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Case Report

Late-onset primary hyperoxaluria diagnosed after renal transplantation presented with early recurrence of disease

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Introduction

Intratubular crystal deposition in transplanted patients is very rare and can be a cause of renal graft failure. Oxalate is a major component of the most common type of kidney stones, calcium oxalate stones. Hyperoxaluria is either inborn or acquired. Primary hyperoxaluria (PH) is a rare autosomal recessive disease resulting from deficiency of hepatic alanine:glyoxylate aminotransferase (AGT) (type I, PH-I) or glyoxylate reductase/D-glycerate dehydrogenase (type II, PH-II). Urinary excretion of both oxalate and glycolate is increased in PH-I, and that of both oxalate and L-glyceric acid is elevated in PH-II. PH results in urolithiasis and systemic oxalosis, often progressing to end-stage renal disease (ESRD) in young people. Late manifestations of PH-I are reported in a few middle-aged patients with recurrent renal stones or systemic oxalosis [1–3]. Recurrence of PH in renal transplants is common [4]. In a few patients, very rapid recurrence of disease has also been described [2].

Here, we report a case of late-onset PH-I, with the diagnosis being made only after transplantation presented with rapid intratubular calcium oxalate crystal deposition in a renal graft.

Case

The patient is a 43-year-old female who received a renal transplant from a living unrelated donor on September 12, 2002. She had shown renal dysfunction since 1991, when renal biopsy showed the features of chronic interstitial nephritis without evidence of oxalate crystal deposition under polarized light microscopy. She did not have a history or symptoms of renal stones nor other signs of systemic oxalosis. Haemodialysis was initiated in February 2000. After transplantation, the patient was treated with prednisolone, mycophenolate mofetil and cyclosporin A. At post-operative day 4, urine volume was abruptly reduced with the rebound of the creatinine level. Under the impression that she was undergoing acute rejection, she received methyl prednisolone pulse therapy 500 mg for 3 days and FK-506. At post-operative day 9, her urine output decreased to 10 ml/h. Eleven days after transplantation, features of obstructive uropathy were present on renal scan together with anuria and, therefore, ureteroneocystostomy was performed.

A renal biopsy was performed on the 15th day after transplantation. Under light microscopy, tubular epithelial cells showed focal severe necrosis or sloughing with occasional disruption of tubular basement membrane. Mitotic figures were rarely observed. Tubular lumens contained numerous rhomboid, polyhedral or cone-shaped crystals attached to the necrotic epithelial cells, in which calcium deposits were evident (Figures 1 and 2). The interstitium was oedematous with patchy infiltration of mononuclear cells. Intertubular arterioles focally exhibited hyaline arteriolosclerosis. There was no evidence of rejection. The glomeruli were unremarkable.

Laboratory data at the time of biopsy were as follows: haemoglobin, 7.8 g/dl; haematocrit, 22%; white blood cells, 8400/mm^3; platelets, 166 000; serum total protein, 4.5 g/dl; albumin, 2.7 g/dl; cholesterol, 246 mg/dl; blood urea nitrogen (BUN), 77 mg/dl; serum creatinine, 4.8 mg/dl; serum Ca/P/Mg, 8.1/8.3/1.3 mg/dl; intact parathyroid hormone (iPTH), 188.9 pg/ml (normal range, 15–65). Urinary sediment contained numerous red blood cells and 10–29 white

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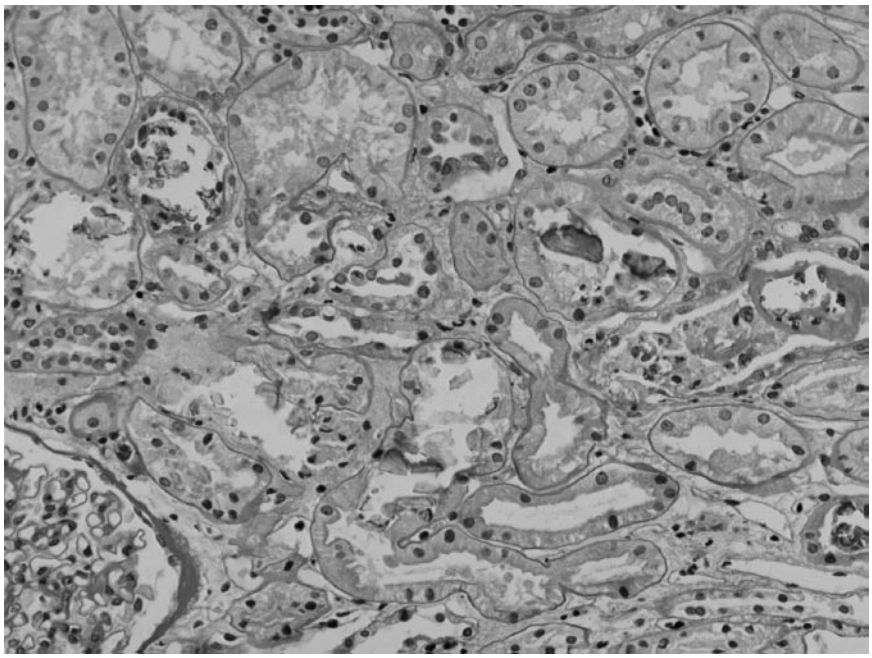

Fig. 1. Widespread intratubular crystal deposits in the renal allograft 15 days after transplantation. Tubular epithelial cells show focal severe necrosis with occasional disruption of tubular basement membrane (PAS, original magnification ×200).

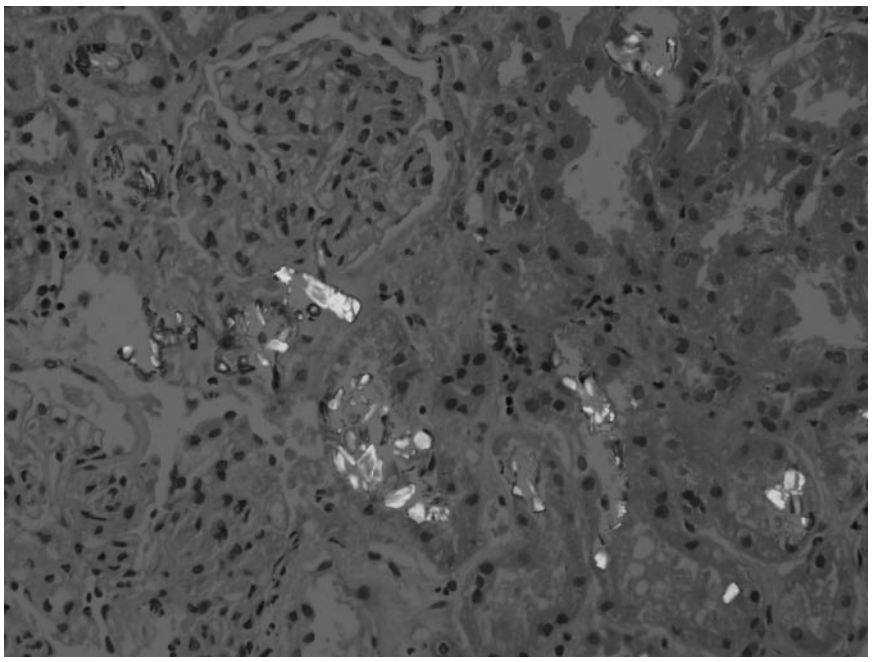

Fig. 2. Calcium oxalate crystal deposits in cortical tubules of renal transplant. Many tubules contain birefringent calcium oxalate crystals (HE, original magnification ×200).

blood cells per high power field. Stone metabolism study on a 24 h urine collection showed that the levels of oxalate were markedly raised to 2.07 mmol (normal range, 0.04–0.32) and those of citrate, calcium and creatinine were low, measuring 0.21 mmol (normal, >1.03), 51 mg (normal, >200 mg) and 0.62 g (normal range, 0.8–1.9), respectively.

Cortical calcifications were not visible on plain abdominal radiography or ultrasound.

Three months after transplantation, a ureteral stone measuring up to 1.5 cm was removed from the graft through ureterolithotomy. The composition of the stone was of calcium oxalate by chemical analysis. However, infrared spectroscopy or X-ray diffraction would have been better methods for analysis, because the chemical method gives incorrect results, which cannot be used for interpretation. Her serum creatinine level of 3 mg/dl was maintained for several months.

However, her renal function gradually worsened, leading her to receive haemodialysis. Her oxalate levels in plasma and urine samples obtained at the end of July 2004 were 0.13 and 0.64 mmol/l, respectively. Liver biopsy was performed at the end of October 2004 to measure AGT activity at the Department of Clinical Biochemistry, University College London Hospitals (London, UK). AGT activity was 2.7 μmol/h/mg protein (reference range 19.1–47.9), and AGT immunoreactivity was negative.

Discussion

We report a case of late-onset PH, with the diagnosis being suspected only after transplantation, because of rapid intratubular calcium oxalate crystal localization in a renal graft associated with severe hyperoxaluria.

Before transplantation, this patient showed neither symptoms nor history of nephrolithiasis nor other signs of systemic oxalosis. In this regard, we tried to exclude the possibility of secondary hyperoxaluria, which is attributable to excessive intake (dietary) or increased intestinal absorption (enteric) of oxalate. Causes of secondary hyperoxaluria include accidental massive 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 (reviewed in [5]). Our patient, however, did not have such a history. Furthermore, she did not have a history of gastrointestinal disorders nor steatorrhoea, excluding the possibility of enteric hyperoxaluria.

Plasma oxalate levels are increased in patients with chronic renal failure as a consequence of impaired renal clearance [6,7]. Renal and myocardial deposits of oxalate may be seen in patients on haemodialysis [7,8]. Sudden oxalate crystal deposition with irreversible failure has also been described in renal transplants, when acute renal failure occurs associated with acute rejection or acute tubular necrosis. Nonetheless, the plasma oxalate level is significantly higher in PH patients with ESRD (>80–100 μmol/l) than in non-PH patients with ESRD (40–60 μmol/l) [6]. Thus, it is likely that some uraemic patients having very high plasma oxalate levels (>80 μmol/l) [7] might actually have an unrecognized PH. Furthermore, some patients who were previously classified as having secondary hyperoxaluria might, in fact, have a type of PH [9,10].

In this context, we analysed plasma samples to look for the possibility of unrecognized PH. The plasma oxalate level in our patient 2 years after transplantation was 130 μmol/l, which was even greater than that of known PH patients with ESRD. In addition, follow-up oxalate concentrations in urine obtained during the course of haemodialysis were still greater than the upper limit of the reference range. Under the impression of her having PH, liver needle biopsy was performed. Finally, diagnosis of PH-I was made by demonstrating deficient AGT activity in the liver samples.

As shown in our patient, a diagnosis of PH is difficult to establish because of clinical heterogeneity [9,10], In this regard, diagnostic studies for PH are recommended in cases of unclassified hyperoxaluria. The diagnosis of PH is especially important in our case with regard to the next transplant procedure, in which combined liver–kidney organ transplantation is completely necessary.

In summary, we report a case of late-onset PH-I leading to rapid recurrence of disease, when the diagnosis was not known before transplantation. The final diagnosis of PH-I is especially important because isolated kidney transplantation is not a matter of choice for the majority of patients with PH-I.

Conflict of interest statement. None declared.

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