

## Case Report

## Secondary Haemochromatosis in a Patient with Thalassaemia Intermedia

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**ABSTRACT:** Haemochromatosis is due to excessive accumulation of iron in tissues and organs impairing their function. The most common haematologic disorders that are subject to an intensive transfusion regimen bringing excess iron in the body are: thalassaemia and myelodysplastic syndrome. The value of serum ferritin in these patients (indicator of iron stores condition) reaches high values. Red cell substitution bringing additional iron intake must be accompanied by administration of chelation therapy in order to prevent haemochromatosis and related complications. We present the case of a patient with thalassaemia intermedia, integumentary secondary haemochromatosis, cirrhosis with haemochromatosis, and secondary diabetes, who died at the age of 33 years because of upper gastrointestinal bleeding due to the rupture of oesophageal varices.

**KEY WORDS:** thalassaemia intermedia, haemochromatosis, cirrhosis, diabetes mellitus

### Introduction

Haemochromatosis is the abnormal accumulation of iron in parenchymal organs, leading to organ toxicity. Secondary or acquired haemochromatosis can be caused by diseases such as thalassaemia or myelodysplastic syndrome, especially if patients have received a large number of blood transfusions, rarely in hepatitis C, alcoholism, chronic liver disease, some types of anaemia, and other illnesses.

### Patient, Methods and Results

Patient B.C. was diagnosed with thalassaemia intermedia at the age of 3 years, by performing haemoglobin electrophoresis which showed a decreased A1 haemoglobin level, and an increase of A2 and foetal haemoglobin level of 45%. At the age of 8 years the patient was splenectomised due to giant splenomegaly, with hypersplenism and compression phenomena.



**Fig.1. Longilin asthenic constitution type, weakness of scapular girdle muscles**

He was given a replacement and chelation iron therapy with intermittent Desferal at the Paediatric Clinic up to the age of 18, when he was guided towards the Clinic of Haematology.

Objective examination: longilina asthenic constitution type (Fig.1), skin hyperpigmentation, ogival palate, dental implant defects, simian hand (Fig.2), weakness of scapular girdle muscles, irregular heart sounds, tachycardia (a.v. 100 beats/min), unorganized extrasystoles, enlargement of abdomen with postoperative scar, caused by giant hepatomegaly occupying the entire abdomen, increased consistency (Fig.3).

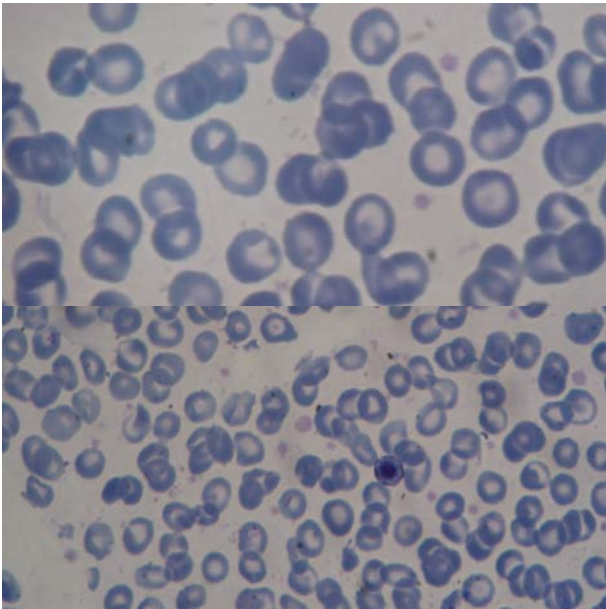


**Fig.2. Simian hand appearance, with hyperpigmentation of the palmar creases**



**Fig.3. Abdomen enlargement caused by giant hepatomegaly occupying the entire abdomen. Postoperative scar (splenectomy)**

Paraclinical testing: ESR 86mm/1h, Hb 5.2g/dl, L 18 200/mm<sup>3</sup>, T 168 000/mm<sup>3</sup>, Mtc 1%, NS 2%, S 43%, Ly 21%, Eo 2%, Mn 6% erythroblasts 25% marked poikilocytosis, erythrocytes that have the appearance of a 'shooting target', Jolly bodies.



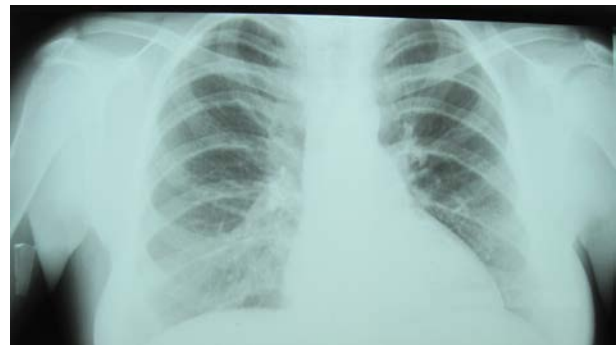
**Fig.4,5. Marked poikilocytosis, with presence of erythrocytes that have the appearance of a 'shooting target', erythroblasts in peripheral blood (a sign of the presence of extramedullary haematopoiesis outbreaks), and appearance of great erythrocyte disorder**

Peripheral blood smear (Fig.4, 5)-microcytes, hypochromia, great erythrocyte disorder, marked poikilocytosis with erythrocytes that have the appearance of a 'shooting target', presence of erythroblasts on smear (a sign of the presence of extramedullary haematopoiesis outbreaks) GPT

145 UI/L, GOT 121 UI/L, FA 345 UI/L, serum protein electrophoresis PT 6.8g/dl, albumins 59%, alpha 1 4%, alpha 2 5.4%, beta 12%, gamma globulins 19.6%, BT 3.2mg/dl, BI 2.1mg/dl, creatinine 0.67mg/dl, blood glucose 376mg/dl, serum iron 279mg/dl, serum ferritin 6 800mg/ml, blood glucose 338mg/dl-245mg/dl-112mg/dl treated with rapid-acting insulin, requiring higher doses to regulate blood glucose values.

Rx heart lung PA (Fig.6) - slightly enlarged heart, there can be seen disseminated haemosiderin deposits on both lung areas.

Echocardiogram - left ventricular ejection fraction (LVEF) 72%, without obvious heart disease. No NMR examination was performed.



**Fig.6. An increased interstitial drawing with the presence of nodules with a diameter of 2-3 mm, due to haemosiderin deposits**

## Discussions

In some patients, noticeably those with thalassemia major, sickle cell disease, myelodysplastic syndrome, aplastic anaemia, hemolytic anaemia, and refractory sideroblastic anaemia, who may become transfusion-dependent and receive excess iron with each transfusion (that the body has no means to excrete), iron gradually accumulates in various tissues, causing morbidity and mortality. Each unit of transfused blood has approximately 250mg of iron. Haemosiderin is an abnormal, insoluble form of iron storage. The human body has no active mechanism for the excretion of iron [1]. Iron homeostasis thus relies on the amount that is absorbed from the small intestine [2]. The ferritin does not circulate in blood but is deposited in tissues and is unavailable when cells need iron. Major organs affected by this surplus iron include the heart, lung, liver, and endocrine glands.

When the plasma iron-binding protein transferrin is oversaturated, as in transfusion-induced iron overload, the excess iron circulates

as relatively free non-transferrin-bound iron (NTBI). This NTBI is rapidly taken up by liver and other tissues. Transferrin-bound iron (TBI) is also taken up by these cells through the hepcidin mechanism, which is increased in such states [3]. It is this excessive iron that damages tissues.

The most common cause of morbidity is cardiomyopathy (30%) that is induced by iron overload [4]. Cardiac involvement in haemochromatosis typically results in congestive cardiomyopathy; a restrictive cardiomyopathy due to haemochromatosis is distinctly rare. The average time for the development of heart failure in transfused, unchelated patients is 10 years [5]. Iron chelation can reverse cardiac changes and improve performance [6]. In the presented patient there were not revealed any echocardiogram changes, LVEF value was preserved without rhythm or management disturbances.

Liver involvement is common in those who undergo long-term transfusions. Early cirrhotic changes can be observed as early as age 7 years in some people with thalassemia [7]. Iron overload has important clinical consequences in patients with thalassemia intermedia. Iron accumulation primarily occurs in hepatocytes can predispose to liver fibrosis and cirrhosis, and potentially hepato-cellular carcinoma [8,9,10]. The presented patient developed cirrhosis with haemochromatosis after 22 years of evolution of the disease, vascularly modified after another six years of evolution, with the presence of oesophageal varices at endoscopic examination, the hepatic portal vein echography 16mm. Patient death occurred in upper gastrointestinal bleeding due to the rupture of oesophageal varices, followed by irreversible hemorrhagic shock and cardiopulmonary arrest. If NMR is available, cardiac iron levels and cardiac function should also be measured by NMR yearly and every 6 months in patients who have intensive chelation therapy [11]. How iron overload contributes to vascular morbidity in thalassemia intermedia is unclear. More frequent vascular disorders are atherosclerosis, microangiopathic haemolytic anemia, vasculitis [12]. T2-NMR value is inversely proportional to the degree of haemochromatosis. T2<20ms indicates a high iron load and is associated with low ejection fraction. By performing NMR there can be identified patients with high risk of deterioration of cardiac function before the onset

of clinical picture and the intensifying of chelation therapy [13,14].

Pulmonary hypertension is another complication that occurs with a relatively high frequency in patients with thalassemia intermedia, and several factors were involved in its pathogenesis: chronic anemia and hypoxia, iron overload, splenectomy, hypercoagulability, microthrombotic disease [15,16,17]. More than one third of transfusion-dependent patients with  $\beta$ -thalassemia major exhibit a restrictive lung function defect, which may improve with chelation therapy [18].

Although heart-lung radiography revealed the presence of haemosiderin deposits, ventilatory function was not impaired, ventilatory tests being within normal limits.

There was also reported an association between elevated liver iron concentration and the occurrence of endocrinopathy, bone disease and vascular morbidity [18]. Up to 14% may develop insulin-dependent diabetes mellitus (IDDM) [19]. Our patient developed secondary diabetes at the age of 28 years, requiring therapy with high doses of insulin in order to correct blood glucose values.

Failure of puberty was the major clinical endocrine problem, and it was present in 51% of boys and 47% of girls, all older than 15 years. Secondary amenorrhea was recorded in 23% of the patients with  $\beta$ -thalassemia major [20].

All patients who are transfusion dependent require careful monitoring of their iron stores. It is advisable to measure ferritin levels at least every 3 months and iron studies every year. Liver iron levels should be measured annually (either by biopsy or noninvasively) and every 3-6 months in patients who undergo intensive chelation for heart failure.

## Conclusions

The case presented in this paper is that of a patient with thalassemia intermedia, integumentary secondary haemochromatosis, cirrhosis with haemochromatosis, and secondary diabetes, who died at the age of 33 years because of upper gastrointestinal bleeding due to the rupture of oesophageal varices. Complications caused by secondary haemochromatosis appeared after the age of 20 years. Chelation therapy with Deferoxamine was intermittently used because it was not consistently available.

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