Primary hyperoxaluria: a rare but important cause of nephrolithiasis

We report on a middle-aged man with end-stage renal failure apparently secondary to recurrent renal stones. He developed systemic oxalosis soon after commencing dialysis. The diagnosis of primary hyperoxaluria type 1 was supported by the finding of high dialysate glycolate excretion. The patient subsequently received an isolated cadaveric renal transplant, but the outcome was a rapid recurrence of oxalosis and early graft failure. Although isolated liver or renal transplantation in addition to various adjuvant measures may be considered in the early stage, combined liver-kidney transplantation remains the only definitive therapy for a patient with end-stage renal failure and systemic oxalosis due to hyperoxaluria type 1. This case illustrates the possible late presentation of primary hyperoxaluria type 1 and the poor outcome with isolated renal transplantation after the development of systemic oxalosis. One should thus have a high index of suspicion in patients with recurrent renal stones of this rare, but nevertheless important, entity.

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GMW Tong
KY Lo
SK Mak
ELK Law
AKM Wong
haematuria and albuminuria. Urine culture was negative. Ultrasonography of his kidneys revealed right hydronephrosis, while the left kidney was demonstrated to have no significant excretion on pentetic acid renography.

Endoscopic removal of the right ureteric stone and double J stent insertion into the right ureter were performed, followed by ESWL to the right renal stones. Analysis of the removed ureteric stone revealed mainly calcium oxalate. The patient had no history of any bowel symptom or gastrointestinal operation. His drug history was also unremarkable, and in particular he had no regular ingestion of ascorbic acid. There was no family history of recurrent renal stones. Blood investigations revealed no obvious risk factors for calcium stone formation. He had a serum calcium level of 1.89 mmol/L (normal range, 2.05-2.55 mmol/L), a phosphate level of 1.2 mmol/L (normal range, 0.8-1.5 mmol/L), an albumin level of 33 g/L (normal range, 35-50 g/L), an alkaline phosphatase level of 78 U/L (normal range, 50-120 U/L), and a urate level of 0.39 mmol/L (normal range, 0.16-0.38 mmol/L).

After the urological intervention, there was no significant improvement in his renal function. Repeated ultrasonography of the kidneys showed no hydronephrosis. However, his clinical course was complicated by recurrent methicillin-sensitive Staphylococcus aureus urinary tract infection; renal function continued to deteriorate despite antibiotic treatment. Three months later, when his serum creatinine level exceeded 1000 µmol/L, the patient was started on continuous ambulatory peritoneal dialysis (CAPD), which was performed with 2.5% Dianeal (Baxter, Illinois, US), 4 x 2 L exchanges per day.

Six months after commencing on dialysis, the patient complained of progressive bilateral weakness affecting the upper and lower limbs. Physical examination showed prominent small muscle wasting over both hands and feet. There were also sensory losses of classic stocking-glove distribution. Deep tendon reflexes were absent bilaterally. His urine output had continued to decline after starting dialysis and by now he was anuric. Laboratory investigations revealed that he had a serum creatinine level of 969 µmol/L, a urea level of 30.3 mmol/L, a calcium level of 2.0 mmol/L, a phosphate level of 1.4 mmol/L, an albumin level of 32 g/L, and a haemoglobin level of 75 g/L (normal range, 140-175 g/L). Serological markers, including antinuclear factor, antineutrophil cytoplasmic antibody, VDRL, complement levels, and immunoglobulin levels, were all within normal limits. His oral glucose tolerance test and thyroid function test were also normal. Urea kinetic study on his prescribed CAPD regimen revealed a weekly Kt/V urea index of 1.66 (where K=clearance, t=treatment time, and V=volume of urea distribution), indicating that he was receiving acceptable dialysis. Nerve conduction study revealed findings compatible with generalised sensorimotor neuropathy of both demyelinating and axonal types. A sural nerve biopsy was performed, and it showed marked vascular deposition of oxalate crystals within the walls of blood vessels in the epineural fat and endoneurium (Fig a). There were also focal oxalate crystals within the nerve fibres themselves. There were diffuse moderate loss and patchy marked loss of axons. Many of the remaining large fibres showed swelling, with disintegration and collapse of the myelin sheath. The overall features were compatible with the diagnosis of oxalate neuropathy with predominant axonal degeneration.

As the patient had become anuric, semi-quantitative organic acid analysis of peritoneal dialysate effluent was performed to investigate for probable primary oxalosis. To this end, his total daily excretion of glycolic acid in the dialysate was compared with that of five anuric controls who were on a similar dialysis regimen, but had no history of

![Fig. Oxalate crystal deposition (arrows) can be seen on (a) perineural blood vessel section; and (b) allograft renal biopsy section viewed under polaroid filter (H&E, x20)
renal stones. The finding that he had a significantly higher glycolate dialysate excretion than the controls (48.3 µmol versus 19.6±5.8 µmol) [Table] was highly suggestive of the diagnosis of PH type 1 (PH1). Definitive diagnosis, however, required the measurement of liver alanine-glyoxylate aminotransferase (AGT) activity—a test that was unfortunately not available locally.

In view of the diagnosis of probable PH1, the patient was switched to haemodialysis four times per week to improve the clearance of oxalate. He was also informed of the likely diagnosis and potentially poor prognosis without a combined liver and kidney transplant.

One month after starting on haemodialysis, the patient went to mainland China for a cadaveric renal transplant. The operative details and graft matching were unknown. His immunosuppressive therapy consisted of induction with tacrolimus, prednisolone, and mycophenolate mofetil. The graft demonstrated immediate function, with a urine output of about 1 L on postoperative day 1, although this rapidly declined and the patient became anuric on postoperative day 4. No specific intervention was given in mainland China, and he presented to us on postoperative day 11 with a non-functioning graft. On presentation, he was anuric and haodynamically stable. His serum creatinine level was 872 µmol/L. Ultrasonography of the allograft showed no hydronephrosis. Urine culture was negative. An allograft renal biopsy was performed, but the specimen showed no glomerular pathology. Nevertheless, 25% of tubular lumina contained refractile and birefringent oxalate crystals (Fig b). Tubular epithelial cells were viable, and no tubulitis was evident. A portion of blood vessel wall in the biopsy specimen also demonstrated oxalate crystal deposition. In view of the renal biopsy findings, the patient was started on daily haemodialysis, 5 hours per session. In addition, he was given high-dose pyridoxine 1 g/day. Oral potassium citrate 6 g/day was also prescribed as a form of potassium replacement for the loss sustained during the intensive daily haemodialysis. His maintenance immunosuppressive drugs were continued.

The patient remained anuric until 8 weeks after the operation, whereupon his urine output started to increase, at one point reaching 1 L/day. However, it subsequently declined over a 1-week period, and he became anuric once more. An allograft renal biopsy was repeated. Light microscopy revealed prominent oxalate crystal deposition with varying degrees of tubular damage and degeneration. No rejection was evident. The glomeruli were normal and immunofluorescent study results were unremarkable. The overall features were consistent with recurrence of oxalosis. In view of the poor outlook for graft function, his haemodialysis frequency was reduced to four times per week, still with 5 hours per session, while other adjuvant therapies, including high-dose pyridoxine and potassium citrate, were continued. The maintenance immunosuppressive drugs were also gradually tapered. Allograft kidney function has thus far failed to return and the patient has remained anuric. A third allograft renal biopsy performed 1 year post-transplant revealed increasing oxalate deposition, with severe tubular atrophy and fibrosis.

Discussion

Three distinct types of PH have been described in the literature. Primary hyperoxaluria type 1, the most common form of PH, is a rare, autosomal recessive, hereditary disorder of glyoxylate metabolism due to a deficiency of the liver-specific peroxisomal enzyme AGT. The defective metabolism causes concomitant increases in hepatic oxalate and glycolate synthesis, and the ensuing hyperoxaluria and hyperglycolic aciduria are regarded as the biochemical hallmarks of PH1. Primary hyperoxaluria type 2 (PH2), a much rarer form of PH, is an autosomal recessive, inherited deficiency of glyoxylate reductase (D-glycerate dehydrogenase), with clinical manifestations that can be similar to those of PH1. Typically, the hyperoxaluria in PH2 is accompanied by L-glyceric aciduria devoid of an elevated glycolate excretion. The third PH subgroup, PH type 3, has been described in patients having increased intestinal oxalate absorption in the absence of any intestinal pathology.

Currently, there are no data on the prevalence and incidence of PH in Hong Kong. Elsewhere, the average prevalence and incidence rates of PH1 in France in 1995 were 1.05 per million per year and 0.12 per million per year, respectively; the mean age at onset was 5 years (range, 0-63 years). Various case series confirm the French experience, ie PH1 is mostly a paediatric disease, although on rare occasions it can also occur in adulthood, in some cases as late as the sixth decade of life. The patient in this study belonged to the late-onset group, with his first renal stone being noticed at the age of 54 years. Primary hyperoxaluria type 1 is clearly a monogenic disease (affecting the AGT gene located at chromosome position 2q36-37), and the factors responsible for the observed clinical heterogeneity remain unknown. It has been suggested that residual AGT enzymic activity and its associated pyridoxine responsiveness may be contributory to late-onset cases of PH1. A study performed by Hoppe et al on a family with four affected individuals in two different generations, however, showed no definite relationship between any genotype, enzymatic phenotype, and disease severity. This author thus suggested that other currently unrecognised genetic and environmental factors, such as periods of

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<td><strong>Total daily output of glycolic acid (µmol/day)</strong></td>
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dehydration, and subclinical renal or enteric infection, might have contributed to the observed highly variable clinical course of PH1.

The clinical presentation of PH1 ranges from recurrent renal stones and nephrocalcinosis in the early stage, to progressive renal failure and systemic oxalosis in the advanced stage. In patients with systemic oxalosis, various organs and tissues may be affected, e.g., the heart, joints, arteries, soft tissues, bones, eyes, and nerves. The patient in this study presented in the advanced stage, with peripheral neuropathy as a major clinical manifestation. Similar cases with prominent peripheral nerve involvement have also been reported in the literature.4,5

Being a rare clinical entity, especially among adults, early diagnosis of PH1 hinges on a high index of clinical suspicion. This, in turn, should be followed by biochemical testing for hyperoxaluria and hyperglycolic aciduria, and confirmation by AGT assay on liver biopsy. The diagnosis becomes more difficult when the patient develops end-stage renal failure (ESRF) and anuria, as urinary analysis becomes impossible. This is especially true where AGT assay on liver biopsy is not available, as is the case in Hong Kong. In the patient in this study, work-up for PH occurred only after he became anuric and was found to have systemic oxalosis. Since oxalate precursors are expected to be retained in renal failure, measuring their content in dialysate may represent a useful approach to diagnosis. We therefore compared the daily peritoneal dialysate glycolate excretion of this patient with five controls with oxalosis-unrelated ESRF. We found that this patient did indeed show a significantly higher glycolate dialysate excretion. Although the literature contains no other reports of studies confirming the usefulness of this test in CAPD patients, Marangella et al6 conducted a similar study in haemodialysis patients. In their study, five PH1 patients had a significantly higher dialysate glycolate excretion compared to one patient with Crohn’s disease–related enteric oxalate hyperabsorption and nine patients with oxalosis-unrelated ESRF. The results in this study could thus be interpreted as controlling the same weight in support of the diagnosis of PH1, although the dialysate L-glycerate content has not been measured.

For patients presenting late with ESRF and systemic oxalosis, as in this case, combined kidney and liver transplantation is regarded as the only definitive treatment. According to the 1998 European PH1 transplant registry report, actuarial graft and patient survival rates at 5 years were 72% and 62%, respectively.7 By comparison, the overall outcome of any form of renal replacement therapy without concomitant replacement of deficient enzymatic activity has been poor. Thus, dialysis alone has been shown to be ineffective in retarding disease progression and preventing further accumulation of oxalate. While it can meet the balance in oxalosis-unrelated dialysis cases, the amount of oxalate removable by dialysis falls short of that produced in patients with PH.9 The outcome with isolated renal transplantation has also been disappointing, as highlighted in this case. In 1990, the European Dialysis and Transplant Association registry reported 3-year survival rates for first kidney grafts of 23% for living-related grafts and 17% for cadaveric grafts.10 The report’s authors noted that recurrence of oxalosis in the graft kidney was a major problem, and suggested it was probably related to the mobilisation of oxalate stores after transplantation on top of the pre-existing oxalate hyperproduction.

On the other hand, the scenario may be different if the diagnosis of PH1 is made in the early stage. This is particularly pertinent when one considers that up to 22.7% of patients have been reported to be responsive to pyridoxine,11 a cofactor in the AGT enzyme pathway. Pyridoxine-responsive patients, who appear more likely to have residual AGT enzymic activity, may show a significant decrease in oxalate and glycolate production when they are treated with high-dose pyridoxine (5-20 mg/kg). A study published in the New England Journal of Medicine showed that orthophosphate and high-dose pyridoxine were useful in prolonging native renal survival in PH1.12 In addition, thiazide diuretics and magnesium and citrate supplementation are helpful in counteracting calcium oxalate crystallisation.13

As oxalate retention accelerates when the glomerular filtration rate falls below 20 mL/min/1.73 m², it has been suggested that pre-emptive isolated renal transplantation could be considered before there is a serious accumulation of oxalate in the body, especially for pyridoxine-responsive patients.14 Some authors have also advocated isolated liver transplantation for patients with preserved renal function (i.e., creatinine clearance >30 mL/min) simply to correct the derranged glyoxylate metabolism, but its clinical role has not been well defined.15

Conclusion

Given the possibility of the late-onset of PH, it is important to have a high index of suspicion for this rare, hereditary condition in all patients with recurrent renal stones, regardless of their age. It is hoped that with early diagnosis and appropriate treatment, the onset of renal failure can be delayed and the long-term prognosis improved, without resorting to combined kidney and liver transplantation.

Acknowledgement

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References

2. Marangella M. Transplantation strategies in type 1 primary hyper-


