the lung. The left, newly-allografted kidney was anteriorly placed, and had a dusky hue. The right, previously (1991) transplanted kidney, was significantly atrophic, and could not be identified. The heart (280 gms) revealed no acute or remote infarcts. The abdominal aorta had an intact stent in place.

Histologic findings of the liver revealed necrosis in the majority of the left lobe, and marked bile stasis in the remaining tissue. The heart had abundant polarizeable oxalate crystals in the myocardium, with associated fibrosis. The kidney showed pigmented tubular casts, and focal calcium oxalate deposition. The final autopsy diagnosis was death due to thrombosis of the hepatic artery and aortic conduit that led to massive liver necrosis/failure, and hemodynamic instability. Pre-mortem cardiac conduction defects were most likely due to the diffuse deposition of calcium oxalate crystals within the myocardium.

Primary hyperoxaluria (PH) is a rare metabolic disorder due to a functional deficiency of the enzyme alanine:glyoxalate aminotransferase (AGT). There are at least 20 documented mutations in the gene encoding AGT (AGXT), but two mutations are associated with about 30% of the disease alleles in PH. More specifically, these mutations are associated with mitochondrial mistargeting and defective peroxisomal uptake of the AGT protein. Symptoms develop in 15% of children less than one year of age, and by five, 50% of patients are symptomatic. Infants may suffer from chronic renal failure and parenchymal oxalosis, and older children may have symptoms of urolithiasis, or complete ureteral obstruction. The kidney is the primary organ of involvement, since one of its functions is to excrete oxalate. Renal failure ultimately occurs, and subsequently, the oxalate crystals deposit in other organs, such as the heart, bone marrow, and soft tissues (systemic oxalosis). Chronic renal failure (uremia) leads to secondary hyperparathyroidism, which in a growing individual can cause marked skeletal abnormalities. Possible causes of death are end stage renal failure, cardiac conduction deficits, or a multitude of complications from surgical intervention. Combined liver-kidney transplant is the recommended treatment for these patients, along with hemodialysis, maintaining a high urine output, and thiazide diuresis.

In conclusion, in the presented case, the clinical picture and autopsy findings demonstrate a case of primary hyperoxaluria. The disease entity has numerous clinical manifestations, including renal failure and cardiac conduction defects, and has a high-risk management, (combined liverkidney transplant); all of which can lead to early, sudden death in these mostly young patients.

Primary Hyperoxaluria, Calcium-oxalate Deposition, Combined Liver-Kidney Transplantation

 ** Presenting Author*