Transplant International

LETTER TO THE EDITOR

Kidney transplantation in a patient with severe adenine phosphoribosyl transferase deficiency: obstacles and pitfalls

doi:10.1111/j.1432-2277.2010.01128.x

Adenine phosphoribosyl transferase (APRT) deficiency is a rare, hereditary cause of nephrolithiasis. APRT is an enzyme in the purine metabolism pathway that converts adenine into adenosine monophosphate. A lack of this enzyme results in accumulation of adenine, which is alternatively converted to 2,8-dihydroxyadenine (DHA) by xanthine oxidase. In plasma, DHA is protein-bound, but it forms insoluble crystals in urine. The symptoms in homozygous patients range from nephrolithiasis in the majority of cases to chronic renal failure in severe cases. Extrarenal manifestations have not yet been reported and are presumably not possible, because DHA is not systemically deposited [1]. The prevalence of APRT deficiency, 1:33 000 to 1:250 000 [2], may be underestimated because of the possible misidentification of DHA concrements as uric acid stones, when standard methods for stone analysis like calorimetry are used. Specialized methods like infrared or mass spectrometry are required to distinguish these two entities from each other [3].

There are only a few reports of kidney transplantation in patients with APRT deficiency [4–9]. It is understood that APRT deficiency cannot be cured by kidney transplantation. Thus, DHA-induced nephropathy may recur in the allograft and is sometimes diagnosed only when its recurrence has already led to allograft loss and the origin of allograft failure has been investigated more carefully. As DHA crystals are insoluble in urine, a massive crystal deposition in the kidney implies a bad prognosis and needs to be prevented. That includes prevention of DHA generation and washing-out of already formed crystals. DHA crystal formation can be minimized by purine-poor diet to reduce adenine accumulation and by xanthine oxidase inhibition to prevent the alternative metabolism of adenine to DHA. The formation of small amounts of DHA crystals may not completely be prevented, but they can be washed out by a strong diuresis. Thus, events with no or with declining diuresis have to be avoided as far as possible.

We report a case of a 56-year-old male patient who suffered from end-stage renal disease caused by recurrent nephrolithiasis since 1987. Nephrolithiasis seemed to be familial, because the patient's sister was affected, as well. The nephroliths were identified as uric acid concrements by standard analysis. In 1990, the patient underwent successful kidney transplantation, but needed renal replacement therapy in 1999 following multiple episodes of nephrolithiasis. Re-analysis of the stones using infrared spectrometry revealed concrements consisting of DHA crystals. Thus, APRT deficiency was identified as the cause for the patient's renal failure. Kidney re-transplantation was performed in 2007. Despite plasmapheresis and medication with allopurinol, the allograft did not function sufficiently and was removed 1 month later. The allograft was interspersed with DHA crystals.

The patient was referred to our transplant center in 2008. As allopurinol inhibits excessive DHA production, a therapy with 150 mg/day was started at this time. His third deceased donor kidney transplantation was performed 2 months later with a cold ischemia time of 14:57 h and a negative crossmatch. HLA mismatch was 1-2-1, actual panel reactive antibodies were 6%. No complications occurred during or after the surgery. The patient received our standard immunosuppression for kidney re-transplantation, which contained tacrolimus (trough levels 12 ng/ml), mycophenolate-mofetil (2 g/day), steroids and an induction therapy with basiliximab. Like the second allograft, this one also did not function initially (maximum diuresis 300 ml/day), and dialysis therapy had to be continued. Allograft biopsy on day 7 revealed acute humoral rejection and intratubular DHA crystals (Fig. 1). Immediately, steroid boli therapy and plasmapheresis were started to reverse humoral rejection. As allopurinol in this dosage obviously was not sufficient to prevent crystal accumulation, we doubled the dosage to 300 mg/day and developed a purine-poor diet for the patient.

In the following days, daily diuresis increased to 2000 ml and the patient started to detoxify. In a follow-up biopsy on day 23, no signs of acute rejection were found, and the number of DHA crystals had receded. On day 37, the patient was discharged to out-patient care with weak but stable allograft function. In the following

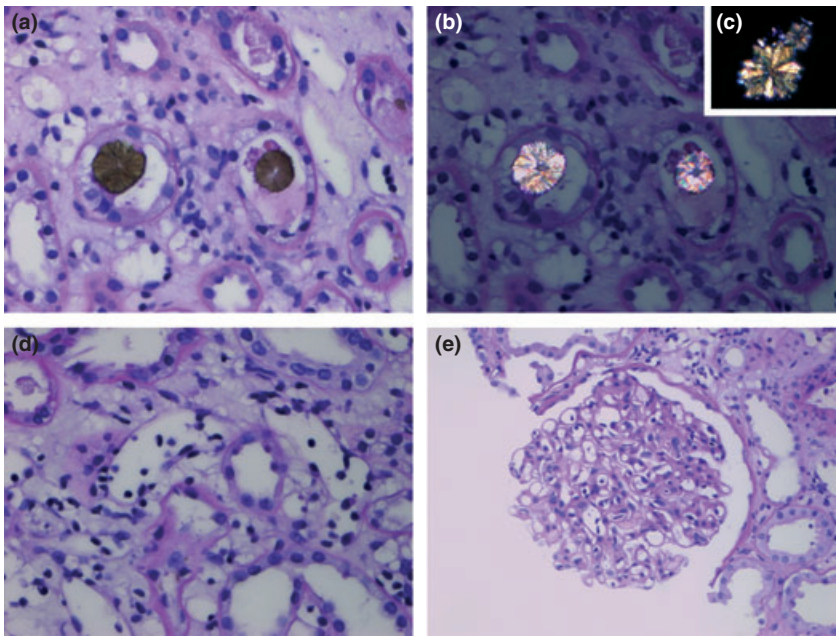

Figure 1 Allograft biopsy on day 7 showing (a) 2,8-dihydroxyadenine (DHA) crystals in tubular lumens with acute tubular injury. (b) DHA crystals are doubly refractile under polarized light and (c) may display a maltese cross-like appearance. (d) Note accumulation of polymorphic mononuclear cells in peritubular capillaries (capillaritis) and (e) inflammatory cells within glomerular capillaries (glomerulitis) with acute tubular injury as histopathological features of acute humoral rejection.

months, the patient had one more episode of humoral rejection that was treated by plasmapheresis and steroid boli. A total of three allograft biopsies were performed within this time, but relevant crystal deposition was not observed anymore. The patient was free from dialysis with a stable creatinine clearance of 25 ml/min. Nevertheless, the intensive immunosuppression, which made the allograft function, took its toll. Nine months after his third kidney transplantation, the patient died from therapy-refractory pulmonal aspergillosis with a functioning graft.

Kidney transplantation in patients with APRT deficiency holds many difficulties. All events with no or with declining diuresis can lead to a massive deposition of DHA crystals in the allograft. As the crystals are insoluble in urine, once accumulated in the tubuli as in this patient, they imply a very bad prognosis for the allograft. At the onset of our case management, we encountered several pitfalls which probably contributed to the recurrence of the disease. The long cold ischemia time and the early humoral rejection in the preimmunized patient promoted delayed graft function. Furthermore, an allopurinol dosage of 150 mg/day was too low. These shortcomings were immediately evident with a massive intratubular accumulation of DHA crystals. Despite the known insolubility of DHA crystals in urine, we attempted to reverse the irreversible. Surprisingly, treatment of humoral rejection, elevation of the allopurinol dosage and the purine-poor diet not only led to diuresis, but also to disappearance of the supposedly insoluble DHA crystals. Altogether, there are six other reports of recurrence of DHA-induced nephropathy in renal allografts in the literature [4–9]. Only one author reported that allopurinol led to stabilization of allograft function after recurrence of DHA crystals, but the crystals had not receded in a biopsy 8 weeks later [5]. To our knowledge, the present case report is the first one in the literature showing that apparently insoluble DHA crystals accumulated in the tubuli are able to regress with sufficient diuresis and metaphylaxis, which points out the importance of this case.

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