Thrombotic thrombocytopenic purpura or Immune thrombocytopenia in a sickle cell/β+thalassemia patient: a rare and challenging condition

Efthymia Vlachaki, Aleka Agapidou, Nikolaos Neokleous, Despoina Adamidou, Evaggelia Vetsiou, Panagiota Boura.

Thalassemia Unit, 2\textsuperscript{nd} Department of Internal Medicine, Aristotle University, Hippokrateon Hospital, Thessaloniki, Greece

Corresponding author: Vlachaki Efthymia, Lecturer in Hematology, Amorgou street 29, 55337, Thessaloniki, Greece. e-mail: efivlachaki@yahoo.gr, phone: +302310892453, mobile +306941586121

Running title: Thrombocytopenia in sickle cell/β+thalassemia
Abstract

The diagnosis of thrombotic thrombocytopenic purpura is one of the possible diagnosis when a patient is admitted with unexpected micro-angiopathic hemolytic anemia and thrombocytopenia. The combination of sickle cell/β⁺-thalassemia and thrombotic thrombocytopenic purpura is rare and triggering. This article describes the poor outcome of a patient with sickle cell/β⁺-thalassemia presenting with gingival bleeding, severe thrombocytopenia and anemia. The patient had normal renal function, no neurological deficit and he was initially treated as immune thrombocytopenic purpura. He eventually died due to multi-organ failure and brain hemorrhage even though he had started plasma exchange sessions. The co-existence of thrombotic thrombocytopenic purpura and sickle cell anemia is making the diagnosis of the former difficult. Early and rapid intervention is critical to the outcome.

Key words: thrombotic thrombocytopenic purpura, sickle cell, β-thalassemia, thrombocytopenia, plasma exchange, ADAMTS-13.
Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life threatening thrombotic micro-angiopathic (TMA) syndrome classically characterized by a pentad of clinical findings including micro-angiopathic hemolytic anemia (MAHA), thrombocytopenia, fever, renal dysfunction, and neurological abnormalities. However, the diagnosis is frequently made when a patient presents with thrombocytopenia, elevated lactic dehydrogenase (LDH), and schistocytes on the peripheral smear, in the absence of any other likely cause. The characteristic fragmented red cells or schistocytes are commonly thought to be formed when red blood cells pass through partially occluded vessels, experiencing shear stress as they encounter platelet thrombi in the microvasculature [1]. Widespread formation of platelet micro-thrombi results in consumptive thrombocytopenia, tissue ischemia, and intravascular hemolysis caused by fragmentation of red blood cells. The characteristic occlusive hyaline thrombi have been shown to consist primarily of von-Willebrand factor and platelets. Most adults with the idiopathic form of TTP have autoantibodies directed against a von-Willebrand-factor-cleaving protease in plasma. This protease has recently been identified as a new member of the zinc metalloproteases, ADAMTS-13 (A DisintegrinAndMetalloproteasewith ThromboSpondin Type 1 motifs) [2]. Standard care is daily plasma exchange, which is typically discontinued when the platelet count exceeds 100–150 * 10^9/L and LDH returns to normal or near normal. Many disorders can be associated with TMA, with clinical features of MAHA and thrombocytopenia, such as severe hypertension, pre-eclampsia, systemic
lupus erythematosus, adverse drug reactions, allogeneic hematopoietic stem cell transplantation, infections and abnormalities of complement regulation.

During an acute episode, the sickle cell haemoglobinopathy like TTP affects the micro-vascular circulation and cause non-inflammatory anoxic injuries to multiple organs. Sickle cell/β+ thalassemia (Hb S/β+ thal) is considered a variant form of sickle cell disease. This condition occurs when an individual inherits two altered genes, one from a parent who is carrier of β- thalassemia and the other from a parent who is carrier of sickle cell anemia. This condition is inherited in an autosomal recessive manner and is caused by mutations in the hemoglobin β-gene [3].

Herein we describe the case of a patient with sickle cell/β⁺thalassemia who presented with thrombocytopenia and anemia without schistocytes in the peripheral blood smear, treated initially as immune thrombocytopenic purpura (ITP) with steroids and immunoglobulin with no response. He progressively deteriorated and died due to multiple organ failure and brain hemorrhage even though he had started plasma exchange sessions as possible TTP.

Case report

A 30-years old male was admitted to the hospital due to gingival bleeding after dental handling. He had regular follow up in Thalassemia Unit due to known history of sickle cell/β⁺-thalassemia since he was at the age of 18 (1994). At that time, the levels of HbA₂ was 7, 1%, HbS was 82%, HbF was 7,1%, his hemoglobin was 9,5mgr/dl and his platelets were 238*10⁹/L. He was negative for Hepatitis B, Hepatitis C and HIV. The Ejection Fraction (EF) was
60%, he had normal renal function, slight increase in transaminase levels (SGOT: 80 IU/l, SGPT: 50 IU/l), LDH 750 IU/m L and the abdominal ultrasound revealed multiple hepatic infarctions, two small stones in the gall bladder and a small spleen (max diameter 7, 5 cm). He was treated since 1999 with hydroxycarbimide (15mg/kg) and he had few sickle cell crises during the years which were usually treated with hydration, antibiotics and analgesics. He was never transfused since he kept an average hematocrit level around 30% only by receiving daily folic acid.

During his last admission his laboratory results were: White Blood Cell (WBC):16,000/μL, hematocrit 23%, hemoglobin:7,1 gr/d L, platelets:7*10^9/L, INR:1.10, fibrinogen: 294mgr/dL, SGOT: 79 IU/dL, SGPT: 43 IU/dL, LDH:784 IU/l, creatinine:0,7 mg/dL, total bilirubin:4,2mgr/dL, direct bilirubin:0,87 mg/dL, vitamin B12 was normal and Direct and Indirect Coombs( DAT) was negative. In the peripheral blood smear had numerous nucleated erythroblasts (40%) with normal differentiation, sickled cells (+3), without schistocytes while in the bone marrow sample an intense erythroblastic reaction was observed. The patient was transfused and started treatment with prezolone(100 mg/d) as ITP. After 4 days, due to poor response, immunoglobulin intravenously (2gr/kgr) and vincristine (2mg) were also added successively. He had no change in his laboratory profile and still no schistocytes in his blood smear. Ten days after his admission, without any improvement in his thrombocytopenia the patient had mild bleeding tendency (epistaxis).He had normal brain Computed tomography (CT) scan and abdominal ultra-sound.

On the eleventh day since his admission, the patient had a dramatic change in his clinical condition as he complained for bone pain, mouth numbness, and
he became agitated. At the same time LDH was highly increased (LDH: 2000 IU/mL) and we observed schistocytes in the peripheral blood smear. Renal function was still normal. These findings suggested the possibility of TTP and he immediately started plasma exchange sessions. The patient quickly presented with hypertension, hematuria and intense headache. A new brain CT scan revealed brain hemorrhage. Unfortunately the patient’s mental status didn’t improve, and he finally died the next day due to multiple organ failure. ADAMTS-13 activity wasn’t measured.

Discussion
Thrombotic microangiopathy (TMA) is a rare, severe micro-vascular occlusive disease characterized by systemic or intra-renal aggregation of platelets, thrombocytopenia and mechanical injury to erythrocytes. Minimal diagnostic criteria include thrombocytopenia and MAHA resulting in fragmentation of erythrocytes in blood smear and elevated LDH levels. It is known to occur in bacterial and viral infections, autoimmune diseases, and is also associated with pregnancy, malignancy and certain medications, such as ticlopidine and calcineurin inhibitors [4]. Thrombocytopenia is defined as a platelet count of less than 100,000 per cubicmillimeter, and MAHA is diagnosed by the finding of schistocytes on the peripheral blood smear along with a negative Coombs’ test. No minimum number of schistocytes has ever been defined. Schistocytes, which are fragmented red cells, are not specific to TTP [5]. It is clear, that schistocytes are seen on the peripheral blood smears of most healthy individuals as well as in various conditions affecting the heart and rest of the vascular system.
Indeed, patients with renal disease, pre-eclampsia, and various cardiac valve abnormalities routinely have large numbers of schistocytes present in their blood. In other words, the finding of schistocytes on a blood smear is a highly sensitive but not at all specific diagnostic finding for TTP. However, it seems that there is an identifiable range for the percentage of schistocytes on peripheral blood smear that is specific for TTP. A schistocyte count greater than 1% appears to be diagnostic of TTP in the appropriate clinical setting. Generally, it is recommend that when the diagnosis of TTP is suspected a quantitative schistocyte count must be performed. In the absence of known valvular conditions, pre-eclampsia, lupus, Disseminated Intravascular Coagulation (DIC), or pre-existing renal disease, the finding of more than 1% schistocytes on a peripheral blood smear along with thrombocytopenia and hemolysis should be taken as putative evidence of TTP and treatment should begin. As more specific tests for TTP, such as quantitative ADAMTS-13 levels, become readily available for immediate diagnosis, this morphologic tool will recede into historical importance [5].

The distinction among the disorders causing TMA became more important when effective treatment for TTP became available. In 1991, a randomized clinical trial documented that the treatment of TTP with plasma exchange (PEX) resulted in 78% survival, compared with only 10% survival 25 years earlier without PEX. The effectiveness of PEX treatment created urgency to diagnose TTP and to begin therapy, which in turn created urgency to exclude alternative causes of MAHA and thrombocytopenia [6].

Sickle cell disease (SCD) is a group of disorders characterized by the polymerization of deoxygenated hemoglobin S into rigid rod-like polymers,
causing the sickling of the erythrocyte. The combination of an SCD crisis with TTP has been reported only rarely [7].

Acute episodes of vaso-occlusive pain crisis are characteristic of sickle cell disorders and are not usually associated with severe complications; some episodes may be complicated by an acute, life-threatening organ dysfunction, such as acute chest syndrome, aplastic events, splenic sequestration, and hepatic sequestration with liver dysfunction. During an acute episode, both TTP and the sickle cell haemoglobinopathy affect the micro-vascular circulation and cause non-inflammatory anoxic injuries to multiple organs. Severe prolonged thrombocytopenia has occasionally accompanied severe vaso-occlusive crises of sickle cell disease [3].

A possible defect in the cleavage of large vWF-multimers through the protease ADAMTS13, during the microcirculation thrombi formation procedure, could add further to the well-established chronic activation of the endothelium and consequently to the severity of the sickle cell disease [8]. For this purpose the activity of the enzyme is measured in order to look for any associations with the clinical phenotype of patients with SCD. It was found higher level of both vWF: Ag and ADAMTS13 in the patients compared to the control group. Furthermore, patients with severe disease had significantly lower ratio ADAMTS/vWF compared to both control group (p<0.001) and patients with mild clinical phenotype. The lower ratio found in patients with SCD and in particular in those with severe disease might indicate the need for higher protease levels in comparison to healthy controls. It looks like in this group of patients ADAMTS13, although normal, it is not sufficient enough to manage the reasonably high vWF levels that characterize the chronic
endothelial activation. This relevant deficiency of the metalloprotease might be caused by either biggest consumption due to large and constant release of its substrate-vWF or by an acquired inhibition of its action as the free intravascular hemoglobin might exhibit an antagonistic role for the binding site of vWF. In conclusion, the low ADAMTS13/vWF: Ag ratio seems to detect patients with severe SCD and would be of interest to prospectively investigate its role both as a prognostic tool as well as a potential therapeutic target [9].

The combination of TTP and thalassemia/sickle cell disease is uncommon. Few cases have been reported [7,10-12]. In all of them, sickle cell crisis was first suspected and then the deterioration of the patient put the diagnosis of TTP. However, according to our knowledge, our case is still the first which had dramatic change in one day with no signs of the typical TTP’s pentad the previous days. In our case the patient presented without the typical sickle cell crisis but with severe thrombocytopenia and concurrent anemia which were recorded for the first time in his medical record. Moreover, he had normal temperature, renal and neurological function and additionally no schistocytes were found. The fact that he remained responseless to the therapy and he suddenly deteriorated directed us to other possible diagnosis. Finally, sustained thrombocytopenia, neurological abnormalities, LDH and the presence of schistocytes on the peripheral blood smear completed the puzzle of the possible diagnosis of TTP, and plasma exchange was immediately initiated.

**Conclusion:** Although careful attention should be paid to the microscopic examination of a blood smear in any patient presenting with anemia and thrombocytopenia, the present case emphasize the need to consider TTP
strongly in the differential diagnosis, in view of the overwhelming improvement in morbidity and mortality with plasma exchange therapy, even in the absence of some of the classic signs of microangiopathic hemolysis[2]. The similarity of the clinical presentation and response to treatment, suggests a common link to the pathophysiology of these two conditions. Early recognition of TTP and prompt initiation of plasma exchange reverses the disease process and is usually a life-saving procedure. It is important to emphasize the hazards of sickle cell disease and the value of reviewing the peripheral blood smears in cases of anemia, associated with thrombocytopenia during hospitalization[7].

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