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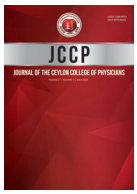

Case Report

Phenotypic evolution of Haemoglobin E beta-thalassaemia over three decades leading to pulmonary hypertension, cardiac cirrhosis, and hepatocellular carcinoma: A case report

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ABSTRACT

Haemoglobin E β-thalassaemia exhibits marked phenotypic heterogeneity, with some patients remaining non–transfusion-dependent for prolonged periods despite ongoing ineffective erythropoiesis and progressive iron loading. We report a 51-year-old woman diagnosed at 22 years of age who remained non–transfusion-dependent for over two decades. Despite minimal transfusion exposure, she developed significant iron overload (peak ferritin 3,490 ng/mL), followed by progressive splenomegaly and hypersplenism. Between 2018 and 2023, worsening anaemia and marrow exhaustion led to a transition to transfusion-dependent thalassaemia, with concurrent pulmonary hypertension confirmed by right heart catheterisation in 2024. After defaulting from care and discontinuing chelation therapy, she presented with decompensated chronic liver disease due to combined iron overload and cardiac cirrhosis. In 2025, further deterioration revealed hepatocellular carcinoma in segment VI (4.4 × 5.3 × 4.6 cm). This case highlights late phenotypic evolution in non–transfusion-dependent thalassaemia and the catastrophic consequences of unregulated iron toxicity, culminating in hepatocellular carcinoma and death within two months of diagnosis. It underscores the critical need for sustained monitoring, continuous chelation, and proactive surveillance for extrahepatic complications, including pulmonary hypertension and hepatocellular carcinoma, in un-transfused, iron-loaded patients.

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Introduction

Haemoglobin E beta-thalassaemia is the most prevalent severe thalassaemia syndrome in South and Southeast Asia and the commonest cause of β-thalassaemia intermedia in Sri Lanka. Its clinical hallmark is extreme phenotypic diversity, ranging from asymptomatic mild anaemia to life-threatening transfusion-dependent thalassaemia. (TDT).[1] Historically, a large cohort of these patients has been categorised as having non–transfusion-dependent thalassaemia (NTDT). While "non-transfusion-dependent" suggests a milder clinical course, it often masks a sinister underlying pathophysiology driven by chronic tissue hypoxia and unregulated iron absorption.[2]

In some patients with NTDT, the absence of regular transfusions allows profound ineffective erythropoiesis to persist unchecked. This paradoxically suppresses hepcidin – the master regulator of iron homeostasis – leading to relentless intestinal iron absorption.[3] Over decades, cumulative non-transfusional iron overload silently damages the liver, heart, and endocrine systems. Concurrently, chronic haemolysis contributes to pulmonary arterial hypertension.[4] We report the case of a patient with HbE β-thalassaemia who, after two decades of stable NTDT, underwent a phenotypic transition culminating in severe pulmonary hypertension, cardiac cirrhosis, and HCC.

Case Presentation

A 51-year-old Sri Lankan woman with haemoglobin E β-thalassaemia was first diagnosed in 1996 at the age of 22, during antenatal evaluation. Haemoglobin electrophoresis demonstrated HbF 39.2%, HbE 40.2%, and HbA 12.4%, consistent with a moderate-to-severe genotype. Despite this, she remained clinically compensated for over two decades without regular transfusion requirements, maintaining a NTDT phenotype. Transfusions were needed only intermittently during pregnancy, and she had no formal haematological follow-up.

The first indication that this apparent stability was deceptive emerged in 2007, at the age of 33, when routine testing revealed a serum ferritin level of 3,490 ng/mL, indicating significant iron overload despite minimal transfusion exposure. Subcutaneous desferrioxamine was commenced, but adherence remained inconsistent. Over the following decade, progressive splenomegaly developed, reaching nearly 18 cm by 2017, and thrombocytopenia worsened, with platelet counts falling below 80×10^9/L, consistent with hypersplenism.

By 2018, the compensatory reserve of her bone marrow began to fail. Baseline haemoglobin fell to approximately 7 g/dL, necessitating intermittent transfusion support. A trial of hydroxyurea, an agent known to increase Hb F/ Haemoglobin synthesis was initiated, with transient benefit, but discontinued due to poor adherence in the setting of pre-existing cytopenias. By early 2023, there was clear evidence of exhaustion of the marrow's compensatory capacity, with escalating transfusion requirements of two to four units of packed red blood cells per month, indicating transition to TDT. Concurrent evaluation at this stage revealed pulmonary hypertension, confirmed by right heart catheterisation in 2024, which demonstrated a mean pulmonary arterial pressure of 27 mmHg and a pulmonary capillary wedge pressure of 20 mmHg, consistent with combined pre- and post-capillary pulmonary hypertension in the context of cardiac cirrhosis. Faced with a recommendation for splenectomy, the patient declined, defaulted from follow-up, and discontinued iron chelation therapy entirely.

She presented again in 2024 with progressive abdominal distension and bilateral lower-limb oedema and was found to have decompensated chronic liver disease with ascites. Abdominal imaging confirmed chronic liver disease with massive splenomegaly and no focal hepatic lesions. She underwent therapeutic paracentesis, which provided partial symptomatic relief, but she did not maintain follow-up.

In October 2025, she was admitted with a four-day history of fever, haematemesis, worsening abdominal distension, and bilateral lower-limb oedema. She reported orthopnoea and paroxysmal nocturnal dyspnoea, with New York Heart Association class III exertional limitation. On examination, she was cachectic, deeply jaundiced, and markedly pale, with generalised cutaneous hyperpigmentation. Cardiovascular examination revealed elevated jugular venous pressure, a left parasternal heave, an accentuated pulmonary component of the second heart sound, a pansystolic murmur of severe tricuspid regurgitation, and bilateral basal crepitations. The abdomen was grossly distended with tense ascites, and bilateral pitting oedema extended to the mid-thigh.

Upper gastrointestinal endoscopy demonstrated severe gastric ulceration without oesophageal varices, and repeated therapeutic paracentesis yielded haemorrhagic ascitic fluid. Repeat echocardiography in November 2025 confirmed worsening pulmonary hypertension with a tricuspid regurgitation pressure gradient of 66 mmHg, severe right ventricular dilatation, and preserved left ventricular systolic function (ejection fraction 60%). Contrast-enhanced computed tomography of the abdomen demonstrated chronic liver disease with hepatic siderosis, massive splenomegaly, and a subcapsular lesion in hepatic segment VI measuring $4.4 \times 5.3 \times 4.6$ cm, radiologically consistent with hepatocellular carcinoma (HCC). Hepatitis B and C infections were excluded serologically, and there was no history of alcohol use, supporting iron overload and cirrhosis as the primary aetiological drivers.

Given the advanced stage of HCC (Barcelona Clinic Liver Cancer stage D), decompensated cardiac cirrhosis, and her exceptionally poor performance status, she was deemed unfit for surgical resection, transarterial chemoembolisation, or systemic targeted therapies. Following multidisciplinary consensus, she was transitioned to palliative care and died from hepatic encephalopathy and right heart failure two months after admission.

Discussion

This case starkly illustrates the deceptive natural history of poorly controlled NTDT and highlights the "silent killers" of thalassaemia: non-transfusional iron overload and chronic haemolysis. The historical binary classification of HbE β-thalassaemia into TDT and NTDT, while useful for initial triage, often fosters a false sense of security among patients and clinicians about the risk of severe end-organ damage.[5]

The pathophysiology of iron loading in NTDT is mechanistically distinct from that in TDT. While TDT

patients acquire iron primarily through senescent transfused red blood cells (reticuloendothelial loading), NTDT patients absorb large amounts of iron via the gastrointestinal tract. This is driven by massive erythroid expansion, which releases erythroferrone (ERFE), a hormone that profoundly suppresses hepatic hepcidin synthesis.[3,6] The resulting extracellular iron rapidly saturates transferrin, leading to the systemic circulation of non-transferrin-bound iron (NTBI) and labile plasma iron (LPI). These highly reactive iron species infiltrate parenchymal organs directly, generating reactive oxygen species (ROS) via the Fenton reaction, triggering lipid peroxidation, organelle dysfunction, and irreversible fibrosis.[7]

In our patient, decades of unregulated iron absorption culminated in catastrophic dual-organ failure. The development of severe pulmonary hypertension was likely multifactorial. In NTDT, chronic intravascular haemolysis releases cell-free haemoglobin and arginase into the plasma. Arginase depletes circulating arginine, the obligate substrate for nitric oxide (NO) synthesis. The subsequent NO depletion leads to profound pulmonary vasoconstriction, endothelial dysfunction, and smooth muscle proliferation.[8] When coupled with right ventricular iron deposition and hypercoagulability (often exacerbated by splenomegaly or prior splenectomy), the resultant right heart failure and chronic hepatic venous congestion (cardiac cirrhosis) form a vicious cycle of decompensation.

The most tragic, yet increasingly recognised complication in this case is the development of HCC. Once considered a rarity in thalassaemia, HCC has emerged as a leading cause of mortality in ageing thalassaemia cohorts, even in the absence of hepatitis B or C viral infections.[9,10] Iron is a potent, direct carcinogen. Chronic hepatic iron overload induces continuous DNA damage via oxidative stress, creates a pro-inflammatory and fibrogenic microenvironment, and directly impairs tumour-suppressor gene function (such as p53).[11] Studies indicate that prolonged hepatic iron concentrations exceeding 15 mg/g dry weight significantly increase the risk of cirrhosis and oncogenesis.[12]

This case highlights several critical imperatives for physicians managing haemoglobinopathies. First, the absence of transfusion requirements does not rule out iron overload; routine monitoring of serum ferritin and non-invasive tissue iron quantification (e.g. Specialised MRI pulse sequence T2* MRI of the liver and heart) is mandatory, though difficult to obtain in Sri Lanka.[13] Second, continuous and compliant iron chelation therapy is life-saving in NTDT, though it requires meticulous titration to avoid over-chelation toxicity.[14] Finally, as the NTDT population survives longer, rigorous HCC surveillance – using biannual abdominal ultrasonography and AFP monitoring – must be strictly implemented in patients with documented hepatic iron overload or cirrhosis, regardless of transfusion phenotype.[15]

Conclusion

This case underscores that a "non-transfusion-dependent" designation in haemoglobin E β-thalassaemia does not imply clinical safety. In endemic settings such as Sri Lanka, apparent stability may mask progressive iron overload and evolving multi-organ complications. Worsening cytopenias, splenomegaly, or rising ferritin levels should prompt timely reassessment rather than reassurance. As this population ages, proactive surveillance for complications such as pulmonary hypertension and hepatocellular carcinoma is essential. Adherence to iron chelation remains the most important modifiable determinant of long-term outcome, emphasising the need for sustained follow-up.

Author Declaration

Conflicts of Interest

There are no conflicts of interest.

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Patient Consent

Written informed consent for publication of this case report, including all clinical details, was obtained directly from the patient prior to her death.

Criteria for Authorship

CUW and APP conceptualised the case report. CUW and SCW conducted the literature review and drafted the initial manuscript, which APP subsequently edited. CUW revised the manuscript. APP supervised and reviewed the revised manuscript. All authors read and approved the final version.

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