

# Recurrent Pulmonary Embolism and Pulmonary Hypertension in a Patient with $\beta$ -Thalassemia Intermedia

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## Abstract

Patients with  $\beta$ -thalassemia intermedia are at increased risk of thromboembolic events and multifactorial pulmonary arterial hypertension. A pro-thrombotic state, including decreased levels of natural anticoagulant proteins and chronic platelet activation, has been shown in these patients, in particular after splenectomy.

We report the case of a 54-year-old splenectomized  $\beta$ -thalassemic patient with a history of unprovoked deep venous (femoro-popliteal) thrombosis, complicated by a pulmonary embolism event at the age of 37, recurrent episodes of superficial vein thrombosis of the lower limbs with leg ulcers, and a progressive severe pulmonary arterial hypertension, related to recurrences of pulmonary embolism, despite long-term, well conducted oral anticoagulant treatment (vitamin K antagonists and apixaban). After the performance of a right heart catheterization, pulmonary endarterectomy was not considered indicated in this patient because of the distal localization of thrombi. Aspirin treatment was added to vitamin K antagonists. Riociguat and ambrisentan therapy induced an improvement of both symptoms and echocardiographic picture over 12-mo follow-up.

Splenectomized thalassaemic patients are at high risk of thromboembolic events, and pulmonary hypertension, despite common, is yet a poorly understood complication. Clear recommendations on the management of such condition are lacking due to the limited data regarding the use of vasodilators, anticoagulants (vitamin K antagonists, heparins, direct oral anticoagulants) and antiplatelet agents.

**Keywords:** Beta-thalassemia; Pulmonary embolism; Pulmonary arterial hypertension; Aspirin; Riociguat; Ambrisentan

## Introduction

Thalassemia is a congenital hemolytic disease caused by defective  $\alpha$ - or  $\beta$ - globin chain synthesis [1,2].  $\beta$ -thalassemia intermedia (TI) is characterized by mild to moderate decrease in  $\beta$  globulin production, and by a wide clinical spectrum that lies between that of thalassemia minor and major (TM) [1,2]. Three main factors lead to the clinical presentation of TI: ineffective erythropoiesis, chronic anemia/hemolysis and iron overload, secondary to increased intestinal absorption [3,4]. Venous thromboembolism (VTE), including pulmonary embolism (PE), deep vein thrombosis (DVT) and portal vein thrombosis, has been reported in adult TI patients [5-8]. A hypercoagulable state has been identified in this setting, attributed to several factors, including pro-coagulant activity of circulating damaged red blood cells (RBCs), high levels of pro-coagulant microparticles, increased platelet activation, decreased levels of anticoagulant Protein C and Protein S, and endothelial injury/activation [7]. These factors have been observed at high rate in splenectomized TI patients [9,10]. Both TM and TI are associated with the development of pulmonary hypertension (PH) [11,12], which has been shown at echocardiography in 10-75% and 40-50% of TM and TI patients, respectively [12].

Limited evidence exists for defining the optimal antithrombotic treatment and the use of vasodilators to treat PH associated with TI [12]. We here report the case of a splenectomized  $\beta$ -thalassemic patient with severe PH due to recurrent PE, despite initial oral anti-coagulation with vitamin K antagonists (VKAs) and then with apixaban.

## Case Report

A 54-year-old man was admitted to our Department in October 2016 because of progressively worsening dyspnea, even at rest, since few

weeks. He was referred for the first time to our tertiary care Department in 1999, at the age of 37, when an apparently unprovoked DVT of the left femoral-popliteal vein, complicated by PE occurred. The patient was affected by  $\beta$ -TI and underwent splenectomy at the age of 20 years. The thrombophilia workup [including FV Leiden and prothrombin (FII) G20210A gene polymorphisms, plasma anticardiolipin and anti- $\beta$  2 glycoprotein 1 antibodies, lupus anticoagulant, plasma antithrombin, Protein C and Protein S, and homocysteine] was negative nor clinical investigation allowed to identify further concomitant diseases. The blood assay showed mild anemia (11.0 g/dL), leucocytosis (14.000/mmc) and thrombocytosis (491.000/mmc), related to the TI and the previous splenectomy. After heparin therapy during the acute phase, oral anticoagulant treatment (OAT) with VKA (INR target 2.0-3.0) was started, without pre-defined time duration because of the idiopathic nature of the thromboembolic episode. Despite OAT and INR within the target range, two episodes of superficial vein thrombosis (SVT) of the lower limbs occurred, four and six years after the first thromboembolic event respectively. They were successfully managed with therapeutic doses of low molecular weight heparin (EBPM). However, the patient developed chronic venous insufficiency and leg ulcers. Clinical follow-

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up was negative for further overt VTE events until October 2016. At that time, a CT-scan showed recurrence of unilateral segmental PE, despite the on-going and well dosed OAT. By a transthoracic echocardiographic exam continuous-wave Doppler highlighted a severe tricuspid valve regurgitation with a retrograde gradient=88 mmHg (estimated pulmonary arterial systolic pressure [PAPs]=93 mmHg) whereas right ventricular (RV) internal cavity dimension was increased with the typical D-shaped configuration of severe PH. Treatment with VKA was stopped and, after 1-week enoxaparin therapy (100 IU /Kg body weight twice daily) the direct anti-Xa inhibitor apixaban (5 mg twice daily) was started. Nevertheless, two months later the patient was urgently re-admitted to our Department because of worsening dyspnea. By the echo exam a further increase of PAPs (144 mmHg) was detected whereas RV function was preserved (TAPSE=22 mm) and right atrial pressure was in the normal or highly normal range (Figure 1). Lung CT-scan evidenced multiple PE recurrence with bilateral segmental and subsegmental arterial thrombosis. Laboratory and instrumental examinations ruled out other conditions associated with acquired thrombophilia, including connective diseases, cancer and myeloproliferative diseases, and paroxysmal nocturnal hemoglobinuria (PNH). The thrombophilia workup was repeated and confirmed as negative. The ventilation/perfusion (V/Q) scan demonstrated small segmental defects of both lungs. At right heart catheterization (RHC), mean and diastolic pulmonary arterial pressures were 44 mmHg and 5 mmHg respectively, with a normal pulmonary wedge pressure (=8 mmHg); cardiac index was 3.5 l/min/m<sup>2</sup>, and pulmonary vascular resistance=4.95 Wood Units. The comprehensive analysis of the cath data allowed therefore to identify a pre-capillary pulmonary hypertension. These findings were consistent with a diagnosis of chronic thrombo-embolic pulmonary hypertension (CTEPH). An inferior vena cava filter was therefore placed while planning a pulmonary endarterectomy. However, the patient was then considered inoperable because of the distal localization of thrombi. He was discharged on combined antithrombotic treatment with VKA (INR target 2-3) plus 100 mg aspirin, diuretics and riociguat. After 6

months, because of the persistence of dyspnea and PH, ambrisentan, 10 mg daily, was added. After six months of such treatment, a significant improvement in functional class, echocardiographic parameters and 6-minute walk test were seen, without significant adverse effects.

## Discussion

The presence of a hypercoagulable state in patients with TI is well recognized [5-8]. Thromboembolic events are more frequent in TI patients than in patients with TM, more venous events occurring in TI and more arterial thrombosis in TM [13]. The hypercoagulable state in patients with  $\beta$ -TI has been attributed to several factors [7,8]. It is widely accepted that patients with thalassemia have chronically activated platelets, and enhanced platelet aggregation, as confirmed by the increased expression of CD62P (P selectin) and CD63, markers of in vivo platelet activation. The platelet survival is shortened as a consequence of platelet activation and consumption [14,15]. Thalassemic patients have also a 4 to 10 fold increase of urinary metabolites of prostacyclin (PGI<sub>2</sub>) and thromboxane A<sub>2</sub> (TXA<sub>2</sub>), compared to control subjects [16]. Thalassemic deformed RBCs have a pro-coagulant effect, that can result from the expression of negatively charged phospholipids, which facilitate thrombin generation [7,15]. Endothelial injury/activation and high levels of pro-coagulant microparticles (of RBC, leucocytic and endothelial origin), also have a pathogenetic contribution in the hypercoagulability of thalassemic patients [7]. Inherited thrombophilia does not play a relevant role in this setting; however, low protein C and S levels have been showed [7,17,18]. The presence of cardiac, hepatic, or endocrine dysfunction in case of severe iron overload may also contribute to such a hypercoagulable state [17,18]. Splenectomy contributes to the increased susceptibility to thromboembolism: splenectomized thalassemic patients have high platelet counts and increased number of abnormal RBCs [7,9].

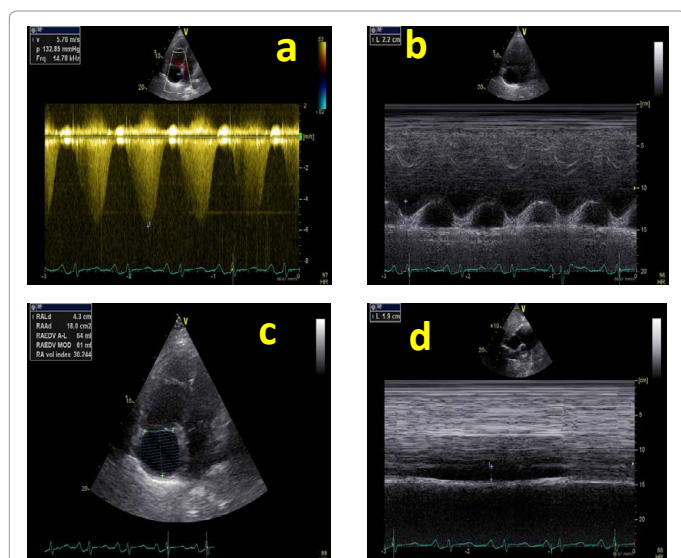
PH is frequent among patients with TI and TM (rate of about 40-50%), and is multifactorial [11,12]. Pathogenic mechanisms include:

1. Chronic hemolysis, with decreased nitric oxide bioavailability and platelet activation, increased expression of adhesion molecules and increase of endothelin-1;
2. Iron overload due to transfusions, that leads to fibrosis and dysfunction of the heart;
3. Hypercoagulability and increased incidence of VTE;
4. Changes in circulating cells after splenectomy [12].

The higher occurrence of PH in splenectomized patients who develop VTE may suggest a common underlying etiology between the two complications [12].

PH is commonly arranged into five separate groups (based on common manifestations, clinical presentation, and therapeutic strategies): 1) Pulmonary arterial hypertension (PAH), 2) PH due to left heart disease, 3) PH due to lung diseases and/or hypoxia, 4) Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions, and 5) PH with unclear and/or multifactorial mechanisms [19]. PH due to chronic haemolytic anaemia is included in group 5, because of its multifactorial mechanisms [12,19-22].

Echocardiography can identify thalassemic patients at risk for PH in whom tricuspid regurgitation velocity is used to estimate RV systolic pressure but is not sufficient to support a treatment and RHC is required [22,23]. In our case, the presence of CTEPH was established



**Figure 1:** Summarization of the echo exam showing a severe continuous wave Doppler derived tricuspid regurgitation with a retrograde gradient=132.85 mmHg (A), preserved RV function (tricuspid annular plane systolic excursion=22 mm) (B), and normal or highly normal estimated RA pressure as derived from a normal RV size (C) and inferior cava vein which is dilated but still keeps a normal respiratory reactivity (D).

by RHC, but the patient was classified inoperable because of the distal thrombosis localization at CT scan.

Recent guidelines for the treatment of PH do not provide specific recommendations for these patients [22], and the literature lacks proper evidence on the role of vasodilators, anticoagulants and antiplatelet agents in the management of PH in thalassemia. A chronic transfusion therapy, in addition to iron-chelation, is thought to prevent and ameliorate PH in these patients [12,24,25].

In particular, data regarding the use of pulmonary vasodilators in thalassemic patients are limited and no randomized trials are available to support the routine use of these treatments [12]. Studies using sildenafil, a phosphodiesterase type 5 inhibitor (PDE-5 inhibitor), or endothelin receptor antagonists (ERAs), particularly bosentan, in patients with PH as a result of sickle cell disease are not conclusive [12].

Randomized, placebo-controlled trials in both PAH and CTEPH patients have shown improvements in WHO functional classification, 6-minute walk distance, and invasive pulmonary hemodynamics with the use of the soluble guanylate cyclase (sGC) stimulator riociguat [26,27]. Soluble guanylate cyclase converts guanosine triphosphate (GTP) to cGMP, leading to vasorelaxation. However, published trials did not include patients with PH related to chronic haemolytic anaemia.

Improvements in both functional class and invasive hemodynamic measurements by RHC are reported in TM complicated by PH after treatment with epoprostenol, a synthetic prostacyclin [28]. A more recent case report describes a patient with TI and severe PH diagnosed on RHC who was successfully treated with epoprostenol for more than 3 years with improvements in symptoms, functional classification, 6-minute walk distance, and invasive hemodynamic measurements [21].

Although platelet activation is considered a pathogenic mechanism of PH in TI, data from the literature suggest that aspirin may reduce the risk of recurrence in patients with a history of thromboembolism; however the difference is not statistically significant [13]. In a recent retrospective study on 63 thalassemic patients with PH, the pulmonary artery systolic pressure was unchanged after 1-year treatment with low-dose aspirin [28,29].

We have here reported a patient with  $\beta$ -TI with recurrent pulmonary embolism complicated by PH, who had clinical and imaging improvements with the association of OAT, aspirin, riociguat and ambrisentan, even in the absence of specific recommendations on the use of these last three drugs.

Therefore, current literature evidence do not allow to draw agreed, standardized approaches for the management of these patients. Further well-designed studies, recruiting sufficient numbers of patients are needed to determine the optimal treatment for this severe condition, often life-threatening, in particular to elucidate the role of aspirin and of the different vasodilator agents.

#### Authorship Contributions

AT and AG wrote the manuscript. AT, AG, AC, GA, PC, MG, MD'A, GDM took care of the patient. All authors approved the manuscript.

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