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Case report

Renal Transplantation in Patients with Rare Diseases

Tea Vukic, Petar Kes and Nikolina Basic-Jukic

School of medicine, University of Zagreb and Clinical hospital centre Zagreb, Zagreb, Croatia

Abstract

Kidney transplantation is the best treatment option for patients with end-stage renal disease, owing to its effect on quality of life and survival. In order to have a successful transplantation it is necessary to set a proper diagnosis. Leading cause of end-stage renal disease in developed countries are diabetes and nephroangiosclerosis. Considering that more than one third of patients with end-stage renal disease do not have a diagnosis of primary kidney disease, we encounter the issue of transplanting these patients without knowing the etiology of patient's condition, which in the end may lead to graft failure. Misdiagnosed patients may have rare diseases for which tests are not routinely available. Very often we fail to recognize the disease due to the lack of awareness even though there are signs and symptoms that point to the possibility to a certain rare disease. Some of the rare diseases mentioned in this case series report are Fabry disease, primary hyperoxaluria type 1, atypical hemolytic uremic syndrome, tuberous sclerosis and syndromes such as Denys-Drash syndrome, Prune-Belly syndrome, Turner syndrome and Branchio-oto-renal syndrome.
Rare diseases are frequently chronic and many start in childhood. Minimizing diagnostic delays by improving genetic testing and disease recognition will prolong both the patient's life and the life of a graft. Raising awareness of rare diseases will aid early and accurate diagnosis.

Keywords: renal transplantation, rare diseases, Fabry disease, Denys-Drash syndrome, Turner syndrome, primary hyperoxaluria

Introduction

Renal transplantation is the best method of renal replacement therapy. Many patient factors influence graft successfulness. Some of these are age, gender, diabetes, cardiovascular status, smoking status and HLA matching, but one of the most important factors is primary disease itself [1,2]. When primary disease is unknown, it imposes great risk for recurrence of disease in transplanted kidney and graft failure [1], while appropriate precaution measures may be omitted. Recognition of a rare disease is of upmost importance due to its influence on the prognosis, course of treatment and successfulness of transplantation.
The most common diseases in developed world that lead to end-stage renal disease are diabetes, nephroangiosclerosis and glomerulonephritis without biopsy [3]. More than one third of people with end-stage renal disease do not have a proper diagnosis or the exact diagnosis is unclear. Additionally, rare diseases may be hidden in diagnoses of diabetes, nephroangiosclerosis and glomerulonephritis without biopsy, considering that one sign or symptom may be shared between two completely different diagnoses. Diagnosing a rare disease affects choice of treatment and immunosuppression as well as the recurrence of a disease after transplantation. Some rare diseases require multisystem approach and other may be treated with specific therapy that stops further deterioration of kidney function. Because some of these diseases are genetic, it is even more important to recognize the patient in order to perform screening on the other members of the family.

Case-series

As an example of importance of accurate and timely diagnosis, we present a 28 year old patient treated at Clinical Hospital Centre Zagreb where he had kidney transplantation. He received renal allograft from a deceased donor after eighteen years on hemodialysis. Primary kidney disease was unknown. Allograft function was immediate with basiliximab induction and cyclosporine, mycophenolate mofetil and steroids used for maintenance immunosuppression. Twenty days after the transplantation he developed severe proteinuria (51 g/day). Biopsy revealed collapsing form of focal segmental glomerulosclerosis (Figure 1).
Disease was resistant to plasma exchanges and it was necessary to perform graftectomy considering the extent of proteinuria.
One of the most familiar rare diseases is Fabry disease that is caused by alpha galactosidase gene mutation [4]. This mutation causes diminished or complete absence of effect of alpha galactosidase A enzyme that degrades globotriaosylceramides. Consequently, there is accumu-

Correspondence to: Nikolina Basic-Jukic, Department of nephrology, arterial hypertension, dialysis and transplantation, University hospital centre Zagreb, Kispaticeva 12. Zagreb, Croatia; E-mail: nina_basic@net.hr

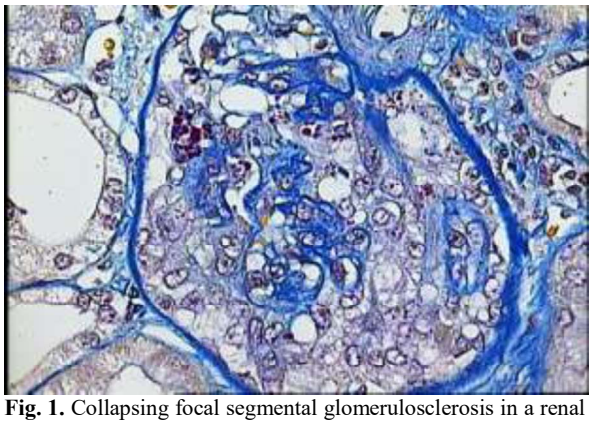

Fig. 1. Collapsing focal segmental glomerulosclerosis in a renal transplant recipient

lation of fatty acids that already in childhood cause symptoms of this disease that appears as pain in their arms and legs. Hence, the children often visit psychiatrist. On the skin of these patients we frequently observe angiokeratomas [5]. Proteinuria is one of the early signs of this disease [6]. Fabry patients can present as neurological patients with transitory ischemic attack or stroke. They suffer early from cardiac diseases [5,6]. Treatment of end-stage renal disease is performed by dialysis or kidney transplantation. In Fabry patients, we have to emphasize the importance of early enzymatic replacement therapy: human alpha galactosidase A [7]. This enzyme is administered intravenously every two weeks, but nowadays there are new peroral medications that will facilitate administration of therapy. A male patient born in 1962 was diagnosed with slowly progressive glomerulonephritis when he was 12. In 2006 diagnosis of Fabry disease was established and since then this patient has been on enzyme replacement therapy. From 2006 to 2010 he was on a regular haemodialysis due to end-stage renal disease. In 2010 he received a renal allograft from a deceased donor. Posttransplant course has been uneventful.

Primary hyperoxaluria type 1 is caused by mutation in alanine-glyoxilate and serin-pyruvate aminotransferase gene. This causes disruption in pathways that convert glyoxilate to glycine and consequently, a product called oxalate accumulates in liver and kidney [8]. Characteristic clinical appearance is a patient with frequent kidney stones [9]. This disease, if not discovered on time, has devastating consequences on kidney graft in post-transplantation period. Conservative treatment is recommended until end-stage renal disease has been reached, when dialysis and preparations for transplantation must be included [10]. Surgery can involve simultaneously liver and kidney transplantation or sequentially liver, then kidney. It is possible to carry out kidney transplantation only, if the liver is not severely damaged. Even though most of procedures of this kind were without success, there are some known existing surgeries with positive outcome. It is also possible to perform liver transplantation only, where kidney damage is not yet present [11]. One of our patients, a female born in 1959, was suffering from multiple urinary and gallbladder stones since 2006. Following cholecystectomy in 2008, she developed acute renal failure and end-stage renal disease of unknown origin. After five years of hemodialysis, she had kidney transplantation. Only seven days after the transplantation the patient stopped urinating and developed acute rejection. By renal biopsy oxalate cristals were found in a renal allograft, but also in bone biopsy specimens (Figure 2).

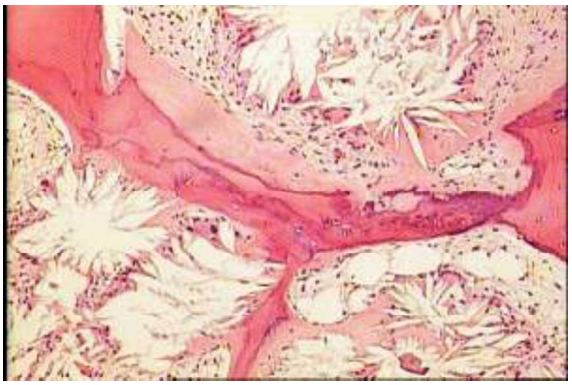

Fig. 2. Bone biopsy revealing oxalate crystals in a patient with primary hyperoxaluria type I

Another patient, a female born in 1958, was healthy until 2009, when suddenly first symptoms appeared along with end-stage renal disease. Etiology of ESRD was unknown. This patient is on hemodialysis since then. Skin biopsy revealed oxalate crystals. A sample was sent abroad for genetic analysis which proved primary hyperoxaluria type I. Good example may be given by comparing these two patients, both female patients, of same age and both suffering from primary hyperoxaluria type 1. The only difference being that one patient was diagnosed prior to transplantation and the other was not. As we could conclude, the consequences of undiagnosed disease in first patient had huge impact on transplanted kidney and overall outcome. Enormous difficulty lies in fault diagnostic tests, lack in screening program and undeveloped genetic tests.

Atypical hemolytic uremic syndrome is a disease primarily caused by genetic mutation in complement system, yet an environment has a huge impact and may provoke this disease [12,13]. Even though this disease present suddenly, it is not an acute disease, but rather chronic multisystem disease. Overly activation of complement system leads to endothelial damage and abnormal clotting. Most patients present with hemolytic anemia, thrombocytopenia and kidney failure [14,15]. Treatment and prevention of atypical hemolytic uremic syndrome after the transplantation is done by plasmapheresis and eclizumab-human monoclonal antibody [16,17]. We must keep in mind that transplantation, together with immunosuppression therapy, activates complement system.

A female patient born in 1967 was admitted to Immunology ward in 2010 where kidney biopsy was done and chronic thrombotic microangiopathy was diagnosed. CKD grade 3 was established at that time and she was treated with plasmapheresis and corticosteroids. Hemodialysis treatment started in 2012 and two years later a diagnosis of aHUS was confirmed by genetic testing. She was treated with eculizumab and successfully transplanted in 2016. Expensiveness of the medication such as eculizumab makes treatment difficult and inconvenient considering that all patients should receive existing treatment. She has already been presented in details [18]. One additional female patient is currently on our waiting list for kidney transplantation with established diagnosis of aHUS.

Tuberous sclerosis is a disease caused by mutations in genes called tuberous sclerosis gene 1 and 2. In 80% of cases there is de novo mutation [19]. It causes benign tumor growth in many organs. Kidney is affected by development of angiomyolipomas and cysts [20]. The bleeding from angiomyolipoma presents a difficulty. This bleeding may require nephrectomy despite the fact that the rest of the kidney may be healthy. In the end, it requires renal replacement therapy. Here, we have to take into account that transplantation could lead to transformation of benign tumors into malignant. mTOR inhibitors play a huge role in cell growth. Tuberous sclerosis does not possess inhibition of cell cycle and cell growth that is why mTOR inhibitors are used in treatment of tuberous sclerosis. These inhibitors treat etiology of tuberous sclerosis [21]. A female patient born in 1982 was diagnosed with TS in childhood following multiple epileptic attacks. Primary disease and arterial hypertension lead to decrease in renal function. Due to the bleeding from angiomyolipoma in the right kidney it was necessary to perform right nephrectomy. This was followed by emergency left nephrectomy because of renal bleeding and development of retroperitoneal hematoma. After few years on dialysis, this patient was successfully transplanted in 2016. Another patient at our Center, also a female, born in 1995 was diagnosed with tuberous sclerosis when she was 2. At the same time polycystic kidneys were noted as well. Due to the decrease in renal function the patient was transplanted in 2016 without precedent dialysis. Transplantation was successful.

Along all diseases mentioned here, there are many syndromes that could lead to end-stage renal disease. These patients are diagnosed in early age. One of these syndromes is Turner syndrome that has a characteristic phenotype due to monosomy X [22]. Turner patients often present with structural kidney malformations such as horseshoe kidney [23]. Clinical Hospital Centre Zagreb holds the only known case of kidney transplantation in a patient with Turner syndrome. Then there is Dandy Walker syndrome, which causes urogenital malformations [24]. These patients have mental retardation; therefore require someone to take care for them in order to have a successful transplantation. At Clinical Hospital Centre there is one patient diagnosed with Denys-Drash syndrome. These patients may have congenital nephropathy, Wilms tumor and gonadal dysgenesis [25]. Two patients are diagnosed with Prune-Belly syndrome that present with abdominal wall defects, criptoorchidism and urinary tract defects-some of which are megaureter, hydroureter, hydronephrosis, vesicoureteral reflux or megacystitis [26]. Branchio-oto-renal syndrome is autosomal dominant disease that appears as hearing impairment together with clefts, fistulas or cysts in the lip or palate region. It affects kidney development and causes malformations such as hypoplasia or dysplasia of the kidney, or kidney cysts [27]. Three patients with this syndrome are transplanted in our Centre.

Conclusion

It is very important to be aware that rare diseases exist and that patients with rare diseases are around us. We always have to consider the possibility of diagnosing a rare disease due to its effect on the outcome. Available treatment exists for many rare diseases. In order to recognize these patients, we need screening program for rare diseases that would simplify diagnosis process. Screening for rare diseases in pre-transplantation period would improve overall outcome of renal transplantations in these patients. It is very likely that screening of transplanted population would show many different genetic mutations that result in deterioration of graft function. An individual approach to each patient is mandatory due to different factors influencing the successfulness of transplantation.

Conflict of interest statement. None declared.

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