CASE REPORT

Refractory Anemia in a Patient with Sickle Cell Nephropathy on Dialysis

SOTUBO SOTOMIWA*, SOURABH SHARMA†, AMISU MUMUNI*, ODEYEMI AYOOLA*, BANJOKO OLUWOLE‡, ADEKOYA ADEBOWALE#, AWOBUSUYI OLUGBENGA#

ABSTRACT

This case highlights a middle-aged female with sickle cell nephropathy (SCN) on maintenance hemodialysis who presented with refractory anemia despite initial erythropoiesis-stimulating agent therapy and dialysis. Intensifying dialysis frequency to alternate-day sessions and switching from erythropoietin to darbepoetin significantly improved the patient's management. This report underscores the critical role of adequate dialysis and optimized anemia management in SCN patients.

Keywords: Sickle cell disease, sickle cell nephropathy, refractory anemia, end-stage kidney disease, erythropoiesis-stimulating agents

Sickle cell nephropathy (SCN) is a progressive complication of sickle cell disease (SCD) that often leads to end-stage kidney disease (ESKD)[1,2]. Anemia in SCN patients is multifactorial, driven by chronic inflammation, hemolysis, and erythropoietin (EPO) resistance[3,4]. Adequate dialysis plays a pivotal role in addressing these contributing factors by improving uremia, reducing inflammation, and stabilizing fluid and metabolic imbalances.

Inadequate dialysis can exacerbate anemia, increasing reliance on erythropoiesis-stimulating agents (ESAs) and blood transfusions[5]. This case report describes the management of a patient with SCN and refractory anemia, emphasizing the impact of increased dialysis frequency and the replacement of EPO with darbepoetin in improving anemia control.

CASE REPORT

A 41-year-old female teacher with a history of SCD diagnosed at the age of 3 years and hypertension for 5 years became dialysis-dependent 2 years ago. Initially, she received once-weekly hemodialysis, which was progressively increased to thrice-weekly sessions over the last 6 months.

In the past year, the patient developed bilateral leg swelling, uncontrolled hypertension, and a progressive decline in hematocrit levels, which ranged between 14% and 18%. She reported no bleeding from any orifice, melena, dark-colored urine, jaundice, recurrent fever, weight loss, or night sweats. However, she experienced easy fatigability and palpitations without associated chest pain, dizziness, syncope, orthopnea, or paroxysmal nocturnal dyspnea. There was no abdominal swelling or facial puffiness, but her urine output had significantly decreased.

On examination, the patient had a blood pressure of 180/100 mmHg, bilateral basal crepitations, and bilateral lower limb edema extending to the distal third of the legs. Initial investigations revealed the hemoglobin 6.2 gm%, packed cell volume (PCV) 14%, white blood cell count 9,700 cells/mm^3, platelet count 2,50,000 cells/mm^3, erythrocyte sedimentation rate 46 mm/hr, C-reactive protein (CRP) 7 mg/L, and reticulocyte count 2.2%. Peripheral blood smear showed a reduced number of red cells, numerous sickle cells, and target cells. Biochemistry evaluation revealed serum lactate dehydrogenase (LDH) 496.8 U/L (normal: 130-300 U/L),

*Consultant Nephrologist, Nephrology Unit, Dept. of Medicine, LASUTH, Ikeja, Lagos, Nigeria
†Assistant Professor, Dept. of Nephrology, VMMC & Safdarjung Hospital, New Delhi, India
‡Consultant Clinical Hematologist, Dept. of Medicine, LASUTH, Ikeja, Lagos, Nigeria
#Professor of Medicine/Consultant Nephrologist, Nephrology Unit, Dept. of Medicine, LASUTH, Ikeja, Lagos, Nigeria
Address for correspondence
Dr Sourabh Sharma
Room No. 239, Super Speciality Block, VMMC & Safdarjung Hospital,
New Delhi - 110 029, India
E-mail: drsourabh05@gmail.com

urea 181 mg/dL, creatinine 9.1 mg/dL, total bilirubin 22 μmol/L, conjugated bilirubin 2.8 μmol/L, serum albumin 32.5 g/L, alanine transaminase 25 U/L, aspartate transaminase 45 U/L, serum β_2-microglobulin 12.4 mg/L (<3 mg/L), serum folic acid 24 ng/mL (4.8-37 ng/mL), and vitamin B12 1,357.5 pg/mL (211-911 pg/mL). Direct and indirect Coombs tests were negative. Urinalysis showed traces of protein; serum protein electrophoresis was normal. Iron studies revealed serum iron 20.6 μmol/L, transferrin saturation 71.03%, transferrin 115.48 μmol/L, total iron-binding capacity 29 μmol/L (normal: 42.9-80.5 μmol/L). Extensive investigations ruled out other causes of anemia, including nutritional deficiencies, chronic inflammation, and infection.

The patient was co-managed by a nephrologist and a clinical hematologist. Treatment modifications included continuing dialysis as alternate-day sessions, adjustments in antihypertensive medications- losartan 100 mg daily, atenolol 25 mg daily, torsemide 60 mg daily, and nifedipine XL 60 mg daily, and increasing EPO dose from 4,000 unit twice weekly to 6,000 units and further increase to 10,000 units (twice weekly) after 1 month.

Despite 2 months of ESA therapy, the patient's PCV remained between 14% and 16%. Hemoglobin level stayed around 6.5 gm%. She required occasional intradialytic blood transfusions for symptomatic anemia. Anti-EPO levels were also checked which were found to be within normal range.

To address persistent anemia, EPO was replaced with subcutaneous darbepoetin alfa 40 μg weekly and dose further increased to 60 μg weekly after 1 month. Patient's PCV and hemoglobin levels started rising after 2 months and during last follow-up, patient was asymptomatic with hemoglobin level of 8.9 gm% without requirement of blood transfusion in past 2 months.

DISCUSSION

Anemia management in SCN patients requires a multifaceted approach, with adequate dialysis being a cornerstone of therapy[6]. In this case, the patient's initial once-weekly dialysis regimen was inadequate to address her metabolic and inflammatory burden. Transitioning to alternate-day dialysis improved uremic clearance, reduced inflammation, and stabilized fluid and metabolic imbalances, creating a more favorable environment for erythropoiesis.

Replacing EPO with darbepoetin alfa was the next step in management. Darbepoetin's longer half-life allows for less frequent dosing, improving patient compliance[7].

Moreover, darbepoetin demonstrates superior efficacy in overcoming EPO resistance associated with chronic inflammation and functional iron overload in SCN[8]. Many studies have reported successful conversion of EPO to darbepoetin alfa in cases with EPO resistance[8,9].

Persistent anemia despite optimized dialysis and ESA therapy highlights the multifactorial nature of refractory anemia in SCN[1-4]. Contributing factors in this patient included:

- **Erythropoietin resistance:** As depicted in various studies[10], in our case too, chronic inflammation, as evidenced by elevated β_2-microglobulin and CRP levels, likely reduced ESA responsiveness.
- **Hemolysis:** Elevated LDH levels and peripheral blood smears showing sickle cells indicated ongoing hemolysis.
- **Iron dysregulation:** Functional iron overload, as suggested by a high transferrin saturation, may have further impaired erythropoiesis.

In this patient, the combination of alternate-day dialysis and switched ESA therapy resulted in modest improvements in PCV and reduced the frequency of blood transfusions. However, challenges such as inflammation and hemolysis remain significant barriers to optimal anemia management.

Future strategies could include the use of anti-inflammatory therapies, hydroxyurea optimization to reduce hemolysis, and novel agents targeting the hepcidin pathway to improve iron utilization. This case emphasizes the importance of adequate dialysis in the management of refractory anemia in SCN patients on maintenance dialysis.

CONCLUSION

This case highlights the critical role of adequate dialysis and optimized anemia management in patients with SCN. Intensifying dialysis to alternate-day sessions and transitioning from EPO to darbepoetin significantly improved anemia control.

We want to reiterate the need for individualized management strategies and further exploration of novel therapies for refractory anemia in this challenging patient population.

REFERENCES

1. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol. 2015;11(3): 161-71.

2. Aeddula NR, Bardhan M, Baradhi KM. Sickle Cell Nephropathy. [Updated 2023 Sep 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526017/
3. Ataga KI, Saraf SL, Derebail VK. The nephropathy of sickle cell trait and sickle cell disease. Nat Rev Nephrol. 2022;18(6):361-77.
4. Elzorkany K, Alsalman M, AlSahlawi M, Alhedhod A, Almulhim NA, Alsultan NJ, et al. Prevalence and predictors of sickle cell nephropathy: a single-center experience. Sci Rep. 2024;14(1):28215.
5. Chung EY, Palmer SC, Saglimbene VM, Craig JC, Tonelli M, Strippoli GF. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database Syst Rev. 2023;2(2):CD010590.
6. Boyle SM, Jacobs B, Sayani FA, Hoffman B. Management of the dialysis patient with sickle cell disease. Semin Dial. 2016;29(1):62-70.
7. Cases A. Darbepoetin alfa: a novel erythropoiesis-stimulating protein. Drugs Today (Barc). 2003;39(7):477-95.
8. Hejaili F. The efficacy of darbepoetin alpha in hemodialysis patients resistant to human recombinant erythropoietin (rHuEpo). Saudi J Kidney Dis Transpl. 2009;20(4):590-5.
9. Khullar D, Muchhala SS, T A. Advancing anemia management in chronic kidney disease: assessing the superiority of darbepoetin alfa over erythropoietin alpha. Cureus. 2024;16(1):e51613.
10. Santos EJF, Dias RSC, Lima JFB, Salgado Filho N, Miranda Dos Santos A. Erythropoietin resistance in patients with chronic kidney disease: current perspectives. Int J Nephrol Renovasc Dis. 2020;13:231-7.

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