



Primary Hyperoxaluria In A Young Patient

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Introduction

- Primary hyperoxaluria (PH) is a rare autosomal recessive metabolic disorder characterized by inborn errors of glyoxylate metabolism in liver¹.
- Estimated incidence is 1 in 58000
- It is basically classified into 3 types.
- PH type 1 is the most common variant and is caused by a mutation in the AGXT gene, which leads to a deficiency of the encoded liver-specific peroxisomal enzyme alanine glyoxylate aminotransferase².
- PH type 2 is caused by mutation in GRHPR gene which encodes, glyoxylate reductase/ hydroxypyruvate reductase (GRHPR enzyme)
- PH type 3 is the rarest type caused by mutation in HOGA1 that encodes the liver-specific mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase (HOGA).

Each of these mutations leads to overproduction and excretion of oxalate that gets deposited primarily in the kidney. Involvement of liver with

oxalate deposits is extremely rare with only 4 cases in the previously reported literature.¹⁻⁴ Because the primary enzymatic defect lies in the liver, isolated kidney transplant is not useful in PH and dual organ transplantation is required. In our case due to late presentation clinically along with kidneys, liver is also effected and facilitated crystal deposition in liver also.⁵

Case

29 year old female presented to us with chronic renal parenchymal disease. Patient complaints started with elevated serum creatinine post her second delivery in 2020, for which work up was done and diagnosed with oxalate nephropathy. Since then patient was on maintenance hemodialysis 4 times a week.

Patient has a gestational diabetes but was not on medication was on diet control. Patient also has recurrent renal stones and evacuation done twice. Patient was referred to our center for evaluation. CT chest revealed normal study no active infection seen. CT scan abdomen revealed bilateral contracted and calcified kidneys with

bilateral non obstructive ureter calculi mild hydronephrosis.

Renal function test revealed elevated creatinine, ammonia, inorganic phosphorous.

Further blood investigation were done liver function test shows elevated total bilirubin (2.30mg/dl), conjugated bilirubin 1.60mg/dl, unconjugated bilirubin 0.1mg/dl with markedly elevated SGOT (18992 IU/ml) ,SGPT (7386 IU/ml),alkaline phosphatase (23), GGT (92) and low albumin and globulin levels.

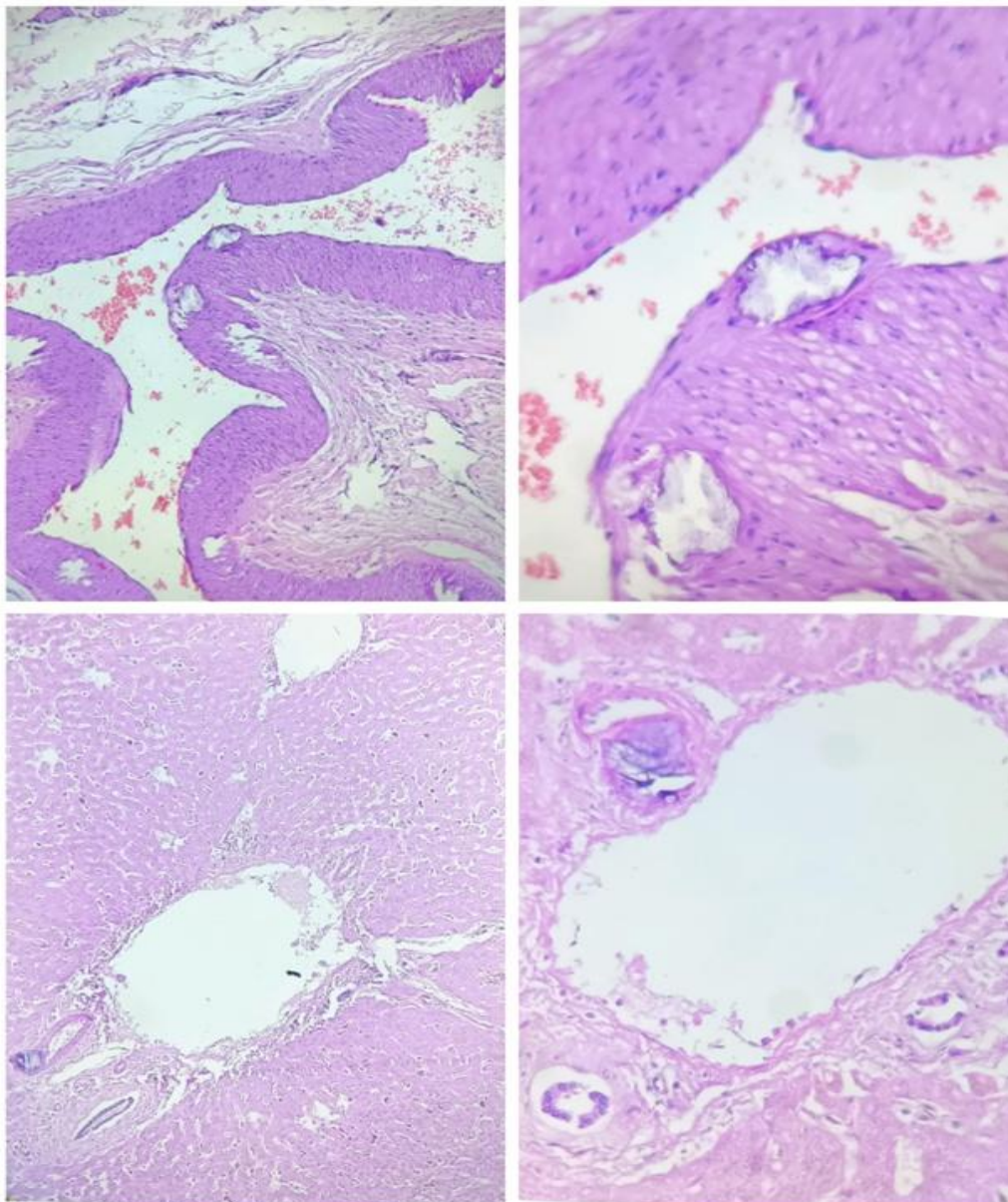
Patient was screened for viral infection (HIV, HBsAg, HCV) revealing negative study, patient was negative for CMV and EBV.

On genetic testing patient was proved AGXT gene mutation, falling under type-1 primary hyperoxaluria.

Patient had other necessary pre-op workup and preanaesthetic check up and she was taken for both kidney and liver transplant.

Explant liver was received at histopathology department, on examining shows massive panacinar hepatic necrosis with birefringent oxalate crystals in hilar vessels and portal arteries.

Oxalate Crystals in Vessel walls



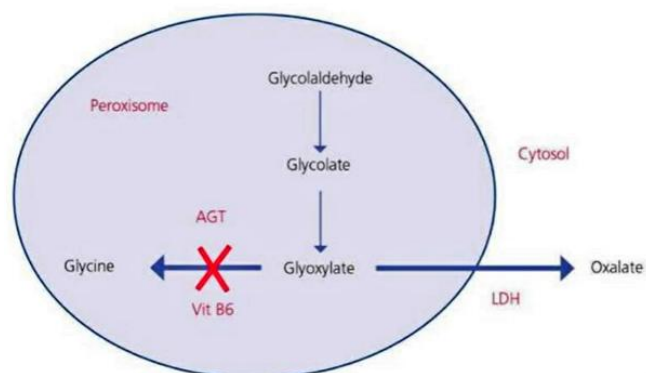
Gross Image**Discussion**

Primary hyperoxalurias (PH) is a rare genetic disorder in which defective glyoxalate metabolism results in excessive oxalate production. In all three types PH type 1, is most common form which is an autosomal recessive disorder caused by a deficiency of the liver-specific enzyme alanine glyoxylate aminotransferase (AGT) resulting in overproduction and excessive urinary excretion of oxalate. Since oxalate excretion is entirely via kidney in the form of insoluble calcium salts, recurrent urolithiasis and nephrocalcinosis are the characteristic features of the disease. As glomerular filtration rate decreases due to progressive renal damage, oxalate accumulates leading to systemic oxalosis and superimposed infections are common. Diagnosis is often delayed and is based on clinical and sonographic findings, urinary oxalate assessment, DNA analysis, and, if

necessary, direct AGT activity measurement in liver biopsy tissue is done.

Early initiation of conservative treatment, including high fluid intake, inhibitors of calcium oxalate crystallization, and pyridoxine in responsive cases, can help to maintain renal function in compliant subjects. Type 1 is typically most severely affected of the 3 types. In end-stage renal disease patients, the best outcomes have been achieved with combined liver-kidney transplantation which corrects the enzyme defect. Since the liver is the only organ responsible for glyoxylate detoxification by AGT, the excessive production of oxalate will continue as long as the native liver is left in place. Therefore, PH1 can be cured only when the deficient host liver has been removed. Liver transplantation is a form of gene therapy as well as enzyme replacement therapy as it will supply the missing enzyme in the correct

organ (liver), cell (hepatocyte), and intracellular compartment (peroxisome).⁶



In Europe, combined liver-kidney transplant has been the preferred approach in the past 25 years. A European PH1 Transplant registry reported 127 liver transplantations including more than 100 liver-kidney transplants in 117 patients between 1984 and 2004.⁷ Results were encouraging with patient survival rates of 86%, 80%, and 69% at 1 year, 5 years, and 10 years, respectively. There were 13 kidney graft failures. Comparable results have been reported from the USRDS, with a patient survival above 80% at 5 years and a death-censored graft survival of 76% at 8 years post transplant.⁸ Such a strategy can be successfully proposed to infants with PH1.⁹ Worldwide experience indicates that once perioperative mortality is avoided, combined liver-kidney Tx seems to be an acceptable treatment for PH1.¹⁰⁻¹¹ The strategy of combined liver-kidney Tx may be influenced by the stage of the disease. Simultaneous liver and kidney Tx is logical in patients with a GFR between 15 and 40 mL/min per 1.73 m², because, at this level, oxalate retention increases rapidly. A sequential procedure (first liver Tx, then dialysis until sufficient oxalate has been cleared from the body, followed by kidney Tx) may be proposed to ESRD patients, mainly infants with a long waiting time.¹²

Preemptive isolated liver Tx might be the first option in selected patients before advanced chronic renal failure has occurred, that is, at a GFR between 60 and 40 mL/min/1.73 m². In the Hamburg experience, 4 pediatric recipients with a

GFR between 27 and 98 mL/min per 1.73 m² received a preemptive liver transplant, and 3 of them still have significant residual renal function after a median followup of ~12 years.¹³ Another group reported good results at 5 years in 4 PH1 children who received a preemptive liver Tx with a mean pretransplant GFR of 81 mL/min/1.73 m².¹⁴ Such a strategy has a strong rationale but raises ethical controversies especially when the GFR is superior to 60 mL/min per 1.73 m². Indeed PH1 is the only peroxisomal disease without psychomotor delay due to cerebral involvement, and the conservative management of PH1 patients has significantly improved during the last 10 years; this may influence the role of preemptive liver Tx in such patients.

Conclusion

Patients with hyperoxaluria should be referred to higher centers for evaluation and management where experienced specialists are available with experience in such conditions and where access to the appropriate biochemical and molecular biological facilities is available. Major advances in biochemistry, enzymology, genetics, and management have been achieved during recent years. Improved awareness and knowledge of the disease can help in early and accurate diagnosis, before renal failure occurs, so that aggressive supportive treatment can be given for good prognosis. In ESRD patients, the greatest benefit has been obtained with one-step combined liver-kidney transplantation. New insights into potential therapies including the restoration of defective enzymatic activity through the use of chemical chaperones and/or recombinant gene therapy for enzyme replacement provides hope for curative treatment of hyperoxaluria in the future.

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