CASE REPORT

Hyperoxaluria After Renal Transplantation
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ABSTRACT
Primary hyperoxaluria is a rare autosomal recessive disorder, characterised by precipitation of insoluble oxalate crystals in the joints, kidneys, heart, eyes, skin, nerves, and bone marrow. The patients of primary oxaluria usually present with renal stone/nephrocalcinosis, and isolated kidney transplantation should not be done in these patients. We present a case report of 31-year lady with acute graft dysfunction due to oxaluria with no history of nephrolithiasis/nephrocalcinosis prior to renal transplantation.

Key Words: Primary hyperoxaluria. Nephrolithiasis. Renal transplant.

INTRODUCTION
Oxalate is an organic salt with chemical formula of C₂O₄⁻. There are two sources of oxalate in the body: exogenous from the diet (80 - 120 mg/24 hours) which is primarily absorbed from the colon, and endogenous production by liver as part of glycolate metabolism. Normal oxalate excretion is about 40 mg/24 hours or 30 mg of urinary oxalate per gram of urinary creatinine.

There are different causes of hyperoxaluria: (1) Absorptive hyperoxaluria: This is caused by conditions leading to chronic diarrhea such as inflammatory bowel disease, chronic biliary/pancreatic diseases, surgical bowel resection or intestinal bacterial overgrowth. In these conditions, utilised biliary salts combine with intestinal calcium, leaving the dietary oxalate unbounded and readily absorbable. (2) Idiopathic or mild hyperoxaluria: This is the most common type of hyperoxaluria with unidentified mechanism so far. Probably, high intake of oxalate in the presence of genetic predisposition of stone formation is the mechanism of nephrolithiasis in these patients. (3) Primary hyperoxaluria: This is an uncommon autosomal recessive disorder due to genetic enzymatic defects leading to blockade of the glycolate metabolism, which results in overproduction of oxalate through alternate pathways.

There are three variants of this rare disease depending upon the deficient enzyme. Most common is primary hyperoxaluria I (PH-I), resulting from mutation in AGXT gene encoding the alanine-glyoxylate aminotransferase (AGT), a pyridoxine-dependent liver enzyme that catalyses the conversion of glyoxylate to glycine. AGT deficiency results in the accumulation of glyoxylate, that leads to overproduction of oxalate and glycolate. Other types are primary hyperoxaluria type-II and type-III (PH-II and PH-III), which are caused by the deficiency of glyoxylate reductase-hydroxypruvate reductase (GRHPR) and 4-hydroxy-2-Oxo-glutarate aldolase (HOGA), respectively. These enzymes are involved in the reduction of glyoxylate (by GRHPR) and hydroxyproline (by HOGA) to glycolate (Figure 1).

Here, we are presenting an unusual case of oxalosis, which was diagnosed after it caused allograft dysfunction in renal transplant.

CASE REPORT
A 31-year married lady, with two healthy children, received a renal transplant from a 5/6 antigen (one A, two-B and two DR antigens) matched live unrelated donor on June 28, 2014. She had history of renal dysfunction and hypertension for 7 months without any
history of renal stones or nephrocalcinosis. Ultrasonography showed bilateral normal sized, highly echogenic kidneys with poor cortico-medullary differentiation, so renal biopsy was not carried out. Hemodialysis was done for 6 months. There was family history of renal stones in one brother and one sister. Brother had history of end-stage renal disease (ESRD) secondary to nephrolithiasis, while sister had no history of renal impairment and died of unknown cause. There was no history of stone disease in father, mother, two other sisters, and other relatives as well as in children. She had history of consanguineous marriage. The patient was not willing to continue long-term dialysis so renal transplantation was initiated.

Kidney transplant operation and postoperative hospital stay was uneventful and there was immediate graft function. The patient was discharged on triple immunosuppression (mycophenolate mofetil, tacrolimus and prednisolone) and had normal renal functions with serum creatinine of 0.9 mg/dl. The patient was on regular follow-up. Her blood tacrolimus levels remained between 6.5 and 9.2 ng/ml (normal: 4 - 11 ng/ml) during this follow-up period. Her serum creatinine remained below 1.0 mg/dl till 4 weeks after transplantation, when it started to rise gradually. One-and-half month after transplantation, she was found to have marked graft dysfunction with elevated blood urea nitrogen (50 mg/dl) and creatinine (2.9 mg/dl). Urine output was normal. Ultrasound of the transplanted kidney revealed no obstruction and good perfusion on Doppler with resistive index (RI) of 0.64. Urine routine examination showed pH of 5, specific gravity of 1.010, protein 1+, no red blood cells (RBC), 10 - 15 white blood cells (WBC)/HPF, no crystals and no growth on culture. Twenty-four hours urinary protein was 930 mg. Urine for decoy cells was negative. Hepatitis B surface antigen, anti-hepatitis C virus, anti-CMV IgM and PCR for CMV, were negative. Apart from low haemoglobin (7.9 g/dl), rest of the blood counts were normal. Liver function tests, serum electrolytes and lactate dehydrogenase (LDH) were within normal limits. Whole blood tacrolimus level was 7.2 ng/ml. Her renal graft biopsy was done to establish the cause of her transplant dysfunction, which showed no evidence of rejection; but there was deposition of birefringent oxalate crystals in the tubules (Figures 2 and 3). After biopsy report, her routine urine examination was repeated and found to have oxalate crystals. Her 24-hour urine was sent for metabolic analysis, and it was found to have oxalate level of 152 mg (normal: 7 - 44 mg/24 hours), calcium, 158.40 mg (normal: 100 - 300 mg/24 hours), phosphate 621 mg (normal: 400 - 1300 mg/24 hours), citrate 450 mg (normal: 320 - 1240 mg/24 hours) and uric acid, 375 mg (normal: 300 - 750 mg/24 hours). Genetic typing of primary oxaluria could not be done due to non-availability of the test in the city.

There was no history of exposure to oxalate precursors, such as ethylene glycol poisoning, star fruit ingestion, methoxyflurane anaesthesia or parenteral administration of large doses of naftidrofuryl or ascorbic acid. Furthermore, the patient had no history of any bowel symptoms or gastrointestinal operations. On review of literature, it was found that there are few oxaluria patients who are diagnosed after kidney transplantation, and she was one of them. Patient was started on pyridoxine 300 mg/day, sodium citrate and antibiotics for urinary tract infection (UTI), along with immuno-suppression. The renal functions improved partially and she is maintaining serum creatinine at 2.0 - 2.3 mg/dl after 2 years of transplantation.

DISCUSSION
Here, we reported a case of 31-year lady with primary hyperoxaluria, the diagnosis being made after renal transplantation, without prior history of nephrolithiasis and nephrocalcinosis. She presented with rapid intratubular calcium oxalate crystal deposition in a renal graft just one-and-half month after transplantation.

Late manifestations of PH-I may occur in adolescence with recurrent renal stones, ESRD as first manifestation or as recurrence of disease after transplantation. The interval between the onset of symptoms and the development of ESRD varies. Calcium oxalate deposits within the renal tissue as nephrocalcinosis or in the form of renal stones (nephrolithiasis). This leads to progressive renal injury and inflammation and tubular obstruction leading to interstitial fibrosis, declining renal function and eventually ESRD. The main presenting symptoms at diagnosis are recurrent nephrolithiasis and progressive nephrocalcinosis. Systemic oxalosis due to crystal deposition may affect the heart, skin, blood vessels walls, bones (fractures), joints, eye (retina), and
central nervous system. Even bone marrow infiltration has been reported. Patients with PH- II appear to have a less severe course but sometimes cannot be distinguished clinically from other varieties. PH- III has the least severe course and may be silent. Nephrocalcinosis and chronic kidney failure are uncommon, and systemic involvement has not been reported so far in this type of hyperoxaluria.6

As a whole, 30% of patients of hyperoxaluria are diagnosed only at ESRD, 10% are diagnosed after failed isolated renal transplantation, and only 13% are diagnosed after family screening.6,7 Diagnosis is usually based on history, urinary oxalate excretion, urinary glycolate and L-glyceric acid excretion, liver biopsy for enzyme defect (AGT and GRHPR enzyme activity), and molecular genetic testing to demonstrate a mutation of the AGXT, GRHPR, and HOGA genes.3,5

Medical management of hyperoxaluria induced renal impairment includes long-term diuresis (iv fluids, neurogastric tube or gastrostomy (especially in children for adequate fluid intake), administration of orthophosphate to increase urinary pyrophosphate and to decrease the urinary calcium excretion by binding with intestinal calcium and making it non-absorbable (but should not be used in renal failure), magnesium and high doses of pyridoxine (as coenzyme for AGT), thiazide diuretics and potassium/sodium citrate. In patients with renal failure, potassium salts can be replaced by sodium citrate.3,5 Isolated renal transplantation in patients of primary hyperoxaluria is frequently followed by recurrence of the stone/nephrocalcinosis in the transplanted kidney, which may have occurred in our case. As the defective enzyme is liver specific in PH-1, these patients require preemptive liver, sequential liver-kidney, or combined liver-kidney transplantation, based on individual presentation. Isolated kidney transplantation may be the procedure of choice for adult patients who are sensitive to pyridoxine, but allograft survival rates have been reported to be inferior in patients with primary hyperoxaluria compared to patients who received renal transplant for a non PH-1 cause of ESRD.5 In 1990, when liver transplant was out of reach, the European Dialysis and Transplant Association registry reported poor outcomes of isolated kidney transplantation with 3-year graft survival of 17 to 20% according to donor source.4,8 More recently, data from 58 PH-1 patients showed a death-censored kidney graft survival of 95% at 3 years with combined liver-kidney transplant versus 56% with isolated kidney transplant.4,8,9 Isolated kidney transplant might be the treatment of choice in patients with PH-II. Indeed, PH-II patients with kidney transplantation alone appear to have a more favourable course than PH-1 patients, and the benefit of liver transplantation in such patients is still unclear.4

Primary hyperoxaluria should be considered not only in cases with history of nephrocalcinosis and/or nephrolithiasis causing ESRD, but also in cases with family history of stone disease. Isolated kidney transplantation is not the treatment of choice in primary hyperoxaluria and these patients should undergo combined liver-kidney transplantation. If a case is diagnosed after kidney transplantation, it may be managed to some extent by heavy doses of Vitamin B6 and sodium/potassium citrate, provided there is partial deficiency of AGT and the variety is pyridoxine sensitive.

REFERENCES