Successful kidney retransplantation after combined liver/kidney transplantation in primary hyperoxaluria type I

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Introduction

Primary hyperoxaluria type I (PHI) is a rare disorder due to a deficiency or mistargeting (mitochondrial) of peroxisomal alanine:glyoxylate aminotransferase (AGT) in the liver cells [1]. The subsequent failure of amination of glyoxylate leads to oxidation of excessive amounts of glyoxylate to oxalate. Glycolate forms a soluble calcium salt and is readily excreted in the urine. Calcium oxalate has a very low solubility leading to nephrocalcinosis, urolithiasis, and progressive renal insufficiency. Once renal function declines, oxalate which is only excreted by the kidney, accumulates and calcium oxalate gets deposited in various tissues—a condition called 'systemic oxalosis'. In case of PHI, renal replacement therapy treatment by haemodialysis or isolated renal transplantation give poor results. Haemodialysis cannot achieve an oxalate removal rate equal to endogenous production rate and systemic oxalosis will progressively worsen. Isolated renal transplantation will invariably result in rapid recurrence and destruction of the graft unless the enzyme deficiency is partial [2]. Thus, combined liver/kidney transplantation or even isolated liver transplantation before the patient reaches end-stage renal disease (ESRD) seems the best approach [3–6]. However, the presence of massive oxalate tissue deposits may destroy the transplanted kidney, even after enzyme replacement therapy. We report a case where recurrence of nephrocalcinosis in the graft led to ESRD 6 years after a combined liver/kidney transplantation and was successfully treated by a second renal transplant.

Methodologies for analysis of oxalate

Plasma oxalate concentration was carried out by means of a soluble oxalate oxidase assay (BioRea kit) with a reference range of 20–40 μmol/l. Prior to analysis, an ultrafiltration of plasma to remove proteins and others molecules was performed.

Urine ion chromatography was used for measuring urine oxalate concentration with a reference range of 100–450 μmol/24 h. Calcium oxalate deposition in the tissue was identified by means of a polarized light technique.

Case report

A 53-year-old female was admitted in 1984 for further management of ESRD. A diagnosis of PHI was made on the basis of bilateral nephrocalcinosis, recurrent nephrolithiasis, markedly elevated plasma oxalate concentration (99.75 μmol/l, normal range 20–40 μmol/l), calcium oxalate deposits (Figure 1a) in skin, vessels, marrow, and liver. Indeed, the liver and marrow biopsies showed a chronic granulomatous inflammation in response to calcium oxalate deposition. Peroxisomal AGT activity in hepatocytes was determined and was absent. Despite intensive haemodialysis (6 h three times per week with a high permeability membrane), systemic oxalosis worsened. A combined liver-kidney transplantation was performed in 1990 with vigorous pre-and postoperative haemodialysis. Postoperatively urine output was maintained in a range of 500 ml/h. Immunosuppression included steroids, azathioprine, cyclosporine and thymoglobulin (IMTIX, Lyon, France) and the patient received crystallization inhibitors. She was discharged with stable renal (serum creatinine 80 μmol/l) and hepatic function but with high plasma (52.44 μmol/l) and urine (1824 μmol/24 h) oxalate concentrations. These concentrations remained high despite normal renal function for the first 2 years. The renal function progressively declined over the next 4 years due to recurrent nephrocalcinosis. Seventy-seven months after transplantation, haemodialysis was resumed on a daily basis until a second isolated renal transplantation was performed three weeks later on December 1996. Postoperative haemodialysis was started daily and then every other day; urine output was maintained in a range of 500 ml/h. At the time of discharge (day 57 from the kidney retransplantation),
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Fig. 1. (a) Hand X-ray taken before the combined liver-kidney transplantation, showing diffuse calcium oxalate deposits in skin and in the vessels. (b) Hand X-ray taken on day 79 after the renal retransplantation, showing significant resolution of soft tissue calcification.

serum creatinine was 66 μmol/l, plasma oxalate 47 μmol/l and 24 h urine oxalate 1612 μmol/24 h. A hand X-ray taken on day 79 showed significant resolution of soft tissue calcification (Figure 1b). Eleven months after transplantation, serum creatinine was 70 μmol/l, plasma (13 μmol/l) and urine (1170 μmol/l) oxalate were within the normal range.

Discussion

The risk of recurrence is of major concern in patients with ESRD due to PHI. A report from the EDTA Registry in 1990 showed an overall 1-year graft survival rate of 26% in 79 PHI patients with first cadaveric renal allografts [7]. This data must be carefully analysed since it includes patients who have been transplanted years before 1990.

Scheinman et al. [8] proposed a specific strategy adapted to isolated kidney transplantation. They recommended intensive pretransplant dialysis, the use of living related donors, antilymphocyte globulin, high urine volume, and inhibitors of crystal growth. Of 10 live related donor transplants treated by such a strategy, seven had a good renal function beyond the first year. However the longterm outcome was poor [9] because of rapid recurrence of nephrocalcinosis due to persistent oxalate overproduction and release of oxalate from tissue stores.

Simultaneous liver-kidney transplantation will reduce the risk of recurrence. Liver transplantation will stop oxalate overproduction and simultaneous renal transplantation will excrete oxalate released from tissue stores. In 1987, Watts et al. reported a successful combined liver-kidney transplantation [10]. The European PHI transplant registry reported the results of 64 liver transplants in 61 patients (58 kidney-liver, three isolated liver, three liver retransplantation). The 1-year actuarial patient and graft survival rate was 88% [11] and the 5-year patient survival rate was 80%.

Timing of the combined transplantation is important. The longer the period from onset of end-stage renal disease, the greater the risk of recurrence of nephrocalcinosis over the years (despite correction of the metabolic defect). Our patient developed ESRD in 1984 and was on dialysis for 6 years before a combined liver-kidney transplantation was performed. She had clear evidence of severe systemic oxalosis with calcium oxalate crystal deposits in skin, vessels, bone marrow, and liver. After transplantation, despite the correction of the metabolic defect, she continued to have high plasma oxalate concentration due to tissue release, leading to high urine oxalate excretion and to subsequent recurrence of nephrocalcinosis in the graft. However, this first kidney graft achieved partial tissue oxalate depletion, allowing a second transplant to be performed.

In summary, this case highlights the fact that combined liver-kidney transplantation should be performed even in those patients presenting for the first time with ESRD and systemic oxalosis. In such conditions, recurrence takes a long time and if needed a second renal transplant can be performed. The second graft will have a much lower risk of recurrence because of the
depletion of the oxalate pool achieved by the first renal graft.
Moreover, some authors [10] suggest pre-emptive or early combined liver-kidney transplantation, avoiding the adverse effects of a prolonged period of dialysis and the development of a systemic oxalosis.

References

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