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(CASE REPORT)

The burden of survival: Secondary cardiac hemochromatosis as a complication of β-thalassemia major: A case report

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Abstract

Secondary cardiac hemochromatosis, or iron-overload cardiomyopathy (IOC), is the most severe and life-shortening complication of chronic transfusion therapy in β-thalassemia and other transfusion-dependent disorders. What begins as a life-saving intervention gradually becomes a silent threat. Clinical manifestations range from subclinical myocardial dysfunction to advanced heart failure, presenting as dilated or restrictive cardiomyopathy. Cardiac magnetic resonance imaging with T2* mapping is the most sensitive method for assessing myocardial iron burden and guiding management. Although iron chelation therapy remains the cornerstone of treatment, advanced disease may progress to end-stage heart failure, leaving heart transplantation as the final therapeutic option.

We report the case of a young patient with β-thalassemia major who developed secondary multivisceral hemochromatosis with severe cardiac iron overload. Remarkably, cardiomyopathy showed substantial improvement following appropriate chelation therapy, highlighting the importance of early detection and timely intervention to prevent irreversible and potentially fatal iron-related complications.

This case highlights the critical role of early cardiac MRI surveillance and sustained chelation therapy in reversing iron-overload cardiomyopathy and improving long-term outcomes, and preventing additional organ complications that may adversely affect prognosis.

Keywords: Secondary cardiac hemochromatosis; Iron overload cardiomyopathy; β-thalassemia major

1. Introduction

β-thalassemia is a common inherited hemoglobinopathy characterized by reduced or absent β-globin chain synthesis and hemoglobin A production (1). The major form of the disease is severe, manifests during the first year of life, and requires lifelong red blood cell transfusion therapy for survival (2,3). Based on transfusion requirements, β-thalassemia is classified into non–transfusion-dependent thalassemia (NTDT) and transfusion-dependent thalassemia (TDT) (4).

Despite substantial advances in transfusion strategies and iron chelation therapy that have significantly improved survival, cardiac disease remains the leading cause of morbidity and mortality in patients with β-thalassemia major (5). Among cardiovascular complications, iron-overload cardiomyopathy (IOC) is the most devastating. It results primarily from chronic transfusion therapy, which progressively overwhelms iron-handling mechanisms and leads to toxic myocardial iron deposition. Without early detection and effective chelation, IOC may progress relentlessly to heart failure, arrhythmias, and premature death (6)

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2. Case report

2.1. Patient Presentation, Clinical Findings, and Diagnostic Assessment

2.1.1. Patient information

A 25-year-old man, the eldest of six siblings born to non-consanguineous parents—both heterozygous carriers of β-thalassemia—was the only family member affected by β-thalassemia major. He was diagnosed at six months of age and had since required regular red blood cell transfusions.

During childhood, by the age of seven, his clinical course progressively diverged from normal development. He exhibited marked growth retardation and delayed pubertal maturation, along with progressive exertional dyspnea, initially NYHA class II and later progressing to class III, prompting further evaluation.

2.1.2. Clinical findings

On physical examination, vital signs were stable. He showed severe growth impairment (height < −4 SD; weight < −3 SD) and markedly underdeveloped external genitalia consistent with delayed puberty. Cardiac auscultation revealed a holosystolic murmur at the mitral area, with no clinical signs of heart failure. Abdominal examination was unremarkable.

2.1.3. Diagnostic assessment

Laboratory investigations demonstrated severe iron overload, with a ferritin level of 11,955 ng/mL, and confirmed hypogonadotropic hypogonadism, in addition to his known chronic anemia.

The ECG was normal. Fig. 1

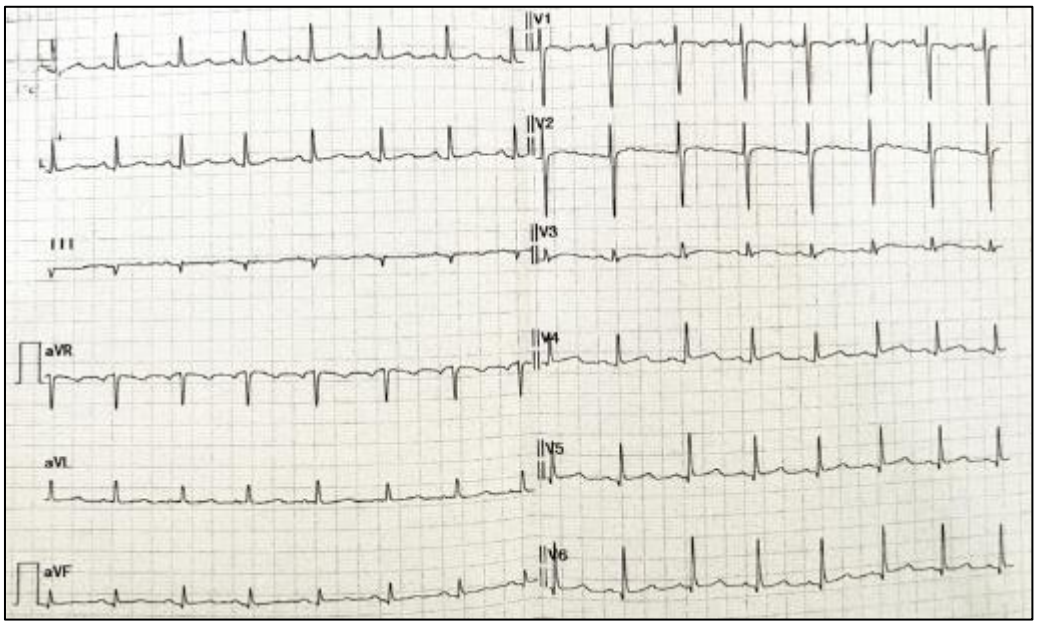

Figure 1 ECG showed a sinus rhythm, with no evidence of chamber hypertrophy or repolarization abnormalities

A transthoracic echocardiogram followed by an urgent cardiac MRI revealed a dilated biventricular cardiomyopathy with global systolic dysfunction, associated with severe myocardial iron overload, with a T2* value < 10 ms, confirming advanced cardiac siderosis. Fig. 2

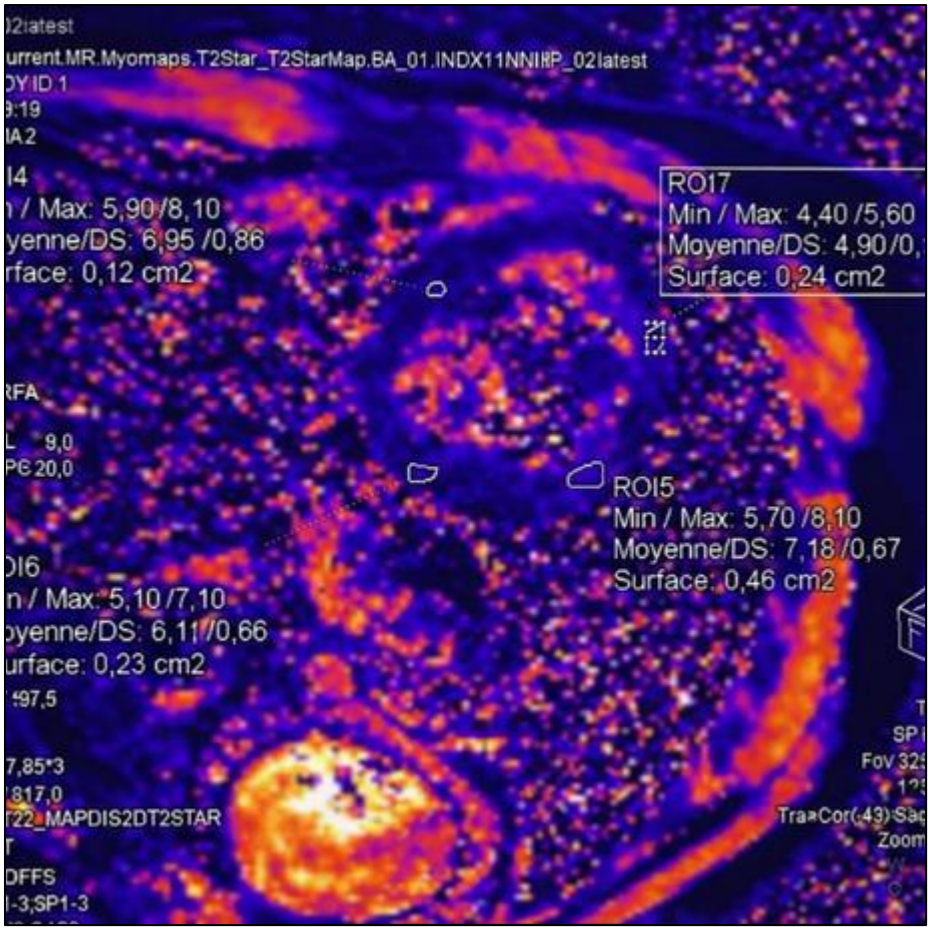

Figure 2 Cardiac MRI T2* sequence reveals marked myocardial iron accumulation, with a T2* value below 10 ms, which is consistent with advanced cardiac siderosis

2.1.4. Diagnosis: Severe cardiac hemochromatosis secondary to chronic transfusion therapy in β-thalassemia major

2.1.5. Therapeutic Interventions

The patient was promptly initiated on intensive iron chelation therapy and standard heart failure management, with close clinical and imaging surveillance.

2.1.6. Follow-up and Outcomes

Over subsequent years, the patient was lost to regular follow-up, although he reported continuing his prescribed therapies. He later returned with profound clinical deterioration, including jaundice with marked skin hyperpigmentation, significant abdominal distension with ascites and collateral venous circulation, and polyuria–polydipsia.

A comprehensive reassessment revealed multivisceral iron overload, predominantly involving the liver and endocrine organs:

- Massive hepatic siderosis leading to advanced cirrhosis, severe portal hypertension, and ultimately metastatic hepatocellular carcinoma with portal and superior mesenteric vein thrombosis.
- Pancreatic and renal cortical iron deposition.
- Insulin-dependent diabetes mellitus secondary to pancreatic involvement.
- Persistent hypogonadotropic hypogonadism.

Remarkably, despite profound hepatic and endocrine deterioration, the patient's cardiac function had completely normalized. Follow-up echocardiography and cardiac MRI demonstrated:

- Full recovery of biventricular dimensions and systolic function.

- Normalization of T2* values, indicating complete resolution of myocardial iron overload.
- No residual cardiomyopathy or valvular abnormalities. Fig. 3

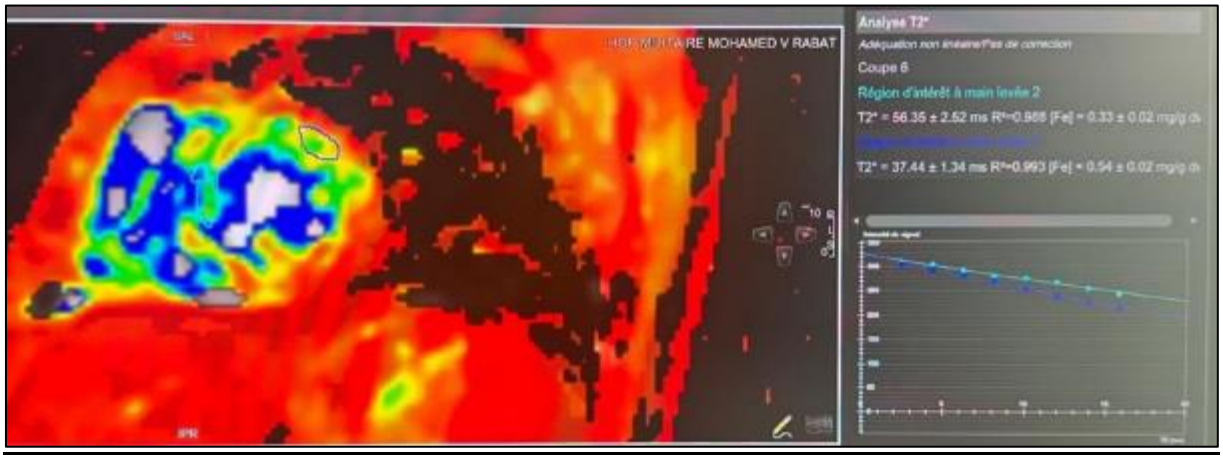

Figure 3 Cardiac MRI T2* sequence performed 18 years later demonstrates normalization of T2 values, indicating complete resolution of myocardial iron overload under long-term iron chelation therapy

This unexpected and dramatic improvement underscores the full reversibility of transfusion-induced cardiac siderosis when chelation therapy is initiated early and maintained adequately

Unfortunately, despite the reversal of cardiac disease, the overall prognosis was determined by irreversible hepatic injury, culminating in cirrhosis, malignant transformation, and vascular invasion.

2.1.7. Patient perspective

The patient reported progressive fatigue and dyspnea that significantly affected daily activities. The diagnosis of iron-related heart disease initially caused considerable concern, particularly regarding long-term prognosis. After initiation of intensive chelation therapy and heart failure management, cardiac function improved markedly, which was confirmed by follow-up imaging. However, despite recovery of cardiac involvement, the patient did not experience significant overall clinical improvement due to advanced hepatic complications that ultimately determined the prognosis. The patient agreed to the publication of this case for educational purposes.

2.1.8. Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

3. Discussion

Iron-overload cardiomyopathy (IOC) results from excessive myocardial iron accumulation and remains a leading cause of mortality in patients receiving chronic transfusion therapy (7). Although iron is essential for normal cellular metabolism, excess iron promotes oxidative stress and tissue injury, leading to multisystem organ involvement affecting not only the heart but also the liver, spleen, pituitary, and pancreas (7).

Under physiological conditions, iron enters cardiomyocytes through transferrin-dependent pathways. During iron overload, transferrin becomes saturated, allowing non–transferrin-bound iron to circulate and enter cardiomyocytes primarily via L-type calcium channels (8). Endosomal pathways may also contribute, with intracellular iron subsequently stored in ferritin and lysosomes (9). Myocardial iron deposition typically begins in the epicardium and progresses toward the endocardium, explaining the relative preservation of systolic function until advanced stages of disease.

Once cellular antioxidant defenses are overwhelmed, iron catalyzes the Fenton reaction, generating highly reactive hydroxyl radicals that induce lipid peroxidation, membrane damage, lysosomal instability, and ultimately cardiomyocyte death. Importantly, myocardial iron accumulation represents a storage rather than an infiltrative process, supporting the potential reversibility of cardiac involvement with effective iron removal (8).

Iron overload alters cardiomyocyte electrophysiology, including reduced action potential amplitude and duration (10). These changes are partly mediated by reduced calcium currents due to the physicochemical similarity between ferrous iron and calcium ions involved in excitation–contraction coupling. Ferrous iron directly interferes with ryanodine-sensitive calcium channels, disrupting calcium handling within the sarcoplasmic reticulum (11). These abnormalities predispose patients to conduction disturbances and potentially life-threatening atrial and ventricular arrhythmias (12).

Clinically, IOC presents with a wide spectrum ranging from asymptomatic myocardial involvement to advanced heart failure. Dyspnea and fatigue are common symptoms, and both ventricles may be affected, with right-sided involvement typically occurring later in the disease course. Two principal phenotypes have been described: a dilated cardiomyopathy with reduced left ventricular ejection fraction, and a restrictive phenotype characterized by diastolic dysfunction, elevated filling pressures, pulmonary hypertension, and right-sided heart failure (13).

Iron deposition may involve the entire cardiac conduction system, particularly the atrioventricular node, leading to atrioventricular block requiring permanent pacing (14). Nonhomogeneous myocardial iron distribution contributes to electrical conduction and repolarization abnormalities, predisposing to atrial and ventricular tachyarrhythmias (15). Paroxysmal atrial fibrillation is the most frequently observed arrhythmia, while ventricular arrhythmias and sudden cardiac death are more common in patients with ventricular dilatation and reduced ejection fraction (16).

Given that cardiac involvement may remain clinically silent for prolonged periods, routine surveillance is essential in patients with β-thalassemia (18). Electrocardiography may provide early clues, as prolonged QRS duration and QT/QTc intervals correlate with myocardial iron burden (19). Although echocardiography lacks pathognomonic features, it remains a valuable tool for longitudinal monitoring of cardiac function and therapeutic response (20–22).

Cardiac magnetic resonance imaging with T2* mapping is currently the only widely available noninvasive technique capable of quantitatively assessing myocardial iron load (23,24). Based on T2* values, patients can be stratified into low-, intermediate-, and high-risk categories for cardiac decompensation, allowing timely intensification of chelation therapy when indicated (23). Early and repeated CMR assessment is therefore essential for guiding management (25).

Iron chelation therapy remains the most effective strategy for reducing cardiac iron burden and improving outcomes in transfusion-dependent patients (26,27). Available chelators include deferoxamine, deferiprone, and deferasirox, each with distinct pharmacologic properties. Combination chelation therapy has demonstrated superior efficacy in reducing myocardial iron and improving cardiac function compared with monotherapy (26). Nevertheless, despite major therapeutic advances, some patients progress to irreversible myocardial damage and end-stage heart failure, in which case heart transplantation may represent the only remaining therapeutic option (8).

This case highlights the unique reversibility of iron-induced cardiomyopathy when myocardial iron overload is detected early and treated aggressively, contrasting with the limited reversibility of iron-related injury in other organs. Continuous surveillance and timely, individualized chelation therapy remain essential to prevent irreversible cardiac damage and premature death (28).

Abbreviations

- **CMR**: Cardiac Magnetic Resonance
- **DFO**: Deferoxamine
- **DFP**: Deferiprone
- **DFX**: Deferasirox
- **ECG**: Electrocardiogram
- **HF**: Heart Failure
- **IOC**: Iron-Overload Cardiomyopathy
- **LVEF**: Left Ventricular Ejection Fraction
- **NTDT**: Non–Transfusion-Dependent Thalassemia
- **NYHA**: New York Heart Association
- **PH**: Pulmonary Hypertension
- **SD**: Standard Deviation
- **T2***: T2-star
- **TDT**: Transfusion-Dependent Thalassemia

4. Conclusion

Iron-overload cardiomyopathy remains one of the most devastating and silent threats in chronically transfused patients. It begins as a slow and silent accumulation of iron and can rapidly progress to electrical instability, ventricular failure, and sudden cardiac death. Yet, despite the severity of this condition, it is also one of the few cardiomyopathies that is truly reversible—if recognized early. Cardiac T2* MRI, together with vigilant ECG and echocardiographic surveillance, offers a crucial window to detect myocardial iron overload before irreversible injury occurs. Chelation therapy—whether with DFO, DFP, DFX, or their combinations—remains the only proven strategy capable of removing intracellular iron, restoring myocardial function, and altering the fatal trajectory of this disease.

Above all, only timely diagnosis and aggressive, individualized chelation can transform a potentially lethal cardiomyopathy into a preventable and treatable condition, averting the catastrophic endpoint of heart transplantation.

Compliance with ethical standards

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Disclosure of Conflict of Interest

The authors declare that they have no conflicts of interest related to this publication.

Statement of Ethical Approval

Ethical approval was not required for this case report according to the institutional policies. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Statement of Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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