



Heart Failure Due to Secondary Haemochromatosis in a Case of Beta Thalassemia Major: A Rare Case Presentation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Hemochromatosis is defined as abnormal accumulation of iron in various organs of the body such as liver, pancreas, skin, joints, heart due to raised gut absorption of iron due to low hepcidin yield. Hemochromatosis is secondary to thalassemia major in this case. In the absence of other concurrent processes, cardiac hemochromatosis is identified as the presence of cardiac dysfunction owing to increased iron accumulation in the heart leading to heart failure.

Unique: Cardiac involvement in secondary hemochromatosis due to thalassemia major.

Take Away lesson: Regular monitoring of serum iron, ferritin, echocardiographic monitoring among thalassemia major patients is essential. Despite the fact that heart failure due to iron overload could be fatal, early diagnosis and intervention could prevent and treat the disease.

Keywords: Hemochromatosis; heart failure; iron overload; thalassemia.

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1. INTRODUCTION

Haemochromatosis can be acquired due to thalassemia major, sideroblastic anemia, chronic hemolytic anemia, parenteral and dietary iron overload and chronic liver disease conditions such as hepatitis C, alcoholic cirrhosis, non-alcoholic steato-hepatitis [1]. Common presentations are bronze skin, joint pains, diabetes mellitus, dilated or restrictive cardiomyopathy and cirrhotic liver. Although rare, myocardial iron deposition can lead to dilated cardiomyopathy which can cause heart failure.

The thalassemias are inherited disorders of alpha or beta globin biosynthesis. The most common thalassemia condition is beta-thalassemia, which has become a global clinical concern as the world's population has grown. The global yearly incidence of symptomatic persons is approximated to be 1 in 100,000, with 1 in 10,000 persons living in the European Union. Approximately 1.5% of the people in the world has thalassemia. In Southeast Asia, the prevalence and carrier rates of -thalassemia are relatively high. In the Mediterranean, Asian, India, Southern China, and South America, beta thalassemia is common. According to recent surveys, between 300,000 and 400,000 newborns are born each year with a significant haemoglobin disease (23,000 with -thalassemia major), with up to 90% of these births taking place in underdeveloped countries [2]. In India, the total prevalence of thalassemia is 3-4 percent, with an estimated 10,000-12,000 infants born with -thalassemia major annually. According to a recent research in India, the overall prevalence of the thalassemia trait was 2.78 percent, ranging from 1.48 percent to 3.64 percent in various states [3].

Patients affected with thalassemia major require blood transfusions throughout the life. Intensive blood transfusions cause deposition of iron in various organs.

According to Metaprop, the overall prevalence of cardiac iron overload/myocardial siderosis (T2* 20 ms) and cardiac problems in thalassemia major patients was 25% (95 percent CI 22–28%) and 42 percent (95 percent CI 37–46%), respectively, in thalassemia major patients globally [4].

In spite of astounding medical care, heart disease lasts as predominant cause of mortality. Nevertheless age of onset of heart failure

prolonged decade later. The typical age of onset of heart failure in the early 1960s was 16 years.

Prevalence of heart failure in patients with early medical intervention in average age group of 27 years was 2.5% indicating delayed onset [5]. Uniqueness about the case is cardiac involvement in hemochromatosis which is usually rare.

2. CASE REPORT

A 32-year old man came with complaints of generalised weakness, distension of abdomen, yellowish discoloration of eyes (as shown in Image 1), joint pains involving knee, ankle, wrist, elbow, metacarpophalangeal joints (as shown in Image 3) since 3 years and bilateral lower limb swelling extending upto one third of leg; pitting type of edema since 1 year, patient has history of easy fatiguability; patient is known case of thalassemia major diagnosed at 6 months of life in view of generalised weakness and easy fatiguability for which he was taken to private practitioner where low haemoglobin was detected and thalassemia major was diagnosed by Hb electrophoresis and HPLC. Since then patient had received multiple blood transfusions, once a month till date. Patient had undergone splenectomy in 2010 followed by pneumococcal, hemophilus and meningococcal vaccination, patient was diagnosed type I diabetes mellitus 1 year back and was treated with insulin in periodic check-up. Patient has no significant similar family history in first degree relatives. No psychosocial, altered behaviour. On physical examination, patient was tachypneic with blood pressure of 90/60 mmHg and irregular heart rate of 110 beats per minute. He has pallor, icterus, raised jugular venous pressure (as shown in Image 2), and pitting edema in both lower limbs (as shown in Image 4), bilateral pulmonary crackles, systolic murmur heard at the apex, ascites, hepatomegaly. On examination patient has bronze skin pigmentation (as shown in Image 1), dilated veins over abdomen, loss of body hair.

ECG showed atrial flutter with AV dissociation. Two dimensional echocardiogram showed mild contractility LVEF 50%, hypokinetic IVS(flattening), biatrial enlargement(dilated left atrium 42mm), D shaped left ventricle (as shown in Image 5), mild systolic dysfunction of right ventricle, mild mitral regurgitation, severe primary tricuspid regurgitation with non coaptation of leaflets, floppy tricuspid valve, grade III diastolic dysfunction, minimal pericardial effusion,

congested IVC with no respiratory collapse, mean pulmonary artery pressure 50mmHg (severe pulmonary hypertension) (as shown in

Image 6). Chest X-ray showed pulmonary congestion with bilateral pleural effusion.



Image 1. Showing yellowish discoloration of sclera and bronze skin pigmentation



Image 2. Showing raised jugular venous pulsation



Image 3. Showing swelling of metacarpophalangeal joints suggestive of arthritis



Image 4. Showing pitting type of pedal edema

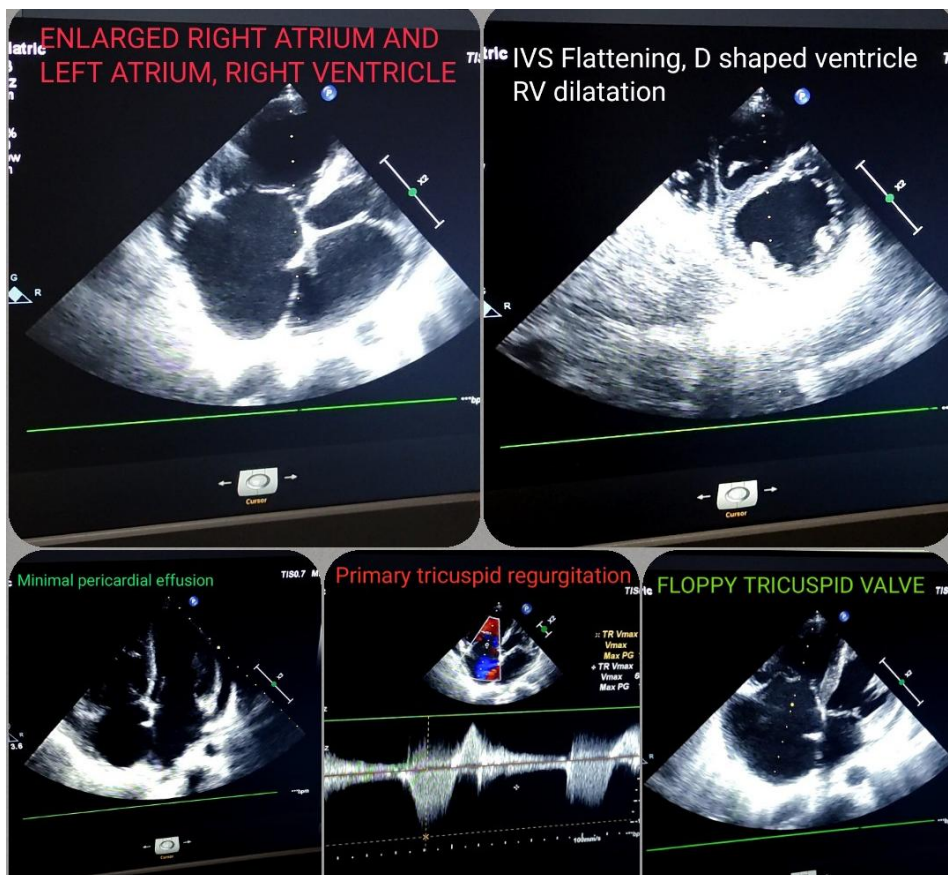


Image 5. Two dimensional echocardiography showing biatrial enlargement and right ventricle, flattened IVS, minimal pericardial effusion, floppy tricuspid valve, primary tricuspid regurgitation

Laboratory findings reveal haemoglobin-7.1 gm/dl, Total leukocyte count-9800 cells/cumm, Red blood cells-2.33 lakhs, platelets-2.79 lakhs, urea 34 mg/dl, creatinine 0.4 mg/dl, sodium 130 mmol/lit, potassium 5 mmol/lit, total bilirubin 2.3 mg/dl, conjugated 1 mg/dl, unconjugated 1.3

mg/dl, SGPT 42 U/L, SGOT 65 U/L, Alkaline phosphatase 108 U/L, raised serum ferritin 8890 ng/ml, raised serum iron 440 microgram/dl.

Magnetic resonance imaging by the T2 method was suggestive of hepatic iron deposition. Liver

MRI shows a time of T2 5.6ms(Normal >11.4), R2= 177.5Hz(Normal <88), LIC(Liver iron concentration)- 4.52mg/g(Normal <2). Liver is moderately enlarged measuring 16.8cm in craniocaudal direction. It is diffusely hypointense as compared to paraspinal muscles on T2WI, T1WI and PD images suggesting severe iron overload. The established treatment based on use of oral tablet Desirox 1000 mg once a day and parenteral iron chelators injectable Desferrioxamine 20mg/kg/day for 5 days as well as cardiac glycosides tab Digoxin 0.25mg once a day for 5 days in a week, Spironolactone and Furosemide therapy, conventional beta-blocker such as Metoprolol 25mg once a day, ACE inhibitor such as Ramipril 2.5mg once a day, bile acid sequestrants.

3. DISCUSSION

Hemochromatosis is a disease characterized by an increase in mucosal iron absorption from the gut than body requirements. Acquired iron from secondary sources accumulates in various organs of the body. Although cardiac involvement is rare it can cause arrhythmias and either restrictive or dilated cardiomyopathy [6]. Secondary hemochromatosis occurs due to ineffective erythropoiesis causing haemoglobin synthesis defect in thalassemia major patients ought to repeated blood transfusions. In this case thalassemia major can be the cause of secondary haemochromatosis.

Chronic RBC infusions increase oxygen supply while masking inefficient erythropoiesis, but the unavoidable after effects, especially iron excess became lethal by the age of 30 [7]. Iron excess and tissue damage happen from administering blood and increased absorption of iron. Iron deposition in heart causes tissue damage leading to biventricular, dilated cardiomyopathy causing congestive cardiac failure remains the leading cause of mortality. Pulmonary hypertension and restrictive cardiomyopathy are other possible manifestations. In beta-thalassemia, pulmonary arterial hypertension is the leading cause of heart failure [8].

The pathophysiology of iron-overload cardiomyopathy is composite. While total body iron levels are around 3 mg/dl, thalassemia patients plasma iron turnover can be 10 to 15 times higher than normal due to the inefficient erythropoiesis of an erythroid marrow that has grown in huge proportions [9]. When the iron binding capability of transferrin is surpassed in

iron overload conditions, proportion of unbound iron increases.

Free iron that is not coupled to transferrin enters cells in the form of ferrous ions through different channels and adept in creating hazardous reactive oxygen species as cytosolic ferritin buffers it, then it is degraded to hemosiderin and stored in lysosomes.

Inefficacious buffering system ends up raising cytotoxic labile iron levels causing oxidative damage to cell membranes, ion channels, and nucleic acids, eventually leading to cardiac failure and arrhythmias. Labile iron species have the ability to alter gene expression, induce apoptosis, and promote fibrosis.

Fatigue, lethargy, and arthralgia are among the most prevalent symptoms in haemochromatosis. In cases of significant iron overload, individuals may present with organ specific symptoms such as breathlessness, bilateral lower limb swelling, abdominal distension, yellowish discolouration of sclera and body, skin pigmentation, arthralgia, raised jugular venous pressure, respiratory distress, bilateral crepitations on auscultation [10].

According to echocardiographic findings myocardial iron deposition in certain thalassaemia major patients may have a direct impact on left ventricular contractility whereas in others it has the potential to produce left ventricular myocardial restriction as well as pulmonary hypertension and right-sided heart failure.

Complete heart block was estimated to be as high as 40% in persons over the age of 15 years prior to the widespread use of chelation treatment. There appears to be significant incidence up to 40% of atrial fibrillation in elderly thalassemia patients [11]. Frequency of pulmonary hypertension in thalassemia patient varies.

Possible arrhythmias are premature supraventricular beats, paroxysmal tachyarrhythmias, atrial flutter, atrial fibrillation, and varying degrees of atrioventricular block. Supraventricular arrhythmias and first-degree atrioventricular blocks occur as disease extends into atrium.

Cardiac Magnetic resonance imaging (CMR) relaxation has been recently implemented as the

gold standard for direct evaluation and quantification of myocardial iron [12].

In Cardiac hemochromatosis, Iron Chelation therapy plays a crucial role in the prediction of prognosis and decreasing the risk of mortality by diminishing the occurrence of heart failure and by preventing cardiomyopathy.

Methods for predicting heart failure are estimated by serum ferritin >2500 µg/L, and liver iron concentration >15mg/kg dry weight. Unfortunately if subjects are not being detected on time for intervention, heart failure became outrageous leading to an increase in mortality rate [13].

Phlebotomy and chelating drugs are the first line of management and diuretics, cardiac glycosides, beta blockers, ACE inhibitors are helpful in treating congestive cardiac failure.

In this case, patient was diagnosed as heart failure due to secondary hemochromatosis based on raised serum iron levels, serum ferritin levels, clinical examination and echocardiographic findings. As patient has symptoms and signs of heart failure, hemochromatosis has been suspected as a root cause of involvement of cardiac tissues. Quantification of iron deposition, echocardiographic findings, biochemical parameters are helpful in assessing severity in all grounds. Haemochromatosis can be managed conservatively with oral and a parenteral chelation therapy. Poor prognosis is due to congestive cardiac failure and refractory arrhythmias. Early initiation of iron chelation therapy has been reported to improve the outcome.

4. CONCLUSION

Even though cardiac complications are less common, it is the main cause of morbidity and mortality in secondary hemochromatosis. Evaluating the high risk conditions causing hemochromatosis and predicting the probability of cardiac involvement due to hemochromatosis by screening methods and early intervention by chelation therapy reduces disease progression.

Take Away Lesson: Regular monitoring of biochemical parameters such as serum iron, serum ferritin, transferrin saturation, echocardiographic monitoring in patients with secondary hemochromatosis due to thalassemia major, who are receiving regular blood

transfusions. As heart failure is curable, early suspicion and active intervention can modify the disease course and outcome.

CONSENT

Informed consent was taken from the patient.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Iglesias, Cassia Pereira Kessler, Duarte, Paulo Vinicios Falcão, Miranda, Jacqueline Sampaio dos Santos, Machado, Luana da Graça, Andrade, Caio Ribeiro Alves. Hemochromatosis: Reversible Cause of Heart Failure. *International Journal of Cardiovascular Sciences*. 2018;31(3):308-311.
2. Hamoudi A, TAQI V. Iron Overload Cardiomyopathy due to Non-Classical Hereditary Hemochromatosis. *Journal of Medical Cases, North America*; 2019. Available: <https://doi.org/10.14740/jmc3240>
3. Gujja P, Rosing DR, Tripodi DJ, Shizukuda Y. Iron overload cardiomyopathy: Better understanding of an increasing disorder. *J Am Coll Cardiol*. 2010;56(13):1001-1012. DOI: 10.1016/j.jacc.2010.03.083 Available: <https://doi.org/10.1016/j.jacc.2010.03.083>
4. Sudmantaitė V, Čelutkienė J, Glaveckaitė S, Katkus R. Difficult diagnosis of cardiac haemochromatosis: A case report. *Eur Heart J Case Rep*. 2020;4(1):1-6. DOI: 10.1093/ehjcr/ytaa012 PMID: 32128489; PMCID: PMC7047056. Available: <https://doi.org/10.1093/ehjcr/ytaa012>
5. Gulati V, Harikrishnan P, Palaniswamy C, Aronow WS, Jain D, Frishman WH. Cardiac involvement in hemochromatosis. *Cardiol Rev*. 2014;22(2):56-68. DOI: 10.1097/CRD.0b013e3182a67805 Available: <https://doi.org/10.1097/CRD.0b013e3182a67805>

6. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. *Circulation*. 2011;124(20):2253-63.
DOI: 10.1161/CIRCULATIONAHA.111.050773
<https://doi.org/10.1161/CIRCULATIONAHA.111.050773>
7. Hahalis G, Alexopoulos D, Kremastinos DT, Zoumbos NC. Heart failure in beta-thalassemia syndromes: A decade of progress. *Am J Med*. 2005;118(9):957-967. Available:<https://doi.org/10.1016/j.amjmed.2005.02.021>
8. Fitchett DH, Coltart DJ, Littler WA, Leyland MJ, Trueman T, Gozzard DI, Peters TJ. Cardiac involvement in secondary haemochromatosis: A catheter biopsy study and analysis of myocardium. *Cardiovasc Res*. 1980;14(12):719-724. Available:<https://doi.org/10.1093/cvr/14.12.719>
9. Schreiber AW. Hemochromatosis and the heart. *Ann Intern Med*. 1957;47:1015-21. [PubMed: 13470725] Available:<https://doi.org/10.7326/0003-4819-47-5-1015>
10. Cutler DJ, Isner JM, Bracey AW, et al. Hemochromatosis heart disease: An unemphasized cause of potentially reversible restrictive cardiomyopathy. *Am J Med*. 1980; 69:923-8. [PubMed: 7446557] Available:[https://doi.org/10.1016/S0002-9343\(80\)80020-9](https://doi.org/10.1016/S0002-9343(80)80020-9)
11. Carpenter JP, Grasso AE, Porter JB, Shah F, Dooley J, Pennell DJ. On myocardial siderosis and left ventricular dysfunction in hemochromatosis. *J Cardiovasc Magn Reson* 2013;15:24 Available:<https://doi.org/10.1186/1532-429X-15-24>
12. Kirk P, Roughton M, Porter JB, Walker JM, Tanner MA, Patel J, Wu D, Taylor J, Westwood MA, Anderson LJ, Pennell DJ. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. *Circulation* 2009;120:1961-1968. Available:<https://doi.org/10.1161/CIRCULATIONAHA.109.874487>
13. Tauchenova L, Krizova B, Kubanek M, Frankova S, Melenovsky V, Tintera J. Successful treatment of iron-overload cardiomyopathy in hereditary hemochromatosis with deferoxamine and deferiprone: a case report. *Can J Cardiol*. 2016;32:1574.e1-1574.e3 Available:<https://doi.org/10.1016/j.cjca.2016.07.589>

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