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Late diagnosis of hyperoxaluria in a patient after kidney transplantation – case report

Późna diagnoza hiperoksalurii u chorej po przeszczepieniu nerki – opis przypadku

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Słowa kluczowe
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Summary

Primary hyperoxaluria (PH) is a rare genetic disorder that leads to elevated excretion of calcium oxalates and its deposition in tissues. First symptoms usually occur under the age of five and consist of massive parenchymal oxalosis or bilateral renal calculi. Clinical manifestations in later stages of disease, when the glomerular filtration decreases, can consist of cardiac conduction defects, distal gangrene, dificulties with vascular access, synovitis. We present a case of a 65-year old female patient referred to the Department of Transplantation Medicine and Nephrology 22 days after kidney transplantation with end stage renal disease (ESRD) after a right-sided nephrectomy due to pyonephrosis caused by incidental unilateral kidney calculi with a history of recurrent urinary tract infections. After receiving a kidney transplantation the patient developed delayed graft function with preserved urine output. Kidney biopsies revealed an increasing amount of tubular calcium oxalate depositions and persistent acute tubular necrosis. Calcium oxalate excretion was insignificantly elevated. Ultrasound scans revealed presence of transplanted kidney nephrolithiasis. We raised a suspicion of PH. We started a 4-weeks course of daily high-flux hemodialysis and also treated the patient with pyridoxamine and citric acid combined with potassium citrate and sodium citrate. Control kidney biopsy 2 months after the transplantation revealed absence of calcium oxalate depositions with present unresolved ATN and moderate *de novo* atherosclerosis. Therapy proved to be unsuccessful and the patient returned to the haemodialysis program. The diagnosis of PH was later confirmed by the presence of a typical C508G > a mutation. Based on this case we conclude that a late onset of PH with non-specific symptoms is possible. Guidelines for the exclusion of PH in adult patients with ESRD of unknown origin are needed, especially before kidney transplantation.

Streszczenie

Pierwotna hiperoksaluria (PH) jest rzadką chorobą genetyczną prowadzącą do zwiększonego wydalania szczawianów wapnia oraz ich odkładania się w tkankach. Pierwsze objawy zazwyczaj pojawiają się poniżej 5. roku życia i obejmują masywne złogi szczawianów w śródmiąższu lub obustronną kamicę nerkową. Manifestacje kliniczne w późniejszych stadiach choroby, kiedy to upośledzeniu ulega filtracja kłębuszkowa, mogą się składać z zaburzeń przewodzenia sercowego, dystalnej martwicy tkanek, problemów z dostępem naczyniowym do hemodializ, zapalenia błony maziowej. Prezentujemy przypadek 65-letniej kobiety przeniesionej do Instytutu Transplantologii 22 dni po przeszczepieniu nerki, ze schyłkową niewydolnością nerek o nieznanej przyczynie, po prawostronnej nefrektomii spowodowanej wodonerczem wikłającym jednostronną kamicę nerkową oraz z wywiadami nawracających zakażeń układu moczowego. Po przeszczepieniu nerki obserwowano u chorej opóźnione podjęcie czynności przez nerkę przeszczepioną z zachowaną diurezą. Biopsje nerki

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przeszczepionej wykazały zwiększającą się ilość złogów szczawianowych oraz utrzymującą się ostrą martwicę cewek. Wydalanie szczawianów wapniowych u chorej było zwiększone. Badanie ultrasonograficzne wykazało kamicę nerki przeszczepionej. Wysunęliśmy podejrzenie PH. Rozpoczęliśmy 4-tygodniowe leczenie codziennymi wysokoprzepływowymi dializami oraz leczyliśmy chorą pirydoksaminą i kombinacją kwasu cytrynowego z cytrynianem potasu oraz cytrynianem sodu. Biopsja kontrolna w 2 miesiące po przeszczepieniu wykazała brak złogów szczawianowych, utrzymującą się ostrą martwicę cewek oraz umiarkowaną miażdżycę *de novo*. Nasza terapia okazała się nieskuteczna i chora powróciła do programu przewlekłego leczenia powtarzanymi zabiegami hemodializ. W późniejszym czasie rozpoznanie PH zostało potwierdzone obecnością typowej mutacji C508G > A. Na podstawie tego przypadku uważamy, iż późne wystąpienie PH z niespecyficznym obrazem klinicznym jest możliwe. Potrzebne są wytyczne dotyczące metod wykluczenia PH u chorych z niejasną przyczyną choroby nerek, zwłaszcza przed kwalifikacją do przeszczepienia nerki.

INTRODUCTION

Primary hyperoxaluria (PH) is a rare autosomal recessive genetic disorder, that leads to elevated serum concentrations and excretion of calcium oxalate, and it's deposition in tissues. PH is a result of enchanced conversion of glyoxalate to oxalate. There are two types of PH. Type I PH is caused by either glyoxalate aminotransferase (AGT) defect or the mistargeting of the enzymes gene to mitochondria (1). Type II PH is caused by deficient glyoxalate reductase/hydroxypyruvate reductase (GRHPR) (2). There are papers describing type III PH, which pathogenesis is not yet described (3). PH shows a lot of heterogenicity in terms of phenotype, ranging from patients suffering from severe to almost no clinical symptoms. Usually the first symptoms of PH occur either before age of five (50%) or age of one (15%) (4). The initial clinical manifestations may include parenchymal oxalosis, bilateral urolithiasis, hematuria, recurrent urinary tract infections (1). Symptoms in later stages of disease, when the glomerular filtration decreases, can consist of cardiac conduction defects, distal gangrene, dificulties with vascular access, synovitis, vision loss, subperiostical bone defects (1). PH may lead to end stage renal disease (ESRD) in up to 50% of the patients (4, 5). Usually the diagnosis is based on markedly increased urinary excretion of oxalates, which is usually greater than 1 mmol/1.73 m^2 per day. The excretion of oxalates is impaired in patients with later stages of chronic renal disease and thus can be of lesser diagnostical value. In these patients higher plasma levels of oxalate can be seen. In dubious cases DNA testing, even though it is not standard, can also prove helpful. Liver biopsy with assessment of AGT activity is the golden standard in diagnosing PH (6). We present a case of a patient diagnosed with PH only after kidney transplantation.

CASE REPORT

65-year old female patient received kidney transplant due to ESRD with a history of recurrent urinary tract infections and after a right nephrectomy due to pyonephrosis caused by incidental unilateral kidney calculi. She had no loss of vision, no history of cardiac arrhythmias. There was no familial history of nephrocalcinosis or recurrent nephrolithiasis. The patient never underwent native kidney biopsy. She was dialyzed for 2 years before transplantation and had no history of difficulties with maintaining of A-V fistula. Abdominal ultrasound scans revealed increased echogenicity of native kidney. The patient received a triple drug regimen consisting of cyclosporine A, mycofenolate mofetile, steroids.

23 days after kidney transplantation the patient was referred from the Surgery Ward to the Department of Transplantation Medicine and Nephrology due to delayed graft function with preserved urine output of around 2000 ml. On admission the serum creatinine concentration was elevated up to 4.92 mg/dl. The patient also presented with high blood levels of cyclosporine C0 680 ng/ml and C2 2556 ng/ml and urinary tract infection symptoms. Urine bacterial cultures showed growth of *Escherichia coli*. We treated the patient with aimed antibiotic therapy. We also lowered the doses of cyclosporine so that therapeutical levels of the drug were reached. Ultrasound scans performed on admission revealed no signs of urinary tract obstruction and Doppler imaging showed no signs of graft vascular pathology. The transplanted kidney function deteriorated and the patient required hemodialysis treatment from day 25 after the transplantation. Due to unknown origin of the delayed kidney graft function we have performed two percutaneous kidney biopsies (25 and 33 days post transplant) which revealed an increasing amount of tubular calcium oxalate depositions and persistent acute tubular necrosis with no signs of acute rejection (fig. 1). Because of the unusual oxalate presence we have measured oxalate excretion which was moderately elevated 0.67 mmol/24 h (ref. range 0.04-0.32). We have raised a suspicion of PH. We have sent patient's blood samples for genetic testing for PH. 6 weeks after the transplantation we started a 4-weeks course of daily high-flux hemodialysis. We also treated the patient with high doses of pyridoxamine and citric acid combined with potassium citrate and sodium citrate. Ultrasound scan 45 days after transplantation revealed the presence of transplanted kidney de novo nephrolithiasis. Control kidney biopsy 2 months after the transplantation revealed absence of calcium oxalate depositions with present unresolved ATN

and moderate *de novo* atherosclerosis with no C4d depositions present. Therapy proved to be unsuccessful and the patient returned to the haemodialysis program. The diagnosis of PH was later confirmed by the presence of a typical C508G > a mutation.

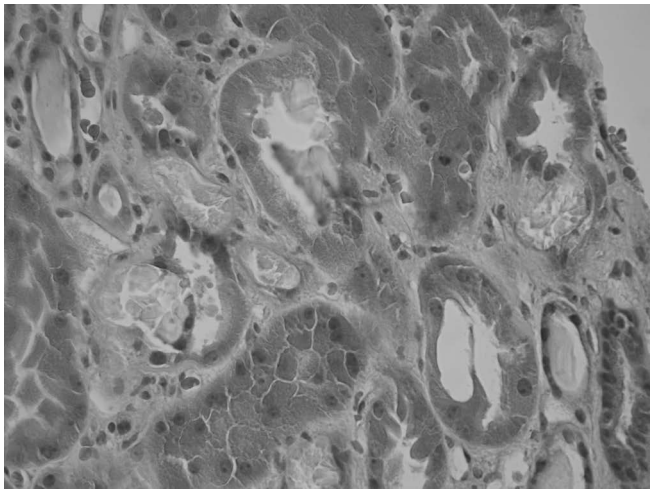

Fig. 1. Light microscope picture with oxalate crystals visible.

DISCUSSION

PH is a very heterogenous disease. Even patients within the same family bearing the exact same mutation can present with various phenotypes of this disease (7). We present a case of a female patient with slow progression of PH who was diagnosed only after kidney transplantation. Even if progression of the disease is slow prior to transplantation, after the transplantation the recurrence of PH usually leads quickly to ESRD of the transplanted kidney, if no countermeasures are undertaken. This can be explained by massive loads of oxalates deposited in tissues that are mobilized after kidney transplantation (6, 7). The results of solitairy isolated kidney transplantation in patients with ESRD due to PH are unsatisfactory with 3-year graft survival only 17 percent for cadaver kidneys and 23 percent for living related donor kidneys (8). Other therapies such as simultaneous kidney/liver transplant or aggressive haemodialysis prior to transplantation prove to be more beneficial (2, 9). Therefore it is crucial to diagnose these patients before kidney transplantation. Diagnosing patients with PH and impaired renal function can prove difficult because usually in those patients oxalate excretion is lowered. Measurement of serum oxalate concentration and genetic testing can be helpful, with similar to liver biopsy accuracy (7).

CONCLUSIONS

A late onset of PH with non-specific symptoms is possible. Guidelines for the exclusion of PH in adult patients with ESRD with a history of recurrent urinary tract infections and renal calculi are needed.

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