Case Report

Kidney Transplantation in Sickle Cell Disease Patients: Case Series and Experience from a Nigerian Kidney Transplant Center

Abstract

Sickle cell nephropathy is one of the long-term complications of sickle cell disease (SCD). About a quarter of SCD patients who survive up to 40 years of age will require some form of renal replacement therapy in their lifetime. Organ transplantation in SCD patients poses great challenges, particularly in lower middle income countries (LMIC) like Nigeria. This report highlights the management of three SCD patients who successfully underwent renal transplantation. The patients were aged 39, 47, and 58 years, respectively, with similarly previous history of multiple blood transfusions, recurrent vaso-occlusive crises, and had all progressed to end-stage renal disease. Preoperative exchange blood transfusion and plasmapheresis were offered in one and two of the patients, respectively. One of them required preoperative vaccination against encapsulated organisms due to autosplenectomy. Antithymocyte globulin was used as induction therapy in two of these patients while basiliximab was used in the third. All patients are alive with good renal function 18, 24, and 48 months post transplantation, respectively. In conclusion, kidney transplantation can be safely carried out on SCD patients with a satisfactory outcome.

Keywords: *Kidney transplantation, Nigeria, sickle cell disease*

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Introduction

Sickle cell disease (SCD) is a common hemoglobinopathy characterized by sickling or insolubility of the hemoglobin tetramer following deoxygenation.[1] The renal complications are attributable to the effect of the relative acidic, hypoxic, and hypertonic medullary environment on the red blood cells in the vasa recta. This predisposes to repeated occlusion of the vasa recta with consequent local ischemia and infarction.[2] These changes manifest with hyposthenuria, papillary necrosis, glomerulosclerosis, and eventual renal failure.

Chronic kidney disease (CKD) is a major cause of morbidity and mortality in this group of patients with a global prevalence of 4%–18% which increases to as high as 20%–30% in SCD patients greater than 40 years old.[3,4] In Sub-Saharan Africa, SCD may present in adulthood with CKD requiring renal replacement therapy (RRT) and kidney transplantation (KT).[3,5] In Nigeria, where an estimated 2%–3% of its population is affected by SCD,[6] very few centers have the capacity for routine and regular hemodialysis and only a handful is offering kidney transplantation services. The poor access stems from lack of skilled manpower and facilities for KT, poor health insurance coverage, poverty, ignorance, and lack of a national constitution backing cadaveric kidney donation in Nigeria.[7] These circumstances put significant pressure on the limited pool of living donors and further limit spaces for KT in SCD patients who require highly specialized care for a successful outcome after transplantation.

From literature review, there has been no previous report of KT on SCD patients performed in Nigeria till date. We described three sickle cell disease patients who underwent KT exploring their clinical presentation, preoperative preparation, and outcomes following transplant surgery.

Case 1

A 39-year-old woman was referred to our facility for RRT. She was diagnosed with SCD at the age of 2 years with repeated episodes of vaso-occlusive crisis and hospital admissions [Baseline characteristics in Table 1]. She began to notice reduced

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Table 1: Baseline characteristics of SCD patients who underwent Kidney transplantation

	CASE 1	CASE 2	CASE 3
Age (Years)	39	47	58
Ethnicity	African	African	African
Sex	Female	Male	Male
BMI (Kg/m^2)	25.3	22.0	19.6
Genotype	HbSS	HbSS	HbSS
Age at Diagnosis of HbSS (Years)	2	4	5
Time to CKD (Years)	34	20	30
Duration on Dialysis Prior to Transplant (Months)	12	3	6
Smoking	No	Yes	No
Hypertension	Yes	Yes	Yes
Average Number of Vaso-Occlusive Crisis	Several	Several	Several
Duration of Post Transplant Follow-Up (Months)	48	24	18

urine output, facial and pedal edema, and hiccups for which she was diagnosed to have CKD five years prior and had progressed to ESRD. She also had avascular necrosis of the right head of femur. Investigations revealed that urinalysis showed proteinuria 3+, packed cell volume of 21%, and renal function was poor with urea of 168 mg/dl and creatinine of 11.3 mg/dl. The abdominal ultrasound showed bilateral shrunken kidneys and ascites. Chest X-ray showed marked cardiomegaly; echocardiography revealed left ventricular hypertrophy and left atrial dilatation. She was commenced on 3-weekly haemodialysis with intra-dialysis blood transfusions of 3 units of blood over 3 months and began preoperative evaluation for living related donor KT. The donor was her younger brother with whom she was ABO blood group compatible and had a human leukocyte antigen (HLA) match of 4/6. Details of histocompatibility, induction agents, and immunosuppression are noted on Table 2. Renal function normalized by the 3rd postoperative day. As at a clinic visit 1 year following surgery, the Urea-18 mg/dl and Cr-0.96 mg/dl. She is currently on tacrolimus, mycophenolate mofetil, prednisolone, calcium carbonate, vitamin C, folic acid, hydroxyurea, and pendopyl with acceptable Tac levels [Table 2]**.**

Case 2

A 47-year-old male SCD patient presented with ESRD and desirous of KT. He was on twice weekly hemodialysis. He had battled several episodes of vaso-occlusive crises in childhood and had about 15 units of blood transfused in his lifetime. His last blood transfusion was 3 months prior to presentation in our clinic. His PCV ranged from 19% to 22% and his presenting renal function was Urea-112 mg/dl and Creatinine-10.1 mg/dl. His potential donor was his brother who was evaluated and found to be compatible with HLA match of 3/6. He had elevated donor specific antigen (DSA) titers of above 2000 for Class I antigens and a negative match for B & T cell lymphocytes. Abdominal ultrasound revealed autosplenectomy and bilaterally shrunken kidneys. On account of the hyposplenic condition, he had vaccination against S. pneumoniae, N. meningitidis, H. influenza type b, and influenza virus 4 weeks before surgery. He required intra-operative transfusion of 1 unit of blood which was well tolerated. His renal function normalized by the 5th day of KT. He has been maintained on his immunosuppressants in the past 1 and half years with a normal renal function and Tac level-6.4ng/mL. On follow-up visits, he has been managed for two more episodes of vaso-occlusive crises.

Case 3

A 58-year-old man presented with severe anemia, CKD, and gout arthritis. He placed on maintenance hemodialysis three times weekly. He was also on his routine hematinics, hydroxyurea, antihypertensives and began preparation for KT. The donor was ABO blood group compatible and had a HLA 2/6 match. There was an unremarkable DSA titer and patient was negative for B & T cell lymphocytes. He has a session of exchange blood transfusion a night before surgery to further reduce the chances of perioperative crisis and had induction therapy using Antithymocyte Globulin (ATG). He had successful KT done with a smooth immediate postoperative recovery. He was noticed to have prolonged drainage of lymph via his abdominal wound drain and continued leakage of lymphatic fluid after discontinuation of the drain. He required ultrasound-guided drainage of the peri-allograft lymphocele 3 weeks post KT. And he is currently doing well on his immunosuppressants. His renal function has remained normal.

Discussion

Sickle cell disease is an uncommon cause of ESRD worldwide and is much more prevalent in sub-Saharan Africa.[8] These SCD patients require multiple blood transfusions in their lifetime, which could have contributed to the positive DSA titers, which necessitated plasma exchange and immunoglobulin administration for desensitization. As from this series, exchange blood transfusion and vaccination against encapsulated organisms (in auto-splenic patients) are important prerequisites to a successful KT in SCD patients with ESRD.

It is known that SCD patients present with ESRD at a relatively younger age than the general population. Considering that these young patients are likely to be good candidates for KT, only few SCD patients eventually had this procedure done.[9] Currently, it has been proven that the survival of SCD patients following KT has significantly improved with no significant overall survival difference between SCD patients and controls (ESRD patients from other causes).[1,9]Though it may be difficult to comment on the long-term survival of both our patients and allografts due to our short follow-up duration, we

Table 2: Post transplant patient characteristics/outcome

	CASE 1	CASE 2	CASE 3
DSATiters/Management Protocol	Class I-200 Class II-120	Class I-2000 Class II-1215	Class I-658 Class II-250
Human Leukocyte Antigen (HLA) Match	4/6	3/6	2/6
Additional Preoperative procedure	Nil	Plasma exchange + Intravenous Immunoglobulin (3 sessions) Vaccination against encapsulated organisms	Exchange blood transfusion
Donor Profile			
Age (Years)	32	26	36
Sex	Male	Male	Male
Hemoglobin Genotype	AA	AA	AA
Perioperative blood transfusion requirements (units)	2	1	1
Induction Agent (T Cell Depleting Antibody)	Basiliximab	Antithymocyte globulin (ATG)	Antithymocyte globulin (ATG)
Immunosuppressive Agents	Mycophenolatemofetil Tacrolimus	Mycophenolatemofetil Tacrolimus	Mycophenolatemofetil Tacrolimus
Corticosteroids	Methylprednisolone Prednisolone	Methylprednisolone Prednisolone	Methylprednisolone Prednisolone
Acute Rejection	NO	NO	NO
Sickle Cell Therapy	Hydroxyurea	Hydroxyurea	Hydroxyurea
Clinical Features (Post Transplant)	Renal function normalized	Renal function normalized	Lymphocele Renal function normalized

can only conclude that the short-term outcome has been encouraging with 100% survival at 2 years. This supports the finding from Ojo *et al*. and Gerardin *et al*. who found no significant difference in 2-year survival of SCD patients vs. controls, however a slightly lower survival in 5 and10 years.[9,10] In our study, living related donors with good HLA compatibilities played a major role in the successful outcome.

To have a successful outcome for the SCD kidney recipient, an intensive work-up for surgery must be followed. Donor selection is also a very important key factor. The peculiarities among sickle cell patients are that many close siblings or relatives might also be carrying the abnormal sickle cell gene. As part of our protocol, genotypes of all potential donors are requested and anyone with the abnormal sickle cell gene is excluded with AA donors favored. In our review though, two out of the three recipients got kidneys from their siblings. Many sickle patients are at high immunological risks as they would have had multiple blood transfusions necessitating the need for desensitization prior to transplant. In the same vein, for those with hyposplenism from autosplenetomy, vaccinations against S. pneumoniae, N. meningitidis, H. influenza type b, and influenza virus are strongly recommended at least 2 weeks before transplant surgery.[11]

Gradual correction of anemia by erythropoietin stimulation can be commenced months prior to surgery in order to limit the need for blood transfusions which could alter the immunologic milieu and hence increase the risk of acute rejection. For individuals who may require blood transfusion, it is advised to delay for a period of 3 months and repeat the cross-matches in order to rule out the presence of new antibodies or plasma exchange. Also, optimal hydration, adequate analgesia, antimalarials, antibiotic therapies, and thromboprophylaxis are all important for achieving good results. The liberal use of hydroxyurea in these patients pre and postoperatively has been shown to reduce incidents of crisis, acute chest syndrome, and mortality by up to 40%.[12] In our practice, hydroxyurea increases the fetal hemoglobin (HbF) concentration while reducing the HbS. This reduces the chances of vaso-occlusive episodes in the transplant period. A wide bore central line for hydration, arterial line for blood gas monitoring, and general anesthesia with good oxygenation gave our series a good outcome. Surgically, gentle dissection, meticulous hemostasis, and short warm and cold ischemic time enabled early graft function with normalization of renal function within 3 days. In the immediate postoperative period, liberal morphine-based patient-controlled analgesia was ensured to avoid pain-induced crisis.

In the post-transplant period, we ensure that all our sickle cell patients get oral hydroxyurea coupled with the immunosuppressants, antimalarial prophylaxis, co-trimoxazole for 6 months, prednisolone which we reduced to 5mg daily at 1 year, atorvastatin daily rabeprazole daily, valganciclovir for 6 months, tuberculosis

prophylaxis for 3 months, antifungal prophylaxis for 3 months, liberal fluid intake, and regular clinic visits.

Septicemic complications are a common cause of perioperative mortality in SCD accounting for up to 23.3% of deaths,[10] hence the need for use of wound drains inserted intraoperatively and aggressive drainage of the peri-allograft collections like lymphocele to forestall progression into a peri-allograft abscesses. The hemoglobin concentrations of these patients improved remarkably following KT perhaps attributable to increased erythropoietin production from the renal allograft. There was no incidence of steroid-induced bony avascular necrosis in the follow-up period.

Conclusion

Kidney transplantation can safely be carried out in SCD patients in Nigeria. There is a need for appropriate donor and recipient selection, proper preoperative preparation with regards to the correction of chronic anemia, and adequate hemaodialysis and plasmapheresis in order to optimize these patients for surgery. The patients'short-term survival outcome in our practice is very encouraging.

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Conflicts of interest

There are no conflicts of interest.

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