Case Report

# From Hemolysis to Heart Block: A Rare Case of Secondary Hemochromatosis Leading to Acute Pulmonary Edema

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## Abstract

**Background:** Acute pulmonary edema is a life-threatening manifestation often resulting from underlying cardiac dysfunction. We report a rare case of a 65-year-old male with a background of transfusion-dependent, previously uncharacterized hemolytic anemia, who presented with progressive breathlessness and orthopnea. Clinical evaluation revealed bradycardia with a pulse rate of 50 bpm and signs of volume overload. Electrocardiography demonstrated complete heart block, while echocardiography showed severe left ventricular systolic dysfunction with an ejection fraction of 32%. Laboratory investigations confirmed anemia with a dimorphic peripheral smear, and markedly elevated serum ferritin levels suggestive of iron overload. MRI-based quantification revealed moderate hepatic and borderline cardiac iron deposition. Genetic analysis identified a homozygous SLC4A1 mutation (c.1984T>C; p. Trp662Arg), consistent with non-immune hemolytic anemia. The patient was managed initially with diuretics, oxygen support, and inotropes, followed by iron chelation therapy. This case highlights a rare interplay between inherited hemolytic anemia, secondary hemochromatosis due to repeated transfusions, and resultant cardiac conduction abnormalities culminating in acute pulmonary edema.

**Keywords:** Hemolysis, SLC4A1, Hemosiderosis.

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## Introduction

Hemochromatosis is a disorder characterized by excessive iron accumulation in tissues, leading to progressive organ dysfunction.[1] While primary hemochromatosis is genetically mediated, secondary hemochromatosis commonly occurs due to repeated blood transfusions, chronic hemolysis, or ineffective erythropoiesis.[2] Excess iron deposition in parenchymal organs such as the liver, pancreas, and heart results in oxidative damage, fibrosis, and eventual organ failure. Cardiac involvement, in particular, is a critical determinant of prognosis, often manifesting as cardiomyopathy, arrhythmias, and conduction disturbances.[3] Cardiac hemochromatosis leads to iron deposition within the myocardium and conduction system, impairing both electrical and mechanical function. This may present as restrictive or dilated cardiomyopathy, reduced ejection fraction, and rhythm abnormalities such as atrioventricular blocks.[4] Progressive myocardial dysfunction can culminate in heart failure, predisposing patients to acute pulmonary edema due to elevated left ventricular filling pressures and pulmonary venous congestion.[5] Early recognition is essential, as timely chelation therapy can reverse or halt disease progression.

Hemolytic anemias comprise a heterogeneous group of disorders characterized by premature destruction of red blood cells. Non-immune hemolytic anemias include membrane defects, enzymopathies, and hemoglobinopathies, often presenting with chronic anemia, jaundice, and splenomegaly.[6] These conditions frequently require repeated transfusions, thereby increasing the risk of secondary iron overload.

The SLC4A1 gene encodes the anion exchanger 1 (AE1) protein, which plays a critical role in chloride-bicarbonate exchange across erythrocyte membranes and renal tubular cells.[7] Mutations in this gene are associated with a spectrum of disorders, including hereditary spherocytosis and distal renal tubular acidosis. The phenotypic expression varies widely depending on the mutation, with some cases presenting predominantly as hemolytic anemia without renal involvement.

We present a rare case of acute pulmonary edema secondary to complete heart block in a patient with transfusion-related hemochromatosis and underlying SLC4A1-associated non-immune hemolytic anemia managed at Rajiv Gandhi Government General Hospital.

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## Case Presentation

A 65-year-old male from a rural background presented with complaints of breathlessness for one week, associated with orthopnea. He also reported abdominal distension for one month, insidious in onset, associated with a dragging sensation. He was a known case of suspected hemolytic anemia with splenomegaly that had not been fully evaluated due to limited facilities and was referred for further management. There was a history of multiple prior blood transfusions at local hospitals. There was no significant past, personal, or family history.

On examination, the patient was afebrile with a temperature of 98.2°F, tachypneic with a respiratory rate of 27 breaths per minute, and had a pulse rate of 50 bpm with a blood pressure of 140/80 mmHg. Oxygen saturation was 98% under CPAP support. Pallor, icterus, and bilateral pedal edema were present. Cardiovascular examination revealed normal S1 and S2 without murmurs. Bilateral air entry was present with diffuse crepitations. The abdomen was soft with splenomegaly corresponding to Hackett grade 4. Neurological examination revealed bilaterally reactive pupils with no focal neurological deficits.

Investigations revealed anemia with a hemoglobin of 9.1 g/dL, elevated white blood cell count, and increased red cell distribution width. Peripheral smear demonstrated dimorphic anemia with anisopoikilocytosis and reactive lymphocytes. Electrocardiography revealed complete heart block [Figure 1]. Echocardiography showed an ejection fraction of 32%, moderate mitral stenosis, and severe left ventricular systolic dysfunction without global hypokinesia. Liver and renal function tests and electrolytes were within normal limits.

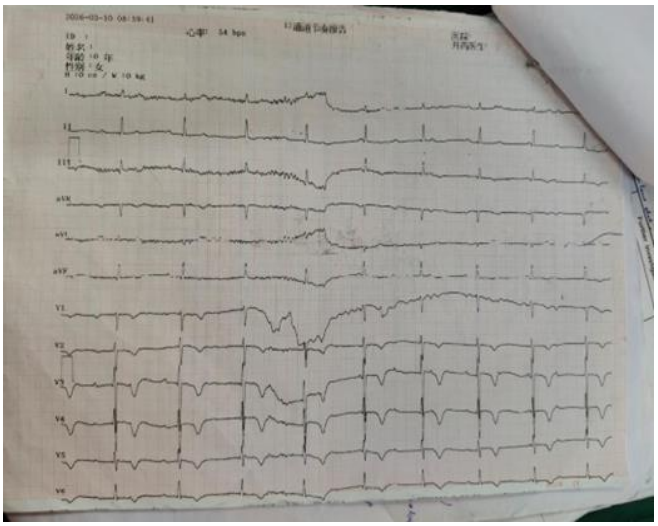

**Table 1: Laboratory investigations**

| Parameter | Value | Reference Range |
|---|---|---|
| WBC | 16.1 ×10³/µL | 4–11 |
| RBC | 2.82 ×10⁶/µL | 4.5–5.9 |
| Hemoglobin | 9.1 g/dL | 13–17 |
| Hematocrit | 25.9% | 40–50 |
| MCV | 91.8 fL | 80–100 |
| MCH | 32.3 pg | 27–33 |
| MCHC | 35.1 g/dL | 32–36 |
| Platelets | 216 ×10³/µL | 150–450 |
| RDW | 18.1% | 11–15 |

Further evaluation for iron overload showed reduced transferrin levels, normal serum iron, and markedly elevated ferritin at 1620.3 ng/mL. MRI-based quantification demonstrated moderate hepatic iron deposition and borderline normal cardiac iron levels. Genetic analysis identified a homozygous SLC4A1 mutation c.1984T>C (p.Trp662Arg).

**Table 2: Laboratory investigations**

| Parameter | Value | Reference Range |
|---|---|---|
| Serum Transferrin | 172 mg/dL | 200–360 |
| Serum Iron | 62 µg/dL | 60–170 |
| Serum Ferritin | 1620.3 ng/mL | 30–400 |
| Liver T2 | 4.3 ms | — |
| Liver R2 | 230.9 $s^{-1}$ | — |
| Cardiac T2 | 45.1 ms | >20 normal |
| Parameter | Value | Reference Range |
| Cardiac R2 | 22.1 $s^{-1}$ | — |

Final diagnosis of acute pulmonary edema due to complete heart block secondary to transfusion- related hemochromatosis in a patient with SLC4A1-associated non-immune hemolytic anemia was made.

The patient was initially managed with intravenous furosemide, oxygen therapy, and norepinephrine for hemodynamic support. Following stabilization, iron chelation therapy was initiated. The patient improved clinically and was discharged on furosemide, metolazone, orciprenaline, omeprazole, and lactulose, with advice for regular follow-up.

## Discussion

This case illustrates the complex interplay between chronic hemolytic anemia, transfusion- related iron overload, and cardiac dysfunction. Secondary hemochromatosis, resulting from repeated transfusions, led to iron deposition in the liver and heart, ultimately causing conduction abnormalities and systolic dysfunction. The resulting complete heart block and impaired cardiac output precipitated acute pulmonary edema, highlighting the severe cardiovascular consequences of untreated iron overload.

The presence of an SLC4A1 mutation further adds to the rarity of this case. While SLC4A1 mutations are well known to cause hereditary spherocytosis and distal renal tubular acidosis, our patient did not exhibit features of dRTA, suggesting phenotypic variability. Chronic hemolysis likely necessitated repeated transfusions, contributing to iron overload and subsequent organ damage.

Previous studies by Yang et al,[8] have demonstrated that SLC4A1 mutations most commonly present with distal renal tubular acidosis, often with nephrocalcinosis, which was absent in our case. Similarly, Sánchez-López et al,[9] reported hereditary spherocytosis associated with SLC4A1 mutations, while Shmukler et al,[10] described Indian patients with combined hemolytic anemia and dRTA. Notably, there are no documented cases linking SLC4A1 mutations directly with hemochromatosis, supporting the conclusion that iron overload in this patient was secondary to repeated transfusions. Furthermore, the absence of

dRTA suggests a potentially novel phenotypic presentation of this mutation.

This case report has certain limitations. Being a single-patient observation, the findings cannot be generalized, and causal relationships between the SLC4A1 mutation, hemolytic anemia, and cardiac manifestations cannot be definitively established. Although iron overload was demonstrated, cardiac MRI findings showed only borderline myocardial involvement, making it difficult to quantify the exact contribution of iron deposition to the conduction abnormality and systolic dysfunction. Additionally, the absence of long-term follow-up limits assessment of disease progression, response to chelation therapy, and potential reversibility of cardiac involvement. Renal evaluation was also limited, and subtle forms of distal renal tubular acidosis may not have been completely excluded.

Future studies should focus on better characterization of the phenotypic spectrum of SLC4A1 mutations, particularly in patients presenting without classical features such as distal renal tubular acidosis. Larger cohort studies and genetic registries may help establish clearer genotype–phenotype correlations. Furthermore, systematic evaluation of iron overload in chronically transfused patients with inherited hemolytic anemias is essential to enable early intervention. Advanced imaging techniques and longitudinal follow-up could provide insights into the progression and reversibility of cardiac involvement, ultimately improving clinical outcomes through timely diagnosis and targeted management.

## Conclusion

His case represents a rare and clinically significant combination of SLC4A1-associated non- immune hemolytic anemia and secondary hemochromatosis leading to cardiac complications, including complete heart block and acute pulmonary edema. It highlights the need for early and comprehensive evaluation of chronic hemolytic states to prevent long-term complications such as iron overload and organ damage.

Future research should focus on expanding the understanding of phenotypic variability associated with SLC4A1 mutations and identifying early markers of organ involvement. Early genetic diagnosis, regular monitoring, and timely initiation of chelation therapy are essential to improve outcomes in such patients.

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## Conflicts of interest

There are no conflicts of interest.

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