

## Anemia Heart Disease in a Patient with Suspected Non-Transfusion Dependent Thalassemia, a Case Report

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### ABSTRACT

*Thalassemia is a genetic blood disorder characterized by reduced production of hemoglobin and poses a significant risk for the development of anemia and subsequent heart disease. Understanding the mechanism linking thalassemia, anemia, and heart disease, highlighting the impact on cardiac function and the associated clinical implications. This interrelationship is crucial for developing targeted management strategies aimed at mitigating the cardiovascular complications of thalassemia-related anemia, thereby improving patient outcomes and quality of life. Case Report. A female, 22 years old, came to the emergency room at Waikabubak General Hospital with complaints of weakness and pallor that had worsened since 1 week ago. Patients feel shortness of breath after heavy work, which improves after resting, nausea, and heart pounding. The patient has some previous medical history and familial history, Physical examination showed facies cooley appearance, short stature with anemic conjunctiva, icteric sclera, and hepatosplenomegaly. Laboratories showed microcytic hypochromic anemia with elevated liver enzymes. Peripheral blood smear showed microcytic anemia with anisocytosis and poikilocytosis with target cells. CXR showed cardiomegaly and USG showed hepatosplenomegaly. Echocardiography showed LV eccentric hypertrophy, LA dilatation, mild AR, mild MR, mild TR with a low probability of pulmonary hypertension, normal systolic function, grade I LV diastolic dysfunction, and ejection fraction 55,2%. This patient was treated with omeprazole injection, blood transfusion, oxygen supplementation, oral lisinopril, and bisoprolol. Over two weeks showed improvement in symptoms and laboratory. Discussion. The diagnosis is made from anamnesis, physical examination, and limited supporting examination. Determining the exact diagnosis, and management of the underlying disease and complication based on patient symptoms and simple laboratory results. Conclusion. Cardiac involvement in thalassemia is a major complication. Management of complications is difficult in limited resources facilities. Education and pre-marital screening are required to reduce the incidence of underlying disease.*

**KEYWORDS** *Thalassemia, Cardiac Complication, Limited Access*

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## INTRODUCTION

Anemia is a reduction in the proportion of red blood cells and is defined by the World Health Organization as a Hb concentration  $< 13.0$  g/dL in men and  $< 12.0$  g/dL in women. Symptoms of anemia usually include the following: weakness, tiredness, lethargy, restless legs, shortness of breath (especially on exertion), chest pain, and reduced exercise tolerance. Most patients experience some symptoms related to anemia when the hemoglobin drops below 7.0 g/dL (Lasocki et al., 2020).

The prevalence of anemia varies widely, ranging from 14% to 56% in outpatient registries to 14% to 61% in hospitalized patients. It is unequivocal that anemia is prevalent in patients with heart failure. Threshold hemoglobin level at which anemia treatment should be initiated is even more complex in every varies (Shah & Agarwal, 2013).

Thalassemia is one of the common hereditary disorders of the developing world, and it is associated with severe anemia and transfusion dependence. Inherited through an autosomal recessive pathway, point mutations and deletions on the genes that code globin chains cause decreased hemoglobin production. The necessity for lifelong treatment, the prevention of complications, and premature deaths in many patients make these disorders a significant health burden requiring public health planning and policy making (Aliyeva et al., 2018; Angastiniotis & Lobitz, 2019).

In the physiological state, the hemoglobin molecule is a heterotetramer consisting of two  $\alpha$  and two non- $\alpha$  globin chains, each carrying a heme molecule with a central iron. The non- $\alpha$  globin chains can be  $\beta$  chains which coupled with  $\alpha$  chains form adult hemoglobin (HbA),  $\alpha$  and  $\delta$  form a minor fraction of adult hemoglobin (HbA<sub>2</sub>), and  $\alpha$  and  $\gamma$  chains form the fetal hemoglobin (HbF). If  $\alpha$  globin chains are not produced in adequate amounts there will be an accumulation of  $\beta$  globin chains ( $\alpha$ -thalassemia); if  $\beta$  globin chains are inadequately produced then  $\alpha$  globin chains will accumulate ( $\beta$ -thalassemia).

Approximately 5% of the world population are carriers of hemoglobinopathies, and 2,9% are of thalassemia. Globally, 300.000 – 400.000 babies are born each year with Hb disorders. Thalassemia is mainly a disease of the developing world, presenting high incidence in the Mediterranean area, the Middle East, Transcaucasia, the Indian subcontinent, and Southeast Asia. Indonesia is located along the ‘Thalassemia Belt’. Around 3-10% of the population carry  $\beta$ -thalassemia and 2,6-11% of the population carry  $\alpha$ -thalassemia (Wahidiyat et al., 2022).

Cardiovascular disease remains the major complication and cause of death in both transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) such as  $\beta$ -thalassemia intermedia and  $\alpha$ -thalassemia with a prevalence of 71% (Akiki et al., 2023).

## RESEARCH METHOD

### Case Report

A female, 22 years old, came to the emergency room at Waikabubak General Hospital with complaints of weakness and pallor that had worsened since 1 week ago. Patients feel shortness of breath, especially after heavy work, which improves after resting. Other complaints include nausea and feeling heart pounding. The patient has no history of taking medication for 6 months. Based on information from her parents, this patient has often been to the hospital for the same complaint and has had blood transfusions since she was 6 years old. History of previous transfusions at age 9 years, 13 years, 18 years. The patient's younger sibling had the same symptoms as the patient and was transfused more frequently every 1-2 years.

Physical examination of the general state showed she was underbuilt, with short stature (height 140cm, weight 34kg, BMI 17,3 kg/m<sup>2</sup>), blood pressure of 90/60 mmHg with tachycardia (rate 120 beats/min). Head and neck examination showed anemic conjunctiva and icteric sclera. Abdomen examination showed hepatomegaly (liver palpable 3 fingers below costal arch) and splenomegaly (Schuffner 3/8). Laboratory showed anemia (Hb 4.9), hypochromic microcytic (MCV 69, MCH 21), and elevated liver function test (SGOT 150, SGPT 60, direct bilirubin 1,27, total bilirubin 3.29). Peripheral blood smear showed microcytic anemia with anisocytosis and poikilocytosis with target cells. HBsAg and HIV were undetected in this patient. CXR showed cardiomegaly, and USG showed hepatomegaly and splenomegaly. Echocardiography showed LV eccentric hypertrophy, LA dilatation, mild AR, mild MR, mild TR with a low probability of pulmonary hypertension, normal LV & RV systolic function, grade I LV diastolic dysfunction, and ejection fraction 55,2%. This patient was treated with 2x 40mg omeprazole injection, blood transfusion 1 bag/ day, oxygen supplementation 3lpm, oral Lisinopril 2,5mg/day, and oral bisoprolol 2,5mg/day.

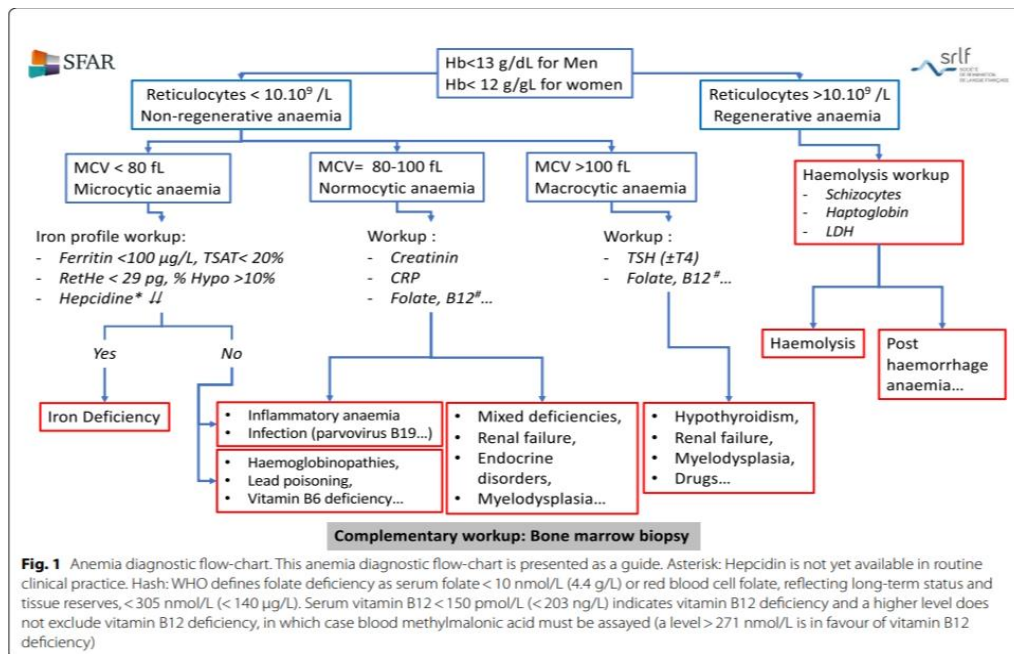
## RESULT AND DISCUSSION

Thalassemia is one of the common hereditary disorders in the developing world. Clinical manifestation in thalassemia varies depending on the type and severity. The following findings can be pallor skin, ulceration, jaundice, deformed facial and other skeletal bones, arrhythmias or heart failure, hepatosplenomegaly, slow growth rate, and endocrinopathies (Bajwa & Basit, 2022).

In this case, we found patient's complaint of weakness and pallor had worsened since 1 week before she came to the hospital, with shortness of breath, nausea, and palpitation. The patient has the same history with these symptoms previously and a familial history with another sibling. On physical examination, we found facies cooley appearance, short stature, underbuilt (height 140cm, weight 34kg, BMI 17,3 kg/m<sup>2</sup>), anemic conjunctiva, sclera icteric, and hepatosplenomegaly. From this anamnesis and physical examination finding, we suggest that the patient has a chronic anemia state due to suspected thalassemia

Several laboratory tests have been developed to screen and diagnose thalassemia. Complete blood count (CBC) showing microcytic hypochromic anemia (MCV <80). Peripheral blood smear showing microcytic hypochromic anemia with

target cells, teardrops, cells with basophilic stipplings, and variation in size and shape (anisocytosis and poikilocytosis). Iron Studies show normal or slightly increased ferritin thalassemia. Transferrin levels are almost normal in thalassemia as compared to iron deficiency anemia. Hemoglobin analysis is most widely used in electrophoresis and high-performance liquid chromatography. It can quantify the number of various hemoglobins, which help in diagnosis (Khan & Rehman, 2022).



**Fig. 1** Anemia diagnostic flow-chart. This anemia diagnostic flow-chart is presented as a guide. Asterisk: Hepcidin is not yet available in routine clinical practice. Hash: WHO defines folate deficiency as serum folate < 10 nmol/L (4.4 µg/L) or red blood cell folate, reflecting long-term status and tissue reserves, < 305 nmol/L (< 140 µg/L). Serum vitamin B12 < 150 pmol/L (< 203 ng/L) indicates vitamin B12 deficiency and a higher level does not exclude vitamin B12 deficiency, in which case blood methylmalonic acid must be assayed (a level > 271 nmol/L is in favour of vitamin B12 deficiency)

Hemoglobinopathy	Red blood cell indices	Hb patterns
β-Thalassemia carrier	↓ MCV, ↓ MCH, ↑ RBC	↑ HbA <sub>2</sub>
β-Thalassemia major/intermedia	↓ Hb	↑ HbF
α <sup>-</sup> -Thalassemia carrier	Normal	Normal
α <sup>o</sup> -Thalassemia carrier	↓ MCV, ↓ MCH	Normal or low HbA <sub>2</sub>
HbH disease	↓ MCV, ↓ MCH	3%–30% HbH
δβ-Thalassemia carrier	↓ MCV, ↓ MCH	Normal or low HbA <sub>2</sub> , ↑ HbF
Hb Lepore	↓ MCV, ↓ MCH	Low HbA <sub>2</sub> , mildly increased HbF, and 5%–15% abnormal Hb fraction
HbS carrier	Normal	35%–40% HbS
HbS homozygote	↓ Hb, normal MCV & MCH	5%–10% HbF, 75%–95% HbS
HbS/β-thalassemia	↓ Hb, ↓ MCV, ↓ MCH	5%–10% HbF, 65%–95% HbS
HbS/δβ-thalassemia	↓ MCV, ↓ MCH	25%–35% HbF, 65%–75% HbS
HbE carrier	Normal	25%–30% HbE
HbE homozygote	↓ MCV, ↓ MCH	5%–15% HbF, 85%–95% HbE
HbE/β-thalassemia	↓ Hb	40%–60% HbF, 40%–60% HbE

**Figure 2.** Diagnostic parameters of the commonest hemoglobinopathies.

In this case, the laboratory showed anemia (Hb 4.9), hypochromic microcytic (MCV 69, MCH 21), and elevated liver function test (SGOT 150, SGPT 60, direct bilirubin 1,27, total bilirubin 3.29). Peripheral blood smear showed microcytic anemia with anisocytosis and poikilocytosis with target cells. HBsAg and HIV were undetected in this patient. Although CBC and peripheral blood smear suggest

thalassemia, we can't make a definite diagnosis due to a lack of other laboratory such as iron load, ferritin, and Hb analysis (HPLC).

Elevated liver enzyme found in patients with high ferritin levels, due to liver injury caused by iron overload (Sarkar et al., 2020). We can't prove this due to a lack of data.

Thalassemia treatment depends on the type and severity. Blood transfusion to maintain Hb at around 10mg/dl to give the patient well-being and also to keep a check on erythropoiesis and suppress extramedullary hematopoiesis. Chelation therapy is due to chronic transfusions and iron deposition in various organs of the body. Splenectomy is the usual recommendation when the annual transfusion requirement is more than 200-220 ml RBCs/kg/year with a hematocrit value of 70%. Cholecystectomy in patients who develop cholelithiasis due to increased Hb breakdown and bilirubin deposition in the gallbladder (Cappellini et al., 2013).

$\alpha$ -Thalassemia hydrops fetalis	Leads to death in utero in most cases
Transfusion-dependent ( $\beta$ ) thalassemia	Leads to death in early infancy unless treated
Non transfusion-dependent thalassemia	Occasional blood transfusions required (may become transfusion-dependent in later life)
Thalassemia minor	Mostly heterozygotes for thalassemia genes (carriers), but may include some homozygotes/compound heterozygotes for very mild $\beta$ -thalassemia mutations and HbE

**Figure 3.** Thalassemia groupings according to clinical severity

In this case, a history of blood transfusion is done approximately every 4-5 years and starts from 6 years old. Clinically patients belong to non transfusion-dependent thalassemia group. Chelation therapy is difficult because it is unavailable in the area, splenectomy and cholecystectomy are not done because there is no indication yet.

The incidence of cardiovascular disease in TDT patients due to iron accumulation from recurrent blood transfusions. However, in the case of NTDT, excess iron increased even in the absence of regular transfusions as a response to ineffective erythropoiesis and hepcidin suppression, which lead to secondary iron overload caused by increased iron absorption in the gut. Complications in these NTDTs appear later in life, mostly in the second and third decades (Aessopos et al., 2007).

The other main pathophysiology of cardiac dysfunctions is due to chronic untreated anemia, leading to prolonged tissue hypoxia. This leads to an increase in pulmonary vascular resistance, a high output state, and pulmonary hypertension (Aessopos et al., 2007; Kremastinos et al., 2010; Wood, 2009). Clinically, dyspnea and fatigue are reported. Chronic anemia in  $\beta$ -thalassemia cases reduced oxygen tissue delivery, co-existent liver disease, and iron overload can contribute to a high output state leading to left ventricular dilatation and eccentric hypertrophy; thus, high output heart failure. Moreover, the reported left cardiac status in thalassemia intermedia patients consists of a pronounced increase in left ventricular diameters, volumes, and mass, with impairment of diastolic function but preservation of systolic function. This condition represents an early, sub-clinical manifestation of left heart failure. Anemic patients have larger hearts on CXR, echo, and MRI



measurements than patients with normal hemoglobin levels, even without any other pathology. Patients with thalassemia have low or normal blood pressure, despite their increased cardiac output, because they have lower vascular resistance.

In this case, patients have symptoms of dyspnea on effort, CXR showed cardiomegaly, and USG showed hepatomegaly and splenomegaly. Echocardiography showed LV eccentric hypertrophy, LA dilatation, mild AR, mild MR, mild TR with a low probability of pulmonary hypertension, normal LV & RV systolic function, grade I LV diastolic dysfunction, and ejection fraction 55,2%. This condition suggests there is a cardiac complication due to chronic anemia in suspected NTDT

Besides main therapy for thalassemia such as blood transfusion and iron chelation therapy, specific cardiac care should be given to treating cardiac complications. ACE inhibitors are known to improve myocardial function. Certain patients unable to tolerate ACE inhibitors due to the development of chronic cough should be treated with ARB, such as losartan. Digoxin has a very specific role in the maintenance of patients with established atrial fibrillation. Diuretics such as furosemide should be used in patients who develop pulmonary congestion or right-side heart failure and used cautiously in a diastolic heart failure state due to a sudden fall in blood pressure. Beta-blocking agents can also be used to control many arrhythmias, and are indicated in patients with stabilized heart failure. Anti-coagulation should be considered in atrial fibrillation patients.

Patient Profile	Basic Evaluation†‡	CMR—T2*	General/Hematologic Measures	Cardiological Interventions
Asymptomatic pts with no evidence of heart disease or myocardial iron load	First at puberty Every 12 months thereafter	First at late teens or early 20s Every 12 to 24 months thereafter	Pretransfusal Hb at 9 to 10.5 g/dL Regular iron chelation  Management of other causes of heart failure§   Life style modifications (smoking, lack of exercise, and excess alcohol)	
Asymptomatic pts with increased cardiac iron load but normal cardiac function	Every 6 to 12 months	Every 12 months	Pretransfusal Hb at 9 to 10.5 g/dL Intensification of iron chelation¶	
Asymptomatic pts with evidence of heart disease	Every 3 to 6 months	At diagnosis of heart disease Every 6 to 12 months thereafter	Pretransfusal Hb at 10 to 11 g/dL Intensification of iron chelation¶	Slow transfusion with diuretics Specific cardiac medications#
Symptomatic heart disease	Weekly to every 1 to 4 months, depending on clinical course	At symptoms onset Every 6 to 12 months thereafter	Pretransfusal Hb at 10 to 11 g/dL Intensification of iron chelation¶	Slow transfusion with diuretics Specific cardiac medications#

CMR indicates cardiovascular magnetic resonance imaging; Hb, hemoglobin.

†Medical history, physical examination, 12-lead electrocardiogram and echocardiogram.

‡Additional tests according to individual clinical problems (ie, 24-hour ECG, functional assessment by exercise testing, etc).

§Hypothyroidism, hypoparathyroidism, renal dysfunction, coincidental valve or structural heart disease, or vitamin C deficiency.

||The measures concern all patient categories.

¶Combination regimens (oral and subcutaneous) or constant infusion (subcutaneous or intravenous).

#ACE inhibitors or Angiotensin II receptors blockers (if ACE inhibitors not tolerated), β-blockers (carefully introduced once acute heart failure stabilized—bisoprolol or carvedilol as first choice), diuretics (for symptomatic relief of fluid overload—use sparingly whilst monitoring renal function—spironolactone should be introduced if possible), digitalis (if in atrial fibrillation), and warfarin (if central line in situ, atrial fibrillation or thromboembolic complications).

**Figure 4.** Cardiovascular Evaluation, Monitoring, and Treatment Plan of β-Thalassemia Patients According to the Guidelines for the Clinical Management of Thalassemia of the Thalassemia International Federation

In this case, blood transfusions are given 1 bag/day, omeprazole injections are given symptomatically, lisinopril and bisoprolol are administered due to cardiac complications. Bisoprolol is given because this patient has stabilized heart failure. Anti-arrhythmia and anti-coagulation are considered when there is an indication. Recommendation for a regular evaluation around 3-12 months depending on patient profile and result, but in this case patient just came to the hospital approximately 3-5 years when symptoms worsened. This situation accelerates and worsens the complications.

## CONCLUSION

From the cases that have been reported, it can be concluded that there are challenges in diagnosing and managing thalassemia in limited facilities. Cardiac involvement due to a chronic anemic state is a major complication in thalassemia. Laboratory tests for iron overload and iron chelation therapy to reduce mortality-related blood transfusion therapy are unavailable. Education and pre-marital screening are required to reduce the incidence of thalassemia or other genetic disorders.

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