Recurrence of primary hyperoxaluria: An avoidable catastrophe following kidney transplant

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ABSTRACT

Primary hyperoxaluria is a rare autosomal recessive disease due to deficiency of an oxalate-metabolizing liver enzyme, which results in nephrolithiasis and renal failure. Concomitant liver and kidney transplant is recommended as isolated kidney transplant is inevitably complicated by recurrence of the disease. We present a 25-year-old man with end-stage nephrolithic renal disease who underwent bilateral nephrectomy, followed by kidney transplantation. There was progressive worsening of kidney function two weeks post transplant. Review of nephrectomy and transplant kidney biopsy showed abundant calcium oxalate crystals and further workup revealed hyperoxaluria, which was previously unsuspected. Later he developed fever, breathlessness, hemiparesis and died 10 weeks after transplant. Autopsy revealed multi-organ deposits of oxalate crystals as well as widespread zygomycosis. This case emphasizes the need for careful pre-transplant evaluation of patients with renal calculus disease in order to exclude primary hyperoxaluria.

KEY WORDS: Primary hyperoxaluria, renal transplantation, recurrence

Primary hyperoxaluria (PHO) Types 1 and 2 are rare autosomal recessive disorders, characterized by oxalate overload due to deficiency of the liver enzymes alanine glyoxalate aminotransferase (AGT) and D-glycerate dehydrogenase respectively.[1] Type 1 PHO occurs in 0.11 to 0.26 per 100,000 births and results in severe disease, while there are less than 30 reported cases of the less severe Type 2 PHO.[2] The excess body oxalate in Type 1 PHO is excreted in urine resulting in nephrocalcinosis, nephrolithiasis and is also deposited in multiple organs. Primary hyperoxaluria is a “nephrologic liver disease” hence, combined liver and kidney transplant is the treatment of choice.[2,3] Isolated kidney transplant has a less favorable outcome and often results in recurrence.[4]

Case History

A 25-year-old male was diagnosed at another institute with end-stage renal disease due to bilateral, multiple nephrolithiasis, and renal transplant was planned. They performed bilateral nephrectomy as part of a strategy aimed at preventing the stones from serving as a nidus of infection in the post-transplant period. After receiving a renal graft from his mother, he was on immunosuppression with Tacrolimus-0.15 mg/kd/day, mycophenolate mofetil - 500 mg twice daily and prednisolone-1 mg/kg/day. Serum creatinine rose from 1.1 mg/dL on the fifth post-transplant day and was 2.6 mg/dL by the fourth week. Graft ultrasonography and Doppler study were normal while biopsy performed in the fourth post-transplant week was reported as acute rejection. He was pulsed with methylprednisolone (500 mg daily for three days) and as the tacrolimus level was low at 4 ng/ml, the dose was increased. There was no improvement in graft function and in the eighth post-transplant week, he was transferred to our institute with a serum creatinine of 3.6 mg/dL. Physical examination and all routine hematological and biochemical investigations were normal except for the raised serum creatinine and hemoglobin of 8.9 gm/dL. We reviewed slides of nephrectomy and graft biopsy and noted extensive deposits of birefringent calcium oxalate crystals in the tubules, interstitium, vascular media and even the sclerosed glomeruli of nephrectomy [Figure 1].

Graft biopsy lacked features of rejection. The possibility of PHO which had been overlooked prior to transplant and now recurred in the graft was considered and this diagnosis was supported by finding high urinary oxalate levels of 124 mg/m2/day. The patient was started on 5 mg/kg/day of pyridoxine.

Later, he developed oral candidiasis, necrotizing skin lesions on the lower limb, fever, abdominal pain, breathlessness and hemiparesis. Skin biopsy showed oxalate crystals in dermal vessels. Chest X-ray was normal but abdominal ultrasonography and CT scans suggested infarcts in transplant kidney and the frontal lobe of the brain. Blood and urine cultures including those for fungal growth were negative. He was treated with antibiotics and systemic anti-fungals and immunosuppression was reduced. However, he developed hypotension and shock...
Primary hyperoxaluria results in nephrolithiasis, nephrocalcinosis and extensive deposits of oxalate crystals in other organs.\(^5\) There is rapid decline in renal function because, in addition to obstruction by calculus, the tissue crystals result in widespread renal parenchymal destruction. Varied clinical manifestations result from multi-organ deposits of oxalate crystals. These particularly occur in the vessel walls of the organs and result in cardiomyopathy, cardiac arrhythmias, polyradiculopathy, dural gangrene, synovitis, chondrocalcinosis, oxalate osteopathy, peripheral gangrene, flocked retinopathy, intestinal infarction and hypothyroidism.\(^6\) Oxalate crystals in tissues may also occur in secondary hyperoxaluria following ingestion of ethylene glycol or can be associated with inflammatory bowel disease and ileo-jejunal bypass.\(^7\) These predisposing factors were not present in our case. Tissue oxalate crystals may also be secondary to oxalate retention in chronic renal disease but deposits are more extensive in primary hyperoxaluria.

Occurrence of recurrent nephrolithiasis in young patients should prompt workup for PHO, especially if nephrocalcinosis and tissue calcifications are detected on ultrasonography or plain abdominal X-ray. Determination of AGT levels on liver biopsy provides definitive diagnosis, but is not readily available.\(^6\) Urinary oxalate levels greater than 90 mg/1.73m\(^2\)/day are a feature of PHO while secondary hyperoxaluria has levels below this value.\(^5\) Paradoxically, some PHOs have low urinary oxalate owing to the inability of diseased kidneys to excrete the oxalate. In this situation, determination of plasma oxalate levels will help. The increase in plasma oxalate is inversely correlated with the fall in glomerular filtration rate and is significantly higher in patients with primary as compared to secondary hyperoxaluria.\(^5\) Urine oxalate to creatinine ratio may be used as a screening modality in children and should be interpreted with the age-specific normal values.\(^5\) In conjunction with the biochemical parameters, kidney, skin and bone marrow biopsies are useful diagnostic tools and the presence of frequent crystals in tissues should prompt the pathologist to alert the clinician regarding the possibility of primary hyperoxaluria.

In our case, renal transplant was performed at the referring institute as hyperoxaluria was unsuspected clinically and even on pathologic examination of pre and postoperative tissue material. There have been instances of similar reports in the literature.\(^7,8\) Since the basic defect is in the liver, the treatment of choice for PHO is combined or staged liver and kidney transplantation.\(^5\) Liver transplantation to correct the enzyme defect should ideally be performed first with subsequent vigorous hemodialysis to reduce the oxalate load, followed by kidney transplant. Schienman et al., proposed a specific strategy for improved transplant outcome in cases of primary hyperoxaluria.\(^9\) They recommend intensive pre-transplant hemodialysis to enhance systemic oxalate removal and prevent tissue accumulation. Live, related donors are to be preferred to minimize risk of rejection and renal failure, which may favor oxalate retention. High-dose pyridoxine is advocated to induce residual AGT activity. Post transplant, it is vital to enhance calcium oxalate solubility by maintaining high fluid intake supported by diuretics and the use of crystal inhibitors like citrate, neutral phosphate and magnesium oxide.\(^6\)

Fulminant zygomycosis is a known complication of immunosuppression and renal failure.\(^10\) It was the terminal event in our case. Recurrence of primary hyperoxaluria resulting in graft failure is well documented.\(^3,6-8\) Despite this, on occasion, the diagnosis is made in retrospect after the transplant is performed. This case illustrates the need for early and accurate recognition of PHO by careful pre-transplant evaluation of patients in the presence of renal calculus disease.

References


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