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CASE REPORT

Recovery From Severe Heart Failure in a Patient With Primary Hyperoxaluria Type 1 After Treatment With Lumasiran, Pyridoxine, and Kidney Transplant

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Abstract
Combined liver and kidney transplant has long been the only therapeutic option for patients with primary hyperoxaluria type 1 (PH1) and advanced chronic kidney disease. The development of lumasiran, a liver-directed RNA interference therapy, has led to effective reduction of hepatic oxalate production in patients with PH1. Despite reports of single cases successfully treated with isolated kidney transplant and lumasiran therapy, data are still scarce. Here, we report the case of a patient with PH1, severe cardiomyopathy, and chronic kidney disease, whose cardiac function improved remarkably after receiving an isolated kidney transplant and therapy with lumasiran and pyridoxine.

Background
Primary hyperoxaluria type 1 (PH1) is caused by genetically determined hepatic oxalate overproduction that leads to oxalate stones and progressive chronic kidney disease (CKD). In advanced stages of CKD, reduced oxalate elimination causes systemic oxalate deposition and functional impairment of the heart, skin, vasculature, and nervous system (1). The small interfering RNA (siRNA), lumasiran, silences the gene hydroxyacid oxidase 1, preventing translation to the enzyme glycolate oxidase. Decreased glycolate oxidase enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production, and thereby inhibits oxalate synthesis. Reduction of oxalate load may improve organ impairment in systemic oxalosis (2). For decades, combined liver and kidney transplant has been the only therapeutic option for patients with PH1 and kidney failure, thus restoring kidney function and avoiding primary disease recurrence in the graft (3–6). After the development of lumasiran, single cases of successful isolated kidney transplant with concurrent lumasiran therapy have been reported (7).

Objective
We report the case of a patient with PH1, severe cardiomyopathy, and heart failure, whose cardiac structure and function improved remarkably after receiving an isolated kidney transplant in combination with lumasiran and pyridoxine therapy.

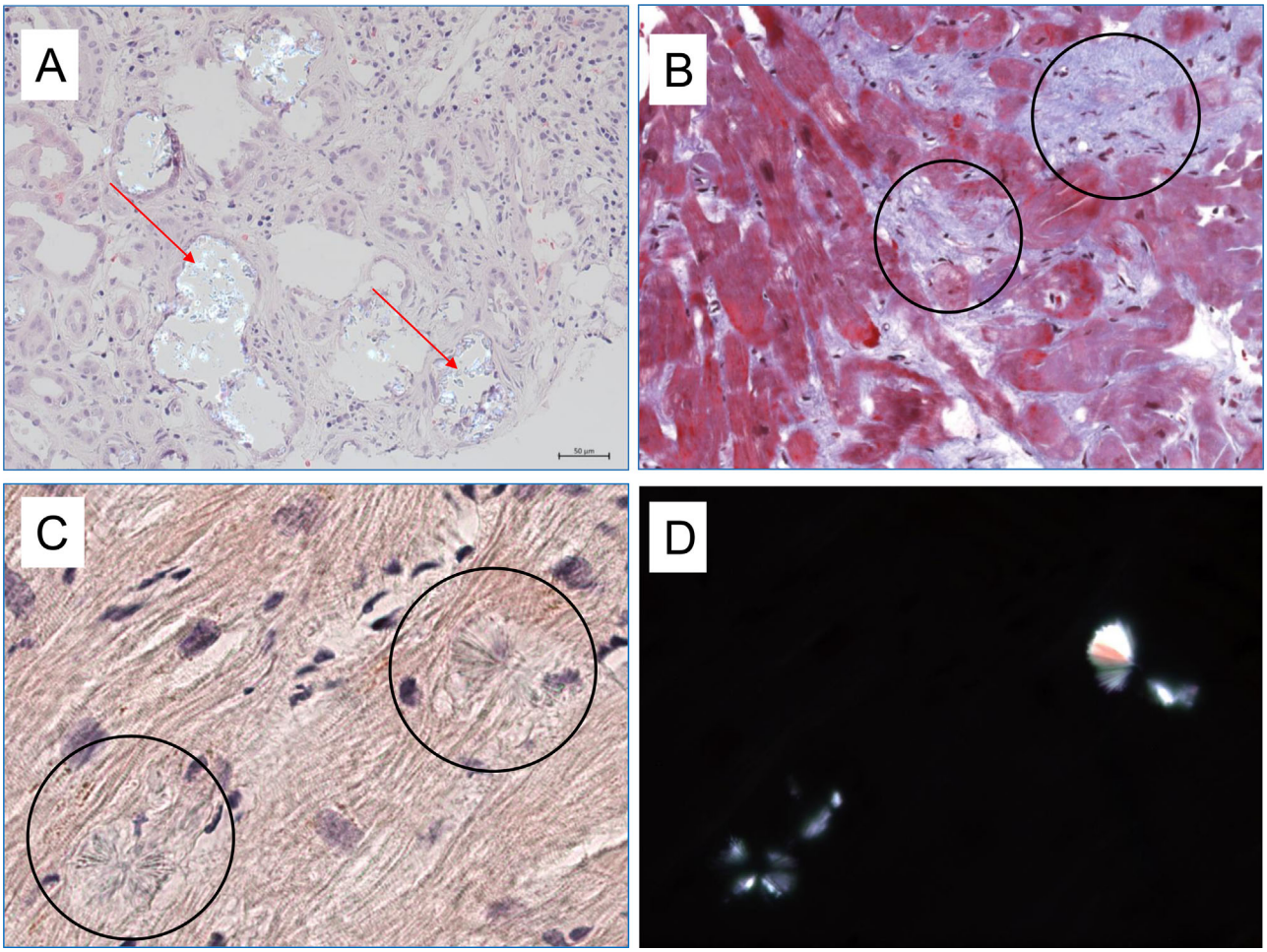

Figure 1. Histopathological staining of kidney and endomyocardial biopsy specimens. (A) Initial biopsy specimens of the patient's native kidney revealed focal interstitial lymphocyte infiltration, acute tubular injury, and focal tubular atrophy with multiple calcium oxalate crystal depositions (*arrows*) (hematoxylin–eosin stain; original magnification, ×40). (B) Endomyocardial biopsy specimen showed diffuse chronic fibrosis (*bcircles*) (Masson´s trichrome stain; original magnification, ×200). (C) With detection of calcium oxalate depositions (b *circles*) (Congo red stain; original magnification, ×630). (D) With polarization.

Case Report

We report the case of a 29-year-old man who was referred to us in March 2022 for heart, liver, and kidney transplants. Kidney failure had been diagnosed in August 2021, after kidney biopsy specimens revealed diffuse interstitial nephritis with massive oxalate deposition (Figure 1A). Genetic testing identified the alanine-glyoxylate aminotransferase gene variants c.473C>A p.(Ser158*) and c.508G>A p.(Gly170Arg) in a compound-heterozygous state (variants according to NM_000030.3 transcript). The c.473C>A p.(Ser158*) nonsense variant is predicted to undergo nonsense-mediated RNA decay. The c.508G>A p.(Gly170Arg) missense variant changes the amino acid glycine to an arginine at a highly conserved residue and represents the most commonly reported allele in patients with features of primary hyperoxaluria (8). Moreover, the c.508G>A p.(Gly170Arg) missense variant is known to be responsive to pyridoxine (vitamin B_6) therapy. The patient received peritoneal dialysis (PD) for 6 months. His initial urine output was approximately 500 mL per day. The patient developed severe heart failure (New York Heart Association class III), with a left ventricular ejection fraction (LVEF) of 25%, marked left ventricular septal hypertrophy (14 mm), and plasma *N*-terminal pro–B-type natriuretic peptide concentrations greater than 50 000 pg/mL. On physical examination, he continued to show signs of volume overload. Endomyocardial biopsy specimens demonstrated interstitial inflammation with severe oxalate deposition (Figure 1B–D). Cardiac magnetic resonance imaging (MRI) showed enlargement of all cardiac chambers with septal hypertrophy (Figure 2A, upper left and middle), and marked elevation of T1 relaxation times suggestive of a storage disease (Figure 2A, upper right). We concluded that myocardial oxalate deposition contributed to his acute heart failure. Medical therapy for his heart failure consisted of the administration of an angiotensin-converting enzyme inhibitor and loop diuretics.

After 7 months of PD, we initiated parallel hemodialysis (HD) treatments 3 times per week to optimize volume overload and to lower plasma oxalate (POx) concentrations. At this time, the patient´s body weight was 86 kg, with a height of 178 cm. The initial POx level in March 2022 was 141.3 µmol/L. It decreased to less than half after combined PD and HD and therapy with pyridoxine, 160 mg per day (Figure 2B). Pyridoxine is thought to increase net expression and catalytic activity of the mutant form

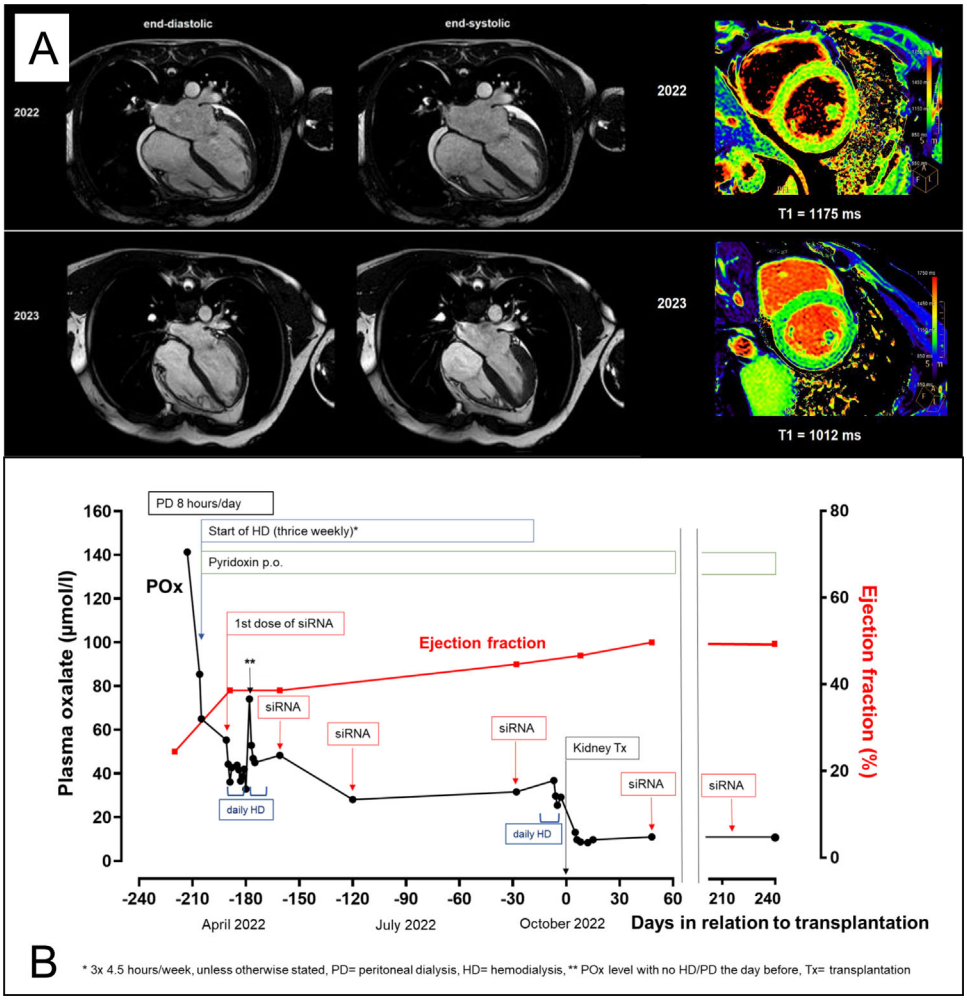

Figure 2. Cardiac imaging and time course of patient treatment. (A) Cardiac MRI at first diagnosis in 2022 showed enlargement of all cardiac chambers and septal hypertrophy (upper left and middle panel) with marked elevation of T1 relaxation times (upper right). Follow-up cardiac MRI 8 months after transplant with marked improvement of all findings (lower row). (B) Plasma oxalate levels (*black line with black dots*) and cardiac ejection fraction (*red line with red squares*) are shown in relation to treatment interventions and kidney transplant. MRI = magnetic resonance imaging.

of the affected enzyme (AGT-170) (9). Combined PD and HD also led to a body weight reduction from 86 kg to 74 kg. In mid-April, we initiated therapy with subcutaneous lumasiran, 3 mg/kg of body weight, with a further decrease of POx to 29 µmol/L. Subsequently, cardiac output improved with an increase of LVEF to 42 to 47%, according to serial echocardiograms (the ejection fraction that improved to 35% after initiation of HD further increased to 43.8 ± 3.2% after starting lumasiran therapy).

In October 2022, our patient received a living kidney donation from his father. Five days before transplant, HD frequency was increased to daily. At that time, the patient's body weight was 74 kg. Standard immunosuppression therapy with corticosteroids, mycophenolate mofetil, and tacrolimus was started. Therapy with oral pyridoxine daily and subcutaneous lumasiran every 3 months were continued. Allograft biopsy specimens collected 1 month after kidney transplant showed no signs of rejection or oxalate deposition. Kidney function 6 months after transplant was stable, with a creatinine of 1.8 mg/dL (estimated glomerular filtration rate of 49 mL/min/1.73 m^2). Posttransplant urinary oxalate had fallen from 91 mg/d at the time of transplant, to 39.5 mg/d 7 weeks posttransplant. The POx level 8 months after transplant was 9.5 µmol/L. His cardiac function had improved to New York Heart Association class I, with an LVEF of 55% and an *N*-terminal pro–B-type natriuretic peptide level of 309 pg/mL. A cardiac MRI 8 months later demonstrated a marked improvement in cardiac output, with reduction of the left ventricular mass index from 86 g/m^2 to 65 g/m^2 (Figure 2A, lower left and middle) and normalization of T1 relaxation times (Figure 2A, lower right).

Discussion

To our knowledge, this is the first case of a patient with PH1 demonstrating complete remission of severe heart failure after receiving an isolated kidney transplant along with lumasiran and pyridoxine therapy. Several factors might have contributed to the full recovery from heart failure. First, implementation of kidney replacement therapy (initially PD, then combined PD and HD, finally HD only) and the subsequent reduction of

volume overload may have led to a major improvement in cardiac function. Secondly, oral pyridoxine and subcutaneous lumasiran administration likely inhibited increased oxalate production. Given the severity of the patient's presentation, lumasiran and pyridoxine therapy were both started within a short period of time. Hence, we were unable to assess the POx concentration in response to isolated pyridoxine administration. Of note, the c.473C>A p.(Ser158*) nonsense variant is predicted to lead to RNA decay. Therefore, this mutation is unlikely to be amenable to pyridoxine therapy and would therefore favor a pharmacologic approach with lumasiran to lower endogenous oxalate overproduction. Peritoneal dialysis does not clear plasma oxalate very effectively. Therefore, the initial use of PD as the only form of renal replacement therapy may have accelerated the oxalosis in addition to the background chronic kidney failure. Plasma oxalate levels decreased effectively after HD and treatment with the siRNA in combination with pyridoxine were started. The beneficial effect of lumasiran on cardiac function and POx levels was observed after the administration of 3 doses. This may be explained by the need to obtain sufficient inhibition of translation by RNA interference following a loading period. Finally, the isolated kidney transplant itself further contributed to a decline of POx to the normal range and an improvement of heart failure symptoms. In addition, improvement of the T1 relaxation time observed in the cardiac MRI scan suggests substantial improvement of cardiac oxalate deposition. These findings extend previous observations in a few patients with PH1 after combined kidney-liver transplant, suggesting reversibility of oxalate-induced cardiac dysfunction (10, 11). Very recently, reversal of cardiomyopathy caused by cardiac transthyretin amyloidosis has also been reported (12). Of note, patients receiving maintenance HD have increased POx concentrations in the absence of a genetic cause of oxalate overproduction that are associated with adverse cardiac outcomes (13). Thus, reversibility of cardiac oxalate deposition may translate into an improved prognosis. Oxalate-induced organ damage is, at least in part, mediated by toll-like, receptor-mediated inflammation. This is consistent with the findings from kidney and heart biopsies of our patient (14). However, although lumasiran stabilizes kidney function, to our knowledge, reversal of kidney damage has not been reported. Thus, our observations also exemplify important interorgan differences in damage resolution and recovery.

Lumasiran effectively reduces hepatic oxalate production, presenting a promising treatment option for patients with PH1. Our patient demonstrated a favorable outcome after receiving a single kidney transplant in combination with lumasiran and pyridoxine therapy instead of combined liver-kidney or triple heart-liver-kidney transplant. Larger trials are warranted to evaluate its safety and efficacy in the long-term.

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