CASE REPORT

A thalassaemia intermedia case with concomitant left atrial thrombus

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SUMMARY

Although marked improvements have been observed in the life expectancy of patients with thalassaemia by regular blood transfusion and strict iron chelation therapies in recent years, these patients still have to deal with several complications, mainly cardiovascular. One of the life-threatening complications is the chronic hypercoagulable state and thromboembolic events which develop due to haemostatic alterations in patients with thalassaemia, although they are more frequently seen in those with thalassaemia intermedia. Many thromboembolic complications, mainly deep venous thrombosis and cerebral thrombosis, have been reported in thalassaemia. However, intracardiac thrombosis is rarely seen. In this manuscript, we presented a case that underwent splenectomy 6 years ago but not regularly attended the control visits and presented to our clinic with gradually increasing exercise dyspnoea for 2 months.

CASE PRESENTATION

A 36-year-old man who had been diagnosed with b-thalassaemia intermedia 20 years ago was admitted to the internal medicine department due to progressive exercise dyspnoea, orthopnoea and oedema in the lower extremity. In his history, it was found that he underwent splenectomy due to hypersplenism 6 years ago and was not regularly attending control visits. In the physical examination, the patient appeared as severely faint with recognisable tachypnea. Blood pressure was found to be 100/70 mm Hg. He had a regular pulse with a rate of 110 bpm. There was venous distention of the neck. It was found that the breathing sound was weaker at the basal region with fine crackles, as the finding of weaker breathing sounds was more prominent on the left side. On cardiovascular examination, there was a grade II/III pansystolic murmur at the lower left parasternal area. On abdominal examination, there was a surgical scar at the left-upper quadrant and hepatomegaly that

BACKGROUND

Thalassaemia with autosomal recessive inheritance is a hereditary disease that is characterised by haemolytic anaemia caused by partial or complete deficiency of globulin chains comprising haemoglobin tetramer. Clinical severity varies depending on the degree of defect in the involved globulin chain. b Thalassaemia major is characterised by profound anaemia which requires frequent blood transfusions for a lifetime. In thalassaemia intermedia, there is a milder anaemia and the need for blood transfusion usually arises in the long term. In recent years, significant improvement has been achieved in the life expectancy of patients with thalassaemia by the introduction of novel therapeutic modalities. Although the major cause of mortality is still cardiovascular complications in patients with thalassaemia, thromboembolic events secondary to a hypercoagulable state comprise an important cause of mortality, especially in patients with thalassaemia intermedia. In patients with thalassaemia, venous and arterial thromboembolic events including mainly deep venous thrombosis and cerebral thrombosis, pulmonary embolism and portal vein thrombosis may be encountered; *and intracardiac thrombosis in about 0.3% of patients.*¹ The aim of this manuscript was to review cardiovascular complications of thalassaemia and of a chronic hypercoagulable state in thalassaemia by presenting a rare case with pulmonary hypertension and atrial thrombosis.

Table 1 Laboratory test results

Test item	Value
Hb (g/dL)	6.1
HCT (%)	18
MCV (fL)	65
Leucocyte count (mm ³)	20.400
Platelet count (mm ³)	602.000
Creatinine (mg/dL)	0.62
Uric acid (mg/dL)	8.5
Calcium (mg/dL)	8.8
ALT (IU/L)	17
Indirect bilirubin (mg/dL)	2.41
Direct bilirubin (mg/dL)	0.51
LDH (U/L)	3355
Albumin (g/dL)	3.2
Serum iron (µg/dL) (normal ranges: 45–182)	122
Iron binding capacity (µg/dL) (normal ranges: 110–370)	71
Ferritin (ng/mL) (normal ranges: 24–336)	1356
Folic acid (ng/mL)	11.8
ft3 (pmol/L) (normal ranges: 3.8–6)	3.68
ft4 (pmol/L) (normal ranges: 7.5–14.4)	11.46
TSH (mIU/mL) (normal ranges: 0.34–5.6)	8.57
Anti-TPO	1.8
D-dimer (ng/mL)	569
proBNP (pg/mL) (normal ranges: 0–100)	294

ALT, alanine aminotransferase; BNP, β natriuretic peptide; Hb, haemoglobin; HCT, haematocrit; LDH, low-density lipoprotein; MCV, mean corpuscular volume; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

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Figure 1 (A) Left atrial thrombus on an apical-four chamber view on transthoracic echocardiography (yellow arrow, interrupted line). (B and C) A thrombus image at the left atrium on transoesophageal echocardiography (yellow arrow, interrupted line). (D) A thrombus image at the left atrium (upper arrow, interrupted line) and a plastered thrombus at the right atrium (lower arrow, interrupted line) on transoesophageal echocardiography.

could be palpated. Bilateral pretibial oedema (++/++) was observed. Laboratory investigations are summarised in [table 1](#).

An ECG revealed sinus tachycardia

On the thyroid sonography, a homogeneous thyroid parenchyma was observed. On the posteroanterior chest X-ray, there were blunted costophrenic angles that were more prominent on the left side. An increase was observed in the cardiothoracic index. *Toraks BT* revealed normal pulmonary arteries. An echocardiography revealed an enlarged right atrium and ventricle with a moderate tricuspid valve insufficiency. He had pulmonary hypertension (estimated pulmonary artery pressure: 50 mm Hg) and a D-shaped interventricular septum. His left ventricular systolic function was normal (60% by modified Simpson's method); however, there was a mass lesion at the left atrium ([figure 1A](#)). His left ventricle was slightly thickened (septum 1.1 cm and posterior wall 1.1 cm) and the transmitral Doppler velocity study showed impaired relaxation (E/A: 0.8). A transoesophageal echocardiography was performed for further evaluation of the mass. A mobile left atrial mass ([figure 1B and C](#)) and a plastered thrombus at the right atrium ([figure 1D](#)) were observed ([video 1](#)). The thrombophilia panel including protein

C-S, antithrombin and homocysteine level and factor V Leiden and prothrombin gene mutation, which was ordered to assess hereditary thrombotic risk factors, was negative.

Video 1 Transesophageal echocardiography showed a mobile left atrial mass and a plastered thrombus at the right atrium.

Figure 2 (A) Left atrial thrombus on an apical-four chamber view on transthoracic echocardiography (yellow arrow, interrupted line). (B) A thrombus image at the left atrium on transoesophageal echocardiography (yellow arrow, interrupted line). (C) There is no thrombus image at this view (compare figure 1C). (D) A plastered thrombus at the right atrium (yellow arrow, interrupted line) on transoesophageal echocardiography.

TREATMENT

A regular transfusion programme was scheduled and chelator therapy was initiated. A diuretic was given for symptoms of heart failure. Anticoagulant therapy was initiated by taking systemic embolism findings into account. The patient achieved clinical improvement and he was discharged by the recommendation of control visits.

OUTCOME AND FOLLOW-UP

Currently, the patient has an uneventful course at month 6 after discharge. His functional class was improved. A control transthoracic and transoesophageal echocardiography showed a decrease in the size of thrombi in the left and right atria (figure 2 and video 2).

DISCUSSION

In the past three decades, the life expectancy has been considerably improved in thalassaemia, which is the most common hereditary cause of anaemia. Unfortunately, an increase in the complication rates accompanies the increased life expectancy. However, the importance of thromboembolic events has been underestimated until recent years. In particular, increased

incidence of thromboembolic events in thalassaemia intermedia played an important role in the identification of hypercoagulability in patients with thalassaemia. The incidence of thromboembolic events has been reported in about 4–5% of patients with thalassaemia. In a study (Turkish Thalassaemia Study Group) conducted in 11 centres in our country, thromboembolism incidence was reported at 3.27% in patients with thalassaemia major or intermedia.² There is a milder anaemia in thalassaemia intermedia than thalassaemia major and a need for transfusion arises in the long term. However, thromboembolic events are more frequently seen in thalassaemia intermedia when compared with thalassaemia major.³ In a recent study on 8860 cases with thalassaemia, which is one of the largest epidemiological studies, it was shown that a chronic hypercoagulable state was found to be 4.38-fold higher in thalassaemia intermedia when compared with thalassaemia major.³

The primary cellular and molecular mechanisms predisposing hypercoagulability in thalassaemia include chronic platelet activation, membrane changes in red blood cells (RBCs), abnormal expression of adhesion molecules in vascular endothelial cells and disorders of the coagulation system. The other pathological mechanisms related to hypercoagulability are cardiac

Video 2 Control transesophageal echocardiography showed decrease in the size of thrombi in the left and right atria.

dysfunction and hormonal disorders such as hypothyroidism and liver dysfunction.⁴ In addition, the presence of hereditary thrombotic risk factors, history of previous thrombotic event, advanced age and positive family history are the other factors that increase risk for thromboembolic events. Frequently, thromboembolic events occur as a result of a combination of these factors.

Chronic platelet activation was clearly demonstrated in cases with thalassaemia. In cases with thalassaemia, the markers of platelet activation are increased platelet aggregation, decreased lifespan of the platelet, increased CD62P (P-selectin) and CD63 expression and increased urinary metabolites of thromboxane A2 and prostacyclin.⁵ Erythrocyte aggregation to endothelial cell adhesion is increased by 10–25-fold in cases with thalassaemia when compared with normal erythrocytes. Free iron at the cellular membrane causes oxidation of membrane proteins and formation of ageing antigens such as phosphatidylserine (PS). Thus, erythrocytes become more rigid and aggregate. The reticuloendothelial system removes aged erythrocytes by recognising them through their higher proportion of PS at the outer layer of the membrane. In addition, phospholipids lead to fibrinogen–fibrin conversion, platelet activation and, thus, thrombus formation by stimulating thrombin regeneration as they have a negative charge. Moreover, in thalassaemia, monocytes and granulocytes also contribute to endothelial injury and a hypercoagulable state via the enhancing phagocytic function.

Splenectomy is another factor that increases the risk of thromboembolic events in patients with thalassaemia. It was suggested that this is caused by failure in the clearance of injured erythrocytes from circulation due to splenectomy, thrombocytosis and the increased number of abnormal RBCs and, thus, the increased tendency to coagulation because of splenectomy.⁶ Moreover, when compared to the thalassaemia intermedia cases without splenectomy, the higher levels of thrombin synthesis in those with splenectomy also contribute to hypercoagulopathy.⁶

Regular blood transfusions significantly reduce the risk of thromboembolic events. It is suggested that the decreased number of pathological RBCs, a marker of membrane injury, due to regular transfusions plays a role in decreased risk of thromboembolic events.

Patients with thalassaemia primarily die due to heart failure. The main causes of heart failure include haemosiderosis and chronic anaemia as well as chronic pulmonary thromboembolism. In the present case, the patient's heart failure is evident from the clinical basal creps due to diastolic dysfunction. It is known that pulmonary thromboembolism and hypertension are

more frequently observed in patients with thalassaemia, particularly in those with thalassaemia intermedia.⁷ Haemolysis, the resultant impairment in arginine metabolism and endothelial dysfunction is reported to be the most important causes of pulmonary hypertension. In addition, platelet activation also contributes to in situ microthrombus formation in the lungs.⁸ In our case, toraks BT was normal, so we ruled out pulmonary emboli. Chronic, recurrent microthromboembolism causes right ventricular dysfunction and right heart failure by increasing the pulmonary artery pressure. In a previous study, pulmonary hypertension was detected in 59.1% of the cases with thalassaemia in which blood transfusion was neither needed nor administered.⁹ In another study, pulmonary hypertension was observed in 68% of the patients with thalassaemia major or intermedia.⁸

In our case, it is thought that profound anaemia, increased platelet count, high iron load, hypothyroidism, previous splenectomy and lack of regular transfusion resulting in increased haemolysis are the factors predisposing thrombosis development. A limited number of cases with intracardiac thrombosis have been reported in the literature, although thromboembolic events are relatively common. Although surgery is the recommended treatment in intracardiac thrombosis, anticoagulant therapy is an alternative in asymptomatic cases. In our case, pulmonary hypertension and findings of right heart failure were also present. An appearance of a plastered thrombus at the right atrium on transoesophageal echocardiography suggested that pulmonary hypertension may be caused by chronic thromboembolism. Endarterectomy is recommended to these patients if a lifetime standard anticoagulant therapy is possible.¹⁰

Learning points

- We intended to stress not to ignore thromboembolic events in patients with thalassaemia, especially in cases which have a history or previous splenectomy and are at high risk for hypercoagulability.
- Cases need for assessment of heart failure, pulmonary hypertension and thromboembolic events by echocardiography and MRI during routine evaluations.

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REFERENCES

- 1 Borgna Pignatti C, Carnelli V, Caruso V, *et al.* Thromboembolic events in beta thalassaemia major: an Italian multicenter study. *Acta Haematol* 1998;99:76–9.
- 2 Akar N, Kemahli S, Uysal Z, *et al.* Thromboembolism in beta-thalassaemia major. *Acta Haematol* 1998;100:166.
- 3 Taher A, Isma'eel H, Mehio G, *et al.* Prevalence of thromboembolic events among 8,860 patients with thalassaemia major and intermedia in the Mediterranean area and Iran. *Thromb Haemost* 2006;96:488–91.
- 4 Taher AT, Otrrock ZK, Uthman I, *et al.* Thalassaemia and hypercoagulability. *Blood Rev* 2008;22:283–92.
- 5 Cappellini MD, Motta I, Musallam KM, *et al.* Redefining thalassaemia as a hypercoagulable state. *Ann N Y Acad Sci* 2010;1202:231–6.
- 6 Cappellini MD, Robbiolo L, Bottasso BM, *et al.* Venous thromboembolism and hyper-coagulability in splenectomized patients with thalassaemia intermedia. *Br J Haematol* 2000;111:467–73.

- 7 Karimi M, Musallam KM, Cappellini MD, *et al.* Risk factors for pulmonary hypertension in patients with β thalassemia intermedia. *Eur J Intern Med* 2011;22:607–10.
- 8 Singer S, Kuypers FA, Styles L, *et al.* Pulmonary hypertension in thalassemia: association with platelet activation and hypercoagulable state. *Am J Hematol* 2006;81:670–5.
- 9 Taher A, Abou-Mourad Y, Abchee A, *et al.* Pulmonary thromboembolism in β -thalassemia intermedia: are we aware of this complication? *Hemoglobin* 2002;26:107–12.
- 10 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2009;30:2493–537.

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