Acute cardiac decompensation in a patient with beta-thalassemia and diabetes mellitus following cessation of chelation therapy

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Key Clinical Message
Patients with higher liver iron stores are likely to have a worse cardiac outcome following noncompliance with chelation. Cardiovascular magnetic resonance identifies myocardial siderosis allowing optimization of iron chelation regimes. Diabetes puts thalassemic patients at increased risk of myocardial fibrosis. Dual chelation therapy with deferoxamine and deferiprone offers improved cardiac outcomes.

Keywords
Beta-thalassemia major, chelation, diabetes, heart failure.

Introduction
Beta-thalassemia major is one of the commonest hereditary hemoglobinopathies, characterized by reduced or absent beta-globin chain synthesis [1]. Management is based on regular blood transfusions to suppress ineffective erythropoiesis, with the goal to maintain pretransfusion hemoglobin concentration above 90 g/L [2]. Repeated transfusions may lead to iron overload toxicity affecting the liver, spleen, heart, and endocrine system. Chelation therapy is used to mitigate against these complications. Endocrine complications from repeated transfusion include secondary hypogonadism (prevalence of 35–55%) [3], short stature (31–35%), diabetes mellitus (6–10%), primary hypothyroidism (3–11%), and hypoparathyroidism (1–7%) [3, 4]. Iron deposition cardiomyopathy is the leading cause of morbidity and mortality in patients with thalassemia with consequent congestive cardiac failure accounting for up to 70% of deaths in patients with thalassemia [3]. The coexistence of diabetes in patients with thalassemia leads to an increased risk for myocardial fibrosis [5], while diabetes and hypogonadism are independently associated with myocardial iron loading [6]. In conditions such as hypertrophic and dilated cardiomyopathy, fibrosis increases the risk of dysrhythmias and heart failure. In thalassemia, although the cardiac burden is principally driven by iron loading per se, fibrosis might further increase the risk of cardiac dysfunction.

This case report describes the congruence of multi-organ dysfunction in an individual who had ceased chelation therapy after a history of repeated red-cell transfusions. The management of thalassemia using modern chelation regimes is discussed.

Case
A 37-year-old man of Indian origin presented with 3 weeks of deteriorating exertional dyspnea and dry cough. He had a history of beta-thalassemia major and had been receiving regular transfusion therapy (averaging four units of packed red cells per month) from 3 months of age. Deferoxamine iron chelation therapy had been used although with suboptimal compliance since childhood. He did not drink alcohol. In early childhood, he was diagnosed with primary hypothyroidism and hypogonadotropic hypogonadism. Use of testosterone replacement had also been erratic. At 18 years of age, he was
diagnosed with insulin-deficient (type 3c) diabetes and commenced continuous subcutaneous insulin therapy (CSII), 30 units over 24 h, with stable control. He had recently switched to multidose injection therapy due to subcutaneous edema and coughing resulting in persistent pump giving set failure. His insulin dose on admission was 60 units/day (15 units basal insulin and 15 units prandial insulin with each meal).

On examination, blood pressure was 95/55 mmHg, pulse 100/min (regular rhythm). Body weight was 53 kg and height 1.52 m (BMI 22.9 kg/m²). Fine bibasal pulmonary crepitations and normal heart sounds were evident on auscultation. His jugular venous pressure was 7 cm above the sternal angle, and he had pitting ankle edema. Abdominal examination demonstrated hepatosplenomegaly without ascites.

Hematology and biochemistry results are presented in Table 1. Abdominal ultrasound scan confirmed hepatosplenomegaly plus evidence of increased reflectivity of the liver parenchyma, in keeping with fatty change. ECG was normal sinus rhythm 98/min. A transthoracic echocardiogram showed a severely reduced left ventricular systolic function and mildly reduced right ventricular systolic function. Right ventricular systolic pressure was 29 mmHg. Cardiac MRI demonstrated severe myocardial iron loading with evidence of severe myocardial fibrosis and T2 of 4.5 msec plus bilateral pleural effusions (Fig. 1). Liver MRI revealed moderate-to-severe iron loading with an average liver iron concentration above 43.0 mg/g dry tissue (normal range 0.17–1.8 mg/g) (Fig. 2). The patient was diagnosed with acutely decompensated cardiac failure secondary to cardiac siderosis. He commenced furosemide 80 mg bd, plus iron chelation with continuous deferoxamine infusion 2200 mg over 24 h, and oral deferiprone 1500 mg tds until repeat cardiac MRI and ferriscan. A negative fluid balance of 9 L was achieved during admission. The levothyroxine dose was increased from 50 mcg to 75 mcg od.

A continuous subcutaneous infusion (CSII) of insulin was commenced, and on discharge, his insulin dose was 30 units/day via CSII, with greatly improved control. Subsequent testing has shown C-peptide 69 pmol/L (ref 298–2350) with concomitant plasma glucose 9.9 mmol/L, demonstrating insulin deficiency. Testosterone treatment was introduced following hospital discharge, once cardiac stabilization had been achieved.

The patient remained clinically stable under ongoing hematological review. Six months later, repeat cardiac MRI and ferriscan were performed. The cardiac MRI indicated severe residual iron loading with cardiac T2 at 5.8 msec but the left ventricular function was remarkably improved and now within normal limits. A decrease was noted in average liver iron concentration with a level of 39.2 mg/g dry tissue (normal range 0.17–1.8) on liver MRI.

**Discussion**

The patient’s presentation of lethargy and dyspnoea was considered the cumulative result of cardiac failure, anemia, hypogonadism, and hypothyroidism. His clinical deterioration was compounded by dysglycemia – with

| Table 1. Biochemical and hematological variables in admission. |
|-------------------|-----------------|-----------------|
| Variable          | Result          | Normal range    |
| Hb (g/L)          | 108             | 130–165         |
| Iron (μmol/L)     | 221.7           | 14–30           |
| TIBC (μmol/L)     | 193             | 50–72           |
| Ferritin (mcg/L)  | 41,382          | 20–300          |
| Urea (mmol/L)     | 7.6             | 3.3–6.7         |
| Creatinine (μmol/L) | 54           | 45–120          |
| Calcium (mmol/L)  | 2.35            | 2.15–2.6        |
| Phosphate (mmol/L)| 0.92            | 0.8–1.4         |
| PTH (ng/L)        | 173             | 10–70           |
| Vitamin D (nmol/L)| 43              | Deficiency <30  |
| Bilirubin (μmol/L)| 29              | 3–20            |
| ALP (IU/L)        | 326             | 30–130          |
| AST (IU/L)        | 183             | 10–50           |
| γGT (IU/L)        | 242             | 1–55            |
| TSH (mU/L)        | 23              | 0.3–5.5         |
| Free thyroxine (pmol/L) | 8.3           | 9–25            |
| Testosterone (nmol/L) | <0.7          | 10–30           |

**ALP**, alkaline phosphatase; **AST**, Alanine aminotransferase; **AST**, Aspartate aminotransferase; **γGT**, gamma-glutamyl transferase; **PTH**, parathyroid hormone; **TIBC**, Total iron binding capacity; **TSH**, thyroid stimulating hormone.

Figure 1. Bilateral pleural effusions are demonstrated on axial view of thoracic MRI.

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Overload of the myocardium. T2 was 4.5 msec and therefore represents severe iron.

The rate of heart failure has been shown to increase dramatically below this value. In this case, the T2 was 4.5 msec and therefore represents severe iron overload of the myocardium. Optimal values are >20 msec, and severe impairment is considered when <10 msec because the rate of heart failure has been shown to increase dramatically below this value. In this case, the T2 was 4.5 msec and therefore represents severe iron overload of the myocardium [9–11].

Labile plasma iron (LPI) is a component of nontransferrin bound iron that is capable of participating in redox reactions and may be transported into extrahepatic tissues. After cessation of chelation therapy, LPI quickly recovers to pretreatment levels [12]. LPI exposure increases with liver iron concentration [13] meaning that patients with higher liver iron stores are likely to have a worse cardiac outcome following noncompliance with chelation (as with this case). Data from the UK Thalassemia register [14, 15] show that the mortality from beta-thalassemia has fallen in the past two decades, mainly due to a reduction in deaths from cardiac iron overload. Similarly, the frequency of cardiac siderosis in patients with beta-thalassemia major from North American and UK registries has fallen to 17–26%, down from 60% over 10 years ago [16, 17]. Serum ferritin and liver iron concentration are poor surrogates of iron loading in the heart, and the improvement in mortality has been attributed, in part, to the introduction of cardiovascular magnetic resonance (CMR) to identify myocardial siderosis and the optimization of iron chelation regimes [18].

Currently, there are three available iron chelators: deferoxamine, deferiprone, and deferasirox. Deferiprone has been shown to clear cardiac iron at nearly double the rate of deferoxamine, with improvement in cardiac performance [19]. There appears to be a synergistic effect between deferiprone and deferoxamine: A randomized controlled trial of 65 patients over 12 months showed that deferoxamine reduced myocardial iron and improved ejection fraction with mild–moderate iron overload, when compared to deferoxamine alone [20]. The 2013 American Heart Association (AHA) guidelines state that patients in acute heart failure should be immediately commenced on continuous (uninterrupted) intravenous iron chelation treatment with deferoxamine 50 mg/kg/day. Deferiprone should be introduced as soon as possible at a dose of 75 mg/kg/day (the total dose given in three divided doses) [2, 20–22]. At the present time, data are lacking for the use of deferasirox in acute iron overload cardiomyopathy. The presence of diabetes puts patients with thalassemia at increased risk of myocardial fibrosis. Caution is advised with diuretic treatment during the acute presentation because of the importance of maintaining preload, as patients are at risk of a restrictive ventricular defect [23]. After resolution of decompensated heart failure, treatment may need to continue for several years to remove cardiac iron in thalassemia [10].

Iron deposition is negatively associated with insulin sensitivity and insulin secretion. Patients with thalassemia may have insulin sensitivity reduced by 40%, with a close correlation ($r = -0.70$) with iron status [24]. Oxidative stress induced by iron may be partly responsible. The beta-cell is particularly sensitive to oxygen radicals and this may explain insulinopenia in many patients with beta-thalassemia. In studies (of limited numbers of patients), iron chelation with deferoxamine may improve glucose handling [25, 26].

Hypogonadotropic hypogonadism is the most frequent endocrine complication in patients with iron overload and thalassemia [3]. There is a close association between insulin resistance (IR) and testosterone deficiency [27]. Free and total testosterone levels are inversely correlated with indices of IR such as insulin levels and homeostatic model assessment of insulin resistance (HOMA-IR) [28–30]. In this case report, the patient’s suboptimal testosterone replacement may have further contributed to poor glycemic control [31] and cardiac performance [32].

Primary hypothyroidism classically affects patients with thalassemia from the second decade of life. Hypothyroidism may have an adverse chronotropic and inotropic...
effect on the heart [33]. If hypothyroidism is diagnosed early, intensification of chelation therapy may improve thyroid function even without thyroid hormone replacement [34].

In conclusion, interruptions to chelation therapy may lead to the rapid development of complications, particularly if hepatic iron content is high. Symptomatology may be a result of the simultaneous involvement of multiple organ systems. Dual chelation therapy with deferoxamine and deferiprone offers improved cardiac outcomes.

Conflict of Interest

None declared.

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