Renal graft failure due to type 1 primary hyperoxaluria

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CASE REPORT

A 51-year-old Yugoslav man, whose medical history revealed an operation for urolithiasis at the age of three, developed ESRD at the age of 40 (1989), which was attributed to chronic obstructive nephropathy. Intermittent haemodialysis was started in Yugoslavia. In 1992 he left for the Netherlands for political reasons. In 1993 thrombosis of his arteriovenous fistula occurred, and a Goretex loop was constructed as an alternative access for haemodialysis. Hand X-rays showed bone resorptions and soft-tissue calcifications and radiographs of his pelvis showed osteosclerosis. An abdominal CT scan revealed small, massively calcified kidneys as well as calcifications in the pancreas and gallbladder. In subsequent years paroxysmal atrial fibrillation occurred for which pharmacological treatment was started. In 1995 left ventricular hypertrophy and mitral regurgitation was diagnosed. He was referred to the University Medical Centre St Radboud, Nijmegen, for a cadaveric kidney transplantation, which was performed in 1996. Severe acute interstitial and vascular rejection with subsequent thrombocytopenia necessitated removal of the graft, three weeks after transplantation. Despite oral anticoagulant treatment, thrombosis in his arteriovenous fistula occurred three times in the subsequent year. In 1997 he suffered from severe brady-tachy arrhythmias and he had to be resuscitated. Antiarrhythmic therapy was started and subsequently a pacemaker was implanted. In 2000, he complained of progressive claudication.

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ABSTRACT

Primary hyperoxaluria type 1 (PH1) usually presents with recurrent urolithiasis, nephrocalcinosis and progressive renal failure at a relatively young age. This report describes a patient who, due to the late onset of end-stage renal disease, had been diagnosed with PH1 only after failure of his second kidney graft. Retrospectively, his vascular problems, skeletal abnormalities and cardiac arrhythmias fit the picture of severe systemic oxalosis. Possible therapeutic options are discussed.

INTRODUCTION

Primary hyperoxaluria is a rare autosomal recessive disorder characterised by overproduction and excessive urinary excretion of oxalate. This results in recurrent urolithiasis, nephrocalcinosis, and systemic precipitation of calcium oxalate (oxalosis).1-3 In primary hyperoxaluria type 1 (PH1), a functional defect of the hepatic peroxisomal alanine-glyoxylate aminotransferase (AGT) results in metabolic overproduction of oxalate and glycolate (figure 1).2 In the vast majority of cases, PH1 presents in early childhood, the median age of onset being five to nine years.4,5 Half of all the patients reach end-stage renal disease (ESRD) before the age of 15.4,6 In the exceptionally rare and usually less severe type 2 primary hyperoxaluria (PH2), deficiency of D-glycerate dehydrogenase/glyoxylate reductase causes overproduction of oxalate and L-glycerate (figure 1).6,7 We present a patient with PH1 and an unusually late onset of ESRD, in whom the diagnosis was not made until after failure of his second renal graft. This case history clearly illustrates the clinical implications of systemic oxalosis. Moreover, the therapeutic options for this disease are discussed.
Digital subtraction angiography of the lower extremities showed multiple arterial stenoses in the distal arteries. In September 2000 he underwent his second cadaveric kidney transplantation. As immunosuppressive therapy, he received a combination of prednisone, tacrolimus and mycophenolate mofetil. Creatinine clearance stabilised at a maximum of 28 ml/min three weeks after transplantation. On day 64 he was readmitted to the hospital because of a rise in the creatinine concentration from 220 to 310 μmol/l. Ultrasonography of the graft showed no abnormalities and rejection was suspected. Intravenous treatment with high doses of methylprednisolone was started, after a biopsy of the kidney graft was taken. The biopsy revealed numerous birefringent crystalline deposits in the proximal and distal tubules, arranged in a rosette-like array, consistent with calcium oxalate crystals, together with acute tubular necrosis. No signs of rejection were seen (figure 2). In the absence of any likely causes of secondary hyperoxaluria, primary hyperoxaluria was suspected. Biochemical urine analysis revealed elevated excretion rates of oxalate (284 μmol/mmol creatinine; reference range 0-80) and glycolate (197 μmol/mmol creatinine; reference range 0-120), whereas no L-glycerate was present. Plasma oxalate concentration was severely elevated up to 72 μmol/l (reference range <5 μmol/l). These investigations confirmed the diagnosis PH1. He was treated conservatively with a high fluid intake, avoidance of high oxalate foods, a thiazide diuretic, and a trial of pyridoxine. Eight months after his renal transplantation, the creatinine clearance had stabilised at 21 ml/min (plasma creatinine concentration 240 μmol/l) and the plasma oxalate concentration had decreased to 29 μmol/l. Repeated measurements of oxalate and glycolate will be performed to evaluate the further response to this conservative treatment regimen.

**DISCUSSION**

Manifestations of systemic oxalosis due to PH1 include urolithiasis and nephrocalcinosis (kidney), bone pain and
Osteosclerosis (skeleton), retinopathy (eye), cardiomyopathy and arrhythmias including heart block (heart), disseminated occlusive vascular lesions and arteriovenous fistula thrombosis (arteries), peripheral neuropathy (nerves), synovitis (joints), and subcutaneous calcinosis and livedo reticularis (skin).1,2,9 Median age of onset of ESRD is 15 to 25 years.10 Considering these divergent symptoms as well as the considerable variation in the age of onset of ESRD, PH1 is a rather heterogeneous disorder.11 Erroneously, because of recurrent urolithiasis, extensive calcifications of his native kidneys and especially the relatively late development of ESRD, a diagnosis of distal renal tubular acidosis was initially made in our patient. In recurrent nephrolithiasis with main constituents of stones other than calcium, a specific diagnosis as cysteinuria or even rarer types like (dihydroxy)adenine stones can generally be made by crystal or chemical stone analysis. In recurrent stones with calcium oxalate, phosphate or struvite as one of the main constituents, conditions such as hyperparathyroidism, medullary sponge kidneys, distal tubular acidosis, enteric hyperoxaluria and recurrent urinary tract infections with or without anatomic abnormalities should all be considered in the differential diagnosis.12,13 Moreover, attention should be paid to special risk factors for stone disease (high urinary concentration of stone constituents or low levels of crystal inhibitors, family history, diet, etc.). In our patient, the diagnosis of PH1 was not made until after failure of his second kidney graft. However, in retrospect, the clinical picture of our patient fits completely with a diagnosis of systemic oxalosis. Because PH1 is a rare and clinically very heterogeneous disease, the diagnosis is usually delayed by more than five years, except among infants.10 The diagnosis of PH1 can be made by measuring the urine oxalate and glycolate excretion rates and by plasma oxalate measurement. Concomitant hyperoxaluria and hyperglycolic aciduria are indicative of PH1.1 The presence of hyperglycolic aciduria is the most important parameter to distinguish PH1 from secondary hyperoxaluria and other forms of hyperoxaluria.2 However, some patients with PH1 have isolated hyperoxaluria without hyperglycolic aciduria.2 Moreover, sporadic cases have been described of concomitant hyperoxaluria and hyperglycoluria in patients with normal AGT activity.14 Therefore, for a definitive diagnosis of PH1, assessments of AGT activity and immunoreactivity in hepatic tissue are required.10 This is particularly important if liver transplantation is considered as a therapeutic option. In our patient, a liver biopsy to confirm AGT deficiency was considered of no additional value because of the lack of therapeutic consequences.

Before renal failure occurs supportive measures are important to limit the concentrations of oxalate and calcium in the urine, preferably below 0.4 and 4 mmol/l respectively, to decrease the risk of stone formation and progressive nephrocalcinosis. This can be achieved by a high fluid intake (>2 l/m²/24 h), supplements of calcium oxalate crystallisation inhibitors (orthophosphate and sodium citrate or potassium citrate), if renal function allows the use of...
these substances. Concomitant use of thiazide diuretics can decrease calcium excretion.\(^5\)\(^,\)\(^6\) Avoidance of high oxalate foods, such as tea, chocolate, spinach and rhubarb, has only limited effects.\(^7\)\(^,\)\(^8\) Responsiveness to 2 to 15 mg/kg/day of pyridoxine, a cofactor of the AGT enzyme pathway, has been reported in 10 to 40% of patients.\(^9\) Combined treatment with orthophosphate and pyridoxine was reported to preserve renal function over a ten-year follow-up period.\(^10\) After kidney transplantation, as excessive production of oxalate in the liver continues unabated, these conservative measures are important to maximise graft survival.\(^1\)

Once PH1 has progressed to ESRD, conventional haemodialysis regimens are insufficient to prevent further systemic oxalate accumulation,\(^1\) making early transplantation the treatment of choice in patients with progressive renal failure. Transplantation should preferably be performed before the glomerular filtration rate drops below 20 to 30 ml/min, because oxalate retention and subsequent systemic oxalosis then increases rapidly with a consequent decrease of graft survival rate.\(^11\) In addition to early transplantation, vigorous haemodialysis immediately before and after this procedure is said to improve graft survival.\(^12\) There is still no consensus about isolated kidney transplantation (KTX) or combined kidney-liver transplantation (K/LTX) being the strategy of choice. In Europe, the approach is directed to K/LTX more than to KTX, mainly because earlier studies on KTX showed a three-year graft survival of only 17 to 23%,\(^13\) whereas, a more recent study on K/LTX showed one-, two-, and five-year patient survival rates of 88, 80, and 72% and graft survival rates of 82, 78, and 62%, respectively.\(^14\) In the United States, however, a recent study concluded that KTX offered better patient survival than K/LTX (six-year survival 84 and 56% respectively).\(^15\) Because of these inconsistencies and difficulties comparing the studies, an individual strategy is required.\(^1\) Theoretically, K/LTX would be preferable in our patient, when renal function further deteriorates. His age and poor cardiovascular condition, however, make this a hazardous operation. If there is a further decline in renal function, a third KTX, with intensive preoperative and postoperative haemodialysis and continuation of supportive measures seems to be a better option.

In conclusion, considering the heterogeneity of PH1, this diagnosis should always be kept in mind in cases of unexplained renal failure, even in middle aged and older patients, if signs of systemic oxalosis are present.

**REFERENCES**