CASE REPORT

Kidney transplantation in an adult with transfusion-dependent beta thalassemia: A challenging case report and literature review

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ABSTRACT

The markedly increased survival of transfusion-dependent beta thalassemia patients has led to the recognition of new complications, such as renal disorders. Kidney transplantation is nowadays the preferred treatment option for end-stage kidney disease (ESKD). We describe a case of a 49-year-old woman with β-Transfusion Dependent Thalassemia, who developed ESKD as a result of focal segmental glomerulosclerosis and received a deceased-donor kidney transplant following hemodialysis for over a decade. The particular challenges of this case are discussed, including the long-term survival in hemodialysis. Our patient had to overcome multiple obstacles, including hypercoagulability issues presented in the form of thromboembolism, infections, such as hepatitis C and gastroenteritis, and the acute T-cell–mediated rejection, which had to be managed postoperatively. A review of the current literature revealed only one previous report of a thalassemia patient who successfully underwent renal transplantation. More than a year after the transplantation our patient presents with a normal glomerular filtration rate (GFR=62ml/min/1.73m^2) and creatinine level (Cr=0.96mg/dL) and is transfused every 3 weeks. In conclusion, renal transplantation is possible in patients with TDT and should not be discouraged. Regular transfusions and optimal follow-up for the elimination of post-transplant complications are required.

KEYWORDS: renal transplantation; thalassemia; glomerulosclerosis; hemodialysis; case report

INTRODUCTION

The thalassemia syndromes are a wide and heterogeneous group of congenital autosomal recessive hemoglobinopathies, caused by globin gene mutations, mostly small nucleotide substitutions. The two main forms of the disorder, namely α-thalassemia and β-thalassemia, are characterized by the reduced or absent synthesis of either the α- or β-globin chains of the hemoglobin molecule, respectively [1]. Thalassemias were first described in 1927 by Cooley and Lee, who reported cases of severe anemia associated with splenomegaly and characteristic bone modifications [2]. An estimated 5% of the global population carries at least one variant globin allele, with a higher prevalence reported in the Mediterranean region, Africa, the Middle East, the Indian subcontinent, and Southeast Asia [3].

Patients with β-thalassemia have variable clinical presentations. This disorder has historically been categorized as thalassemia major, intermedia (TI), and minor, according to the α/β-globin chain ratio, degree of anemia, and clinical course. Patients with β-thalassemia minor (carrier or trait) often have asymptomatic microcytic anemia. Currently, based on clinical severity and transfusion requirement, thalassemia syndromes are phenotypically distinguished into two main types: TDT and Non-Transfusion-Dependent Thalassemias (NTDT). The TDT patients are incapable of producing sufficient hemoglobin for survival without transfusions. NTDT patients do not frequently require transfusions [4]. TDT requires maintaining a baseline pre-transfusion hemoglobin level of 95-105 g/l, which provides adequate erythropoiesis suppression, also allowing a reduction in blood consumption.

The reduction of β-globin chains results in a relative excess of α chains, which accumulate in erythroid precursors and form inclusion bodies. This leads to oxidative damage and premature death of the erythroid precursors, thus, ineffective erythropoiesis. Moreover, membrane damage to peripheral erythrocytes (hemolysis) occurs. As a response to ineffective erythropoiesis and anemia, erythropoietin is increased,

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giving rise to bone marrow expansion, skeletal changes, and a hypermetabolic state. Additionally, iron absorption is increased, resulting in iron loading in vital organs and organ failure, if left untreated [5].

The complexity of β-thalassemia is reflected in the multiple morbidities, that are nowadays more frequently seen, as survival has significantly increased owing to advanced management. Thus, thalassemic patients experience cardiovascular disease, including thromboembolic, cerebrovascular events and vascular abnormalities, endocrine and bone disorders, infections, and liver impairment [6]. Due to the prolonged life expectancy, the previously unrecognized complication of renal disease is now being acknowledged. The most common manifestations of renal dysfunction in β-thalassemia patients are tubular and glomerular dysfunction, which have been associated with risk factors such as chronic anemia and hypoxia, iron overload, and iron chelation. The effect of thalassemia on the kidney has not been thoroughly studied. Renal impairment can lead to life-threatening renal failure. For ESRDs, a kidney transplant is the preferred choice of treatment [7]. This can be rather challenging, carrying multiple risks for β-thalassemia patients. Namely, the numerous red blood cell transfusions that thalassemic patients require over the course of their lives are inevitably linked to iron overload, which in turn results in a variety of major organ dysfunctions, including those of the heart and liver. These dysfunctions may not enable the patient either to undergo or to recuperate from such a demanding surgery. Additionally, critical immunological side effects, particularly the production of anti-HLA antibodies, may delay or even prevent the transplantation, as the patients become sensitized against numerous HLA antigens. To our knowledge, there is only one case of successful renal transplantation in a TDT patient previously reported [8]. We aim to present a case of a 49-year-old woman with transfusion-dependent β-thalassemia, who successfully underwent a challenging renal transplantation following 12 years of hemodialysis.

CASE PRESENTATION

Our patient is a 49-year-old female diagnosed with TI (genotype IVS1-110 G to A/-87 C to G) on monthly blood transfusions since her diagnosis at the age of 3 in 1976. She underwent splenectomy at the age of 6. Subcutaneous deferoxamine (DFO) injection 3 times weekly started when she was 15 years old. The patient had poor compliance both to transfusion and iron chelation therapy and her pre-transfusion hemoglobin was around 7g/dL. Three years later she was prescribed hydroxycarbamide, in an effort to manage the thrombocytosis that had developed after splenectomy and to increase hemoglobin. Her medical history also included cholecystectomy at the age of 19, due to cholelithiasis, superficial thrombophlebitis of the lower limb one year later, osteoporosis, painful thoracic extramedullary hemopoiesis masses, and positive antibodies to hepatitis C virus (HCV) since 1992. In 2003, deferiprone was added to her chelation treatment, due to her low compliance with DFO. At the age of 33, she was hospitalized for gastroenteritis (Yersinia enterocolitica negative), with progressive deterioration of her renal function and albuminuria. A renal scintigraphy was performed and showed mild renal impairment with no signs of obstruction. Ten months later, a kidney biopsy revealed FSGS. Erythropoietin was added to her treatment to avoid severe anemia and reduce the need for transfusions. Her renal function continued to deteriorate and 3 years after the renal biopsy, she initiated hemodialysis. The first year of hemodialysis was complicated with thrombosis of the arteriovenous hemodialysis fistula twice, pulmonary embolism, and the development of pulmonary hypertension. Immunologic and thrombophilia testing was performed in order to exclude other possible situations that could lead to thromboembolism, and was negative. It included anti-neutrophil cytoplasmic antibodies, antinuclear antibodies, anti-cyclic citrullinated peptide, autoantibodies to double-stranded DNA, C3 and C4 complement and rheumatoid factor, cardiolopin IgG and IgM antibodies, protein C and S level, antithrombin III, factor V Leiden and prothrombin G20210A mutation detection. The patient received acenocoumarol, as an antithrombotic drug for the treatment of thromboembolism. While on hemodialysis, she was under chelation therapy with deferoxamine 3 to 5 days per week. Her ferritin level was maintained at around 600ng/ml. Cardiac T2* magnetic resonance imaging (MRI) was 38 milliseconds (ms) and liver T2* MRI was 23 ms. In April 2022, following 12 years of hemodialysis, she received a transplant. The kidney transplant was a deceased-donor one after brain death (DBD), estimated age 55 years old. It was 1-1-2 HLA mismatched, CMV IgG D^+/R^+, with a cold ischemia time of 17 hours. The pre-operative Hb was 9.2 g/dl, and in the first week after surgery, she was transfused with 3 units of packed red blood cells targeting a Hb level between 9-10 g/dl. The immediate post-operating anticoagulation administered was low molecular weight heparin (tinzaparin 8000 IU subcutaneous daily). An anti-factor Xa assay was used to monitor anticoagulant therapy and to prevent postoperative hemorrhage. Her pretransplant calculated panel-reactive antibody was 50% with no preformed donor-specific antibodies (DSA). Basiliximab was used as an induction regimen and tacrolimus, steroids, and mycophenolate mofetil as maintenance therapy. On the 10^{th} post-operative day, the patient presented with acute deterioration of the kidney allograft function, and a diagnosis of acute TCMR was established by kidney allograft biopsy. TCMR was treated with methylprednisolone pulse and antithymocyte globulin (ATG) and the allograft function was restored. The patient was discharged without any complications. Four months later serum creatinine was within normal range (Cr=0.8mg/dL), as well as proteinuria. The post-operative Cr trends are presented in Figure 1. Additionally, no de novo DSA were detected using Luminex-based single antigen bead assay. The patient is under close follow-up until today, one year after the transplantation. Her hemoglobin is maintained at over 9 g/dL, supported by transfusion of packed red cells every 3 weeks. Despite the short period since the transplant occurred the patient is well without any sign of early rejection. She receives maintenance immunosuppression and DFO as chelation therapy and her renal function parameters are frequently measured. She refuses erythropoietin administration as the previously received epoetin beta (NeoRecormon) is no longer available in Greece and she is afraid of allergic reactions to the other types of erythropoietin. The most interesting points of the patient's history are illustrated in Figure 2.

DISCUSSION

Kidney transplantation in thalassemia patients is rare. Only one case report has been previously published.

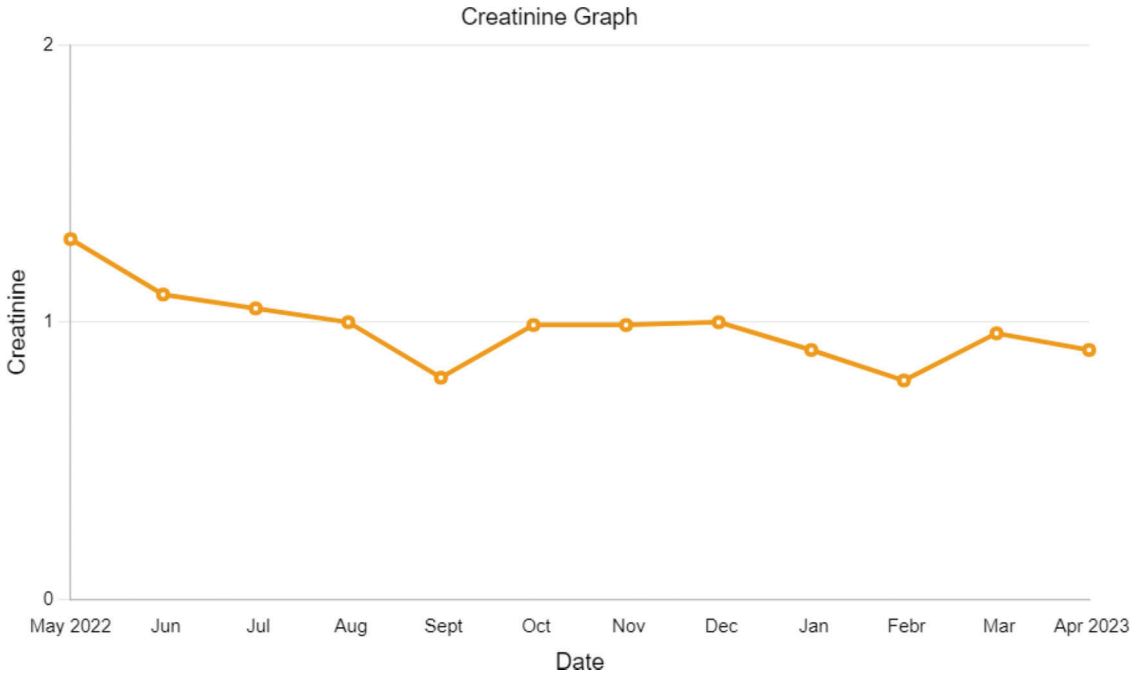

Fig. 1. Line graph presenting the monthly patient's creatinine level (mg/dL) for one year after the renal transplantation.

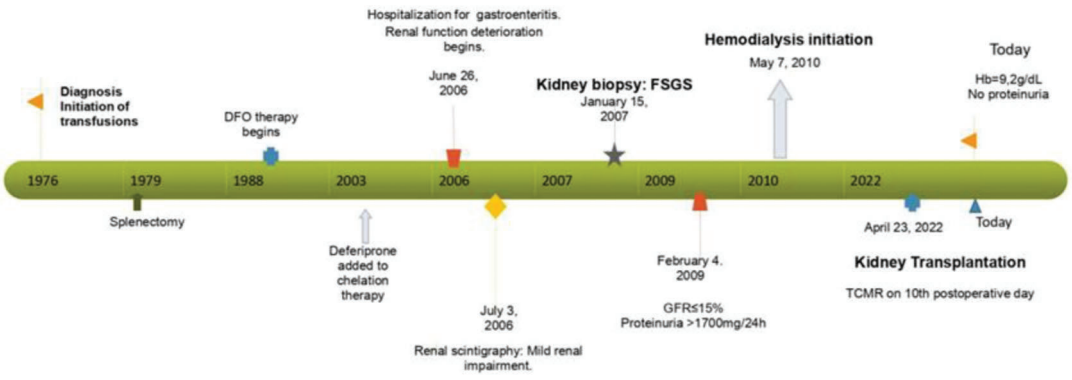

Fig. 2. Timeline illustrating the patient's history.

In particular, Emam and colleagues reported the kidney transplantation of a patient with thalassemia major and ESRD due to chronic tubule-interstitial nephritis [8]. The present case study is the second report of a TDT patient who successfully underwent a kidney transplant with many challenges and risks.

There are references on renal function abnormalities in thalassemia patients since 1975. However, only a limited number of studies have investigated the effects of β-thalassemia on the kidney [9]. Multiple factors have been suggested to contribute to the renal manifestations in thalassemia, including chronic anemia, hypoxia, iron overload, acquired Fanconi syndrome, iron chelator agents, infections, nephrotoxic drugs, splenectomy, and nephrolithiasis [10]. It has been demonstrated that chronic hypoxia causes proximal tubular cell dysfunction and interstitial fibrosis, which, may lead to progressive renal disease. Moreover, persistent anemia seems to induce renal hyperperfusion and glomerular hyperfiltration, thus, affecting the podocytes and resulting in secondary FSGS [11]. Additionally, chronic renal iron deposition has been associated with glomerulosclerosis, fibrosis of the interstitium, and atrophy of the proximal tubules. Free iron also directly catalyzes lipid peroxidative reaction inducing oxidative stress toxicity [10,12]. Finally, iron chelation therapy has also been related to the deterioration of renal function. DFO impairs mitochondrial function and production of adenosine triphosphate, activating the tubule-glomerular feedback and causing vasoconstriction of the afferent glomerular arterioles. On the other hand, deferiprone is not considered nephrotoxic, although it lacks the support of large randomized controlled trials. Deferasirox is well known to increase creatinine levels and close monitoring is indicated, but our patient never received deferasirox [10]. A combination of these risk factors was present in our case, including chronic anemia and iron overload, which was deteriorated by the unsatisfactory compliance to transfusions and chelation therapy, the use of iron chelators, especially DFO, infections (HCV, gastroenteritis), and previous splenectomy.

Kidney transplantation is the preferred option for treatment of ESRD, as it improves survival and quality of life and is cost-effective, compared to hemodialysis [13]. Our patient had ESRD due to secondary FSGS. Notably, the patient survived long-term hemodialysis, which lasted for over a decade. In Greece, the mean waiting time for a renal transplant is 8.8 years, but 57% of patients on dialysis die within five years [14]. The deceased donor kidney transplantation rates are, unfortunately, among the lowest in Europe for individuals of all ages [15]. Blood transfusion is a well-known cause of HLA sensitization and repeated transfusions might lead to broad sensitization limiting the likelihood of finding a crossmatch-compatible transplant donor [16]. Other centers caring for similar patients could process faster the pretransplant evaluation by referring them to transplant units experienced in the specific challenges faced by these patients.

A primary obstacle that had to be confronted in the present case, was the adverse effects of hypercoagulability. Our patient presented with a series of thromboembolic events, including superficial thrombophlebitis, pulmonary embolism, and thrombosis of the arteriovenous fistula. These are related to the hypercoagulable state of thalassemia. TI is the group with the highest incidence of these events, compared to the other thalassemia types. The coagulation activation is attributed to various factors, such as cellular (chronic platelet activation, alterations in red blood cells, endothelial cells, monocytes, and peripheral blood activation), splenectomy, as well as inherited thrombophilic DNA mutations and acquired changes in coagulation factors and inhibitors [17]. Our patient received the vitamin-K antagonist (VKA) acenocoumarol for the treatment of the aforementioned disorders. Acenocoumarol prevents the activation of the vitamin K-dependent blood clotting factors, thus limiting the initiation of the coagulation cascade. However, other vitamin K-dependent proteins, such as the matrix Gla-protein are also inactivated. MGP has a pivotal role in inhibiting the development of vascular calcifications. Several studies suggest that the use of the VKA could promote the development of vascular calcifications [18]. This side effect was of great importance for our patient, as calcification of the middle layer (tunica media) of the iliac vessels was developed, a particularly challenging characteristic for the arterial anastomosis performed during the operation.

Another demanding factor in our case was HCV infection. The patient tested positive for antibody to hepatitis C, although HCV RNA quantification by real-time polymerase chain reaction was negative. This result was suggestive of an inactive, past infection, that could be associated with the numerous blood transfusions. The HCV RNA PCR test had been negative for many years before transplantation. Therefore, no prophylaxis for HCV recurrence was implemented. A planned test for HCV RNA PCR was used as a surveillance strategy for HCV. HCV infection among patients on hemodialysis is related to higher hospitalization, mortality, anemia-related complications, and lower quality of life [19].

Additionally, the post-transplant period was not uncomplicated. TCMR occurred on the 10th postoperative day and was biopsy-proved. Over the last decades, significant improvements have been made in immunosuppressive regimens, reducing the rate of acute rejection in kidney allografts. However, acute rejection still comprises a critical cause of graft loss in renal transplant recipients [20]. Increased incidence of humoral alloimmune responses, with detection of de novo DSA following TCMR seem to contribute to this outcome [21]. The patient was administered methylprednisolone pulse and ATG, according to the guidelines [22] and this treatment was effective.

Every two weeks our patient receives follow-up care with serum creatinine measurements, GFR calculation, urine analyses and transfusion. As a new era is rising in thalassemia treatment, luspatercept seems to be an alternative agent that could reduce transfusion requirements in thalassemic patients. Up until 2019, the only available treatment for β-thalassemia was blood transfusions, which were associated with fatal adverse effects. Therefore, there is a significant need for agents such as luspatercept. This recombinant protein is thought to enhance late-stage erythropoiesis by binding to TGF-ligands. It intensifies late-stage erythroid development in the bone marrow, lowers Smad 2/3 signaling, and ameliorates hematological parameters. It has been shown in thalassemia clinical studies that it causes a prolonged excess of hemoglobin and a decrease in transfusion requirements [23].

CONCLUSION

More longitudinal studies are required to unravel the true incidence and mechanisms of renal dysfunction in thalassemia. Early recognition of renal dysfunction is of great importance to prevent the onset of renal impairment. Kidney transplantation in this group of patients may pose extreme challenges but is possible and should not be discouraged. Nevertheless, optimal management with regular transfusions and close monitoring of renal function is vital, in order to eliminate post-transplant complications.

Disclosure

The authors declare no conflicts of interest.

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Consent

Informed consent has been obtained from the patient to publish her medical history.

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