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NEPHROLOGY - CASE REPORT

Late diagnosis of primary hyperoxaluria after failed kidney transplantation

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Abstract Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inborn error of the glyoxylate metabolism that is based on absence, deficiency or mislocalization of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase. Hyperoxaluria leads to recurrent formation of calculi and/or nephrocalcinosis and often early end-stage renal disease (ESRD) accompanied by systemic calcium oxalate crystal deposition. In this report, we describe an adult female patient with only one stone passage before development of ESRD. With unknown diagnosis of PH, the patient received an isolated kidney graft and developed an early onset of graft failure. Although initially presumed as an acute rejection, the biopsy revealed calcium oxalate crystals, which then raised a suspicion of primary hyperoxaluria. The diagnosis was later confirmed by hyperoxaluria, elevated plasma oxalate levels and mutation of the *AGXT* gene, showing the patient to be compound heterozygous for the c.33_34InsC and c.508G > A mutations. Plasma oxalate levels did not decrease after high-dose pyridoxine treatment. Based on this case report, we would recommend in all patients even with a minor history of nephrolithiasis but progression to chronic renal failure to exclude primary hyperoxaluria before isolated kidney transplantation is considered.

Keywords Primary hyperoxaluria · End-stage renal disease · Graft failure · *AGXT* gene

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Introduction

Primary hyperoxaluria type 1 (PH1, OMIM 259900) is a rare autosomal recessive inborn error of the glyoxylate metabolism that is based on absence, deficiency or mislocalization of the liver-specific peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT). A massive elevation of urinary oxalate excretion results in recurrent kidney stones and/or progressive nephrocalcinosis and often to early end-stage renal

disease (ESRD). There is a high clinical heterogeneity of the disease with the infantile form presenting very early with severe bilateral nephrocalcinosis and renal failure usually by the age of 2 years at one end and adult patients with occasional passage of single calculi and preserved renal function at the other end of the spectrum [1–3]. With disease progression, even in the stage of mild renal insufficiency, plasma oxalate levels begin to increase and calcium oxalate deposition occurs in various tissues such as bones, heart, thyroid, retina, nerves and blood vessels. It is to imagine that such systemic oxalosis leads to serious complications and a fatal outcome if unrecognized and untreated. Thus, early diagnosis is of utmost importance to start aggressive medication in order to prevent progression to ESRD. Nevertheless, the treatment armamentarium of patients with PH is limited, consisting of high fluid intake and medication to increase the urinary solubility of calcium oxalate [1–3]. Treatment with pyridoxine, the cofactor of the defective AGT enzyme, helps to reduce urinary oxalate excretion only in about a third of patients. In ESRD, only combined liver-kidney transplantation can cure the defect. Isolated kidney transplantation will definitively lead to the disease recurrence [2–4].

In this report, we describe an adult patient with a very silent and unusual clinical course (of primary hyperoxaluria) toward ESRD. The patient received an isolated kidney graft and experienced early graft failure presumed to be an acute rejection. However, the biopsy revealed birefringent calcium oxalate crystals, which raised suspicion of primary hyperoxaluria.

Case report

A 48-year-old female presented at the Department of Nephrology with bilateral flank pain and signs of advanced chronic renal failure (CRF) in the beginning of 2006. It was her first clinical consultation, and the diagnostic workup revealed shrunken kidneys (90 mm× 40 mm), hyperechogenic kidney parenchyma, multiple small stones in the calyces of both kidneys and suspected nephrocalcinosis. She had a small calculus in the bladder and a history of elimination of only one calculus a few years ago. There were crystals of oxalate and uric acid seen in the urinary sediment, without proteinuria and microscopic hematuria. Primary hyperparathyroidism and metastatic bone depositions were excluded after performing appropriate diagnostic procedures. Total alkaline phosphatase was 65 U/L, serum calcium 2.3 mmol/l and phosphate 1.7 mmol/l, with an increased intact parathyroid hormone of 341.5 pg/ml (ref. range 10–65 pg/ml), reflecting secondary hyperparathyroidism in chronic renal failure. There were no morphological and functional disorders of other parenchymal organs or any visual problems. The patient entered chronic dialysis program, and her general health condition subsequently improved.

Since cadaveric kidney transplantation in Macedonia is not well established and the patient did not have a possibility for any living related donor transplantation, one year later (January 2007), she underwent a living unrelated paid transplantation in Pakistan. The initial graft function was excellent with diuresis around 2–3 L and normalization of serum creatinine at the 10th postoperative day without any perioperative complication. She was put on triple maintenance therapy with cyclosporine, mycofenolate mofetile and prednisone. A few days after her return from Pakistan, she consulted at our Department at three weeks after transplantation. The laboratory assessment revealed increased serum creatinine of 299 μmol/l. Abdominal ultrasound was performed, and an approximately 300 ml fluid collection between the kidney graft and the bladder was found (lymphocele); the graft parenchyma was edematous as a consequence of a slight obstructive uropathy, showing normal resistant index of 0.62. A surgical correction of the lymphocele was performed (marsupialization for spontaneous drainage into the peritoneum). Since the graft function did not normalize at one week after the surgery, a percutaneous graft biopsy was performed. Histologically, there were changes suggesting borderline acute rejection and 3 × 500 mg of methylprednisolone were administered with only a transient but not satisfactorily improved graft function (the lowest serum creatinine was 191 μmol/l). In the following two months, episodes of urinary tract infection, diarrhoea and herpes zoster infection were treated as appropriate. Since she had a gradual increase in serum creatinine levels to 423 μmol/l, the patient had a second kidney graft biopsy at 4 months after transplantation, which now showed ischemic tubular lesions and calcifications (oxalosis). A diagnostic workup for primary hyperoxaluria was performed [5], and screening of a random urine sample revealed an increased oxalate/creatinine ratio of

902 mmol/mol (ref. range <32 mmol/mol), with a normal urinary excretion of glycolate at 61 mmol/mol (ref. range 6–80 mmol/mol). Daily oxalate excretion was moderately increased with 0.98 mmol/1.73 m^2/d (ref. range <0.5 mmol/1.73 m^2/d).

The diagnosis of PH1 was then confirmed with mutational analysis of the *AGXT* gene, which showed that the patient was compound heterozygous for the c.33_34InsC and the c.508G > A mutations. The general condition of the patient was additionally complicated by a bleeding episode from duodenal ulcer that was treated endoscopically. The graft function further deteriorated, and the patient was put again on dialysis in July 2007. Since she was anuric, the monitoring of plasma oxalate was performed during a 2-month trial with increasing doses of pyridoxine up to 10 mg/kg/day. Pretreatment plasma oxalate was 89.6 μmol/l compared to mean value of 90.3 μmol/l during the 4-week treatment with a high pyridoxine dose. Nevertheless, the patient showed signs of systemic oxalosis such as retinal, myocardial and articular oxalate deposits.

Discussion

We present an adult patient with PH1, who was only diagnosed after an isolated kidney transplantation had failed. Although she had multiple kidney stones, as well as nephrocalcinosis at the time of preparation, she was not screened for primary hyperoxaluria, most probably because she had had very few previous symptoms and had silently progressed to ESRD. Many patients with this disease remain undiagnosed due to a mild clinical presentation. In a survey from the Netherlands, 59% of adult patients were diagnosed with PH1 only when reaching chronic renal failure [6]. Paradoxically, there may be different clinical pictures within families, although the patients harbor the same *AGXT* mutations. Some present with early and severe clinical manifestations, whereas others may be asymptomatic for many years and even with a near-normal urinary oxalate excretion [3].

There are several reports in the literature where PH1 was recognized only after kidney transplantation due to early graft dysfunction [7–14]. In a few cases, there was a clinical suspicion of acute rejection, but allograft biopsy could only demonstrate deposits of birefringent calcium oxalate crystals [9, 10, 12]. Other undiagnosed PH1 patients came to attention only after experiencing symptoms of systemic oxalosis (e.g. retinal, cardiac, cutaneous or neurological complications). In Butani's series of 13 children with ESRD of unknown etiology, the diagnosis of PH1 was established in two children [14]. In the first patient, the biopsy of the native kidney revealed calcium oxalate deposits, and in the other, the diagnosis of PH1 was established due to graft failure two months after isolated kidney transplantation.

In the setting of chronic renal failure, it may be difficult to make the diagnosis of primary hyperoxaluria. Along with the decrease in GFR, urinary excretion of oxalate may appear normal, and in such situation, age reference values for oxalate/creatinine ratio may point to the diagnosis of hyperoxaluria [1, 3]. Wong et al. presented an anuric adult patient with chronic renal failure and previous history of bilateral nephrolithiasis [11]. He developed prominent small muscle wasting over both hands and feet, while the nerve conduction study revealed a generalized sensorimotor neuropathy. The biopsy of the sural nerve revealed focal deposits of oxalate crystals within the nerve fibers and in the walls of the surrounding blood vessels. Glycolate measurement in the peritoneal dialysis fluid revealed significantly higher levels compared to five CAPD patients with non-PH1 pathology. The sural nerve biopsy findings and the dialysate glycolate levels highly suggested PH1, and the patient was switched to hemodialysis. One month later, the patient moved to another center where isolated kidney transplantation was performed, but unfortunately on the 11th postoperative day, the graft function failed and the patient was again retransferred to hemodialysis. The allograft biopsy revealed oxalate crystal deposits.

Measurement of plasma oxalate values may be helpful to distinguish non-PH patients with chronic renal failure (usually <60 μmol/l) from PH1 patients (>60 μmol/l) [1–3] Also, determination of plasma glycolate levels can be of some help, as they are elevated only in patients with PH1. However, these tests are not available in the routine biochemistry laboratories. Measurement of AGT activity in the liver biopsy tissue is the gold standard for the diagnosis of PH1, but a few laboratories can perform this test, and there is a problem with shipment of this material (on dry ice) [15, 16].

Today, mutational analysis of the *AGXT* gene is widely used and complete AGXT-sequencing is able to establish the diagnosis of PH1 with an accuracy that competes liver biopsy in most cases. Genotyping has also therapeutic implications since a proportion (if not all) of patients homozygous for the c.508G > A mutation will react to supraphysiologic doses of pyridoxine with a (partial) decrease in urinary oxalate excretion. There might also be a (lesser) reduction in the c.508G > A heterozygotes [3]. Unfortunately, there are no data on efficacy in the ESRD population. Since our patient was heterozygous for the c.508G > A mutation, we tested pyridoxine responsiveness by measuring plasma oxalate concentration before and under treatment with pyridoxine. We, however, did not observe a favorable effect. Interestingly, Leumann et al. reported an infant with PH1 and pyridoxine resistance; when this patient was reevaluated at the age of 14 years, he showed pyridoxine responsiveness [1].

Why do patients with PH1 display such prompt recurrence in the allograft, even those who have had mild and slow clinical course until reaching chronic renal failure? A possible explanation might be that there is a steady and continuous deposition of oxalate in the tissues when GFR declines below 45 ml/min or when the plasma oxalate levels are >30 μmol/l, reaching the plasma supersaturation for calcium oxalate [1–3]. In cases of isolated kidney transplantation, the oxalate is mobilized from the body pool and a huge oxalate load "attacks" the graft. If appropriate aggressive measures are not undertaken to increase the urinary calcium oxalate solubility (extremely high fluid intake and alkaline citrate medication), there is a nearly 100% risk for early graft failure. Thus, a combined kidney-liver transplantation is preferred particularly in those patients who are pyridoxine resistant. Here, the liver transplantation enables substitution of the enzymatic defect.

In conclusion, we present an adult female patient with late-diagnosed PH1 who displayed slow progression to ESRD. The suspicion of PH1 was only raised after the finding of calcium oxalate deposits on the allograft biopsy and confirmed with molecular analysis of the *AGXT* gene. Thus, in all patients with a history of nephrolithiasis and chronic kidney disease progression, the urinary oxalate excretion, or in case of ESRD, plasma oxalate and glycolate levels should be determined to find evidence for an appropriate diagnosis. Hence, not only infants and children with repeated kidney stones but also adult patients (especially kidney transplant candidates) should be screened for elevated urinary oxalate excretion. Early diagnosis is mandatory in the patient with PH1 to prevent early ESRD, but especially multisystemic calcium oxalate deposition and its devastating complications!

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