

# Acute non-atherosclerotic ST-segment elevation myocardial infarction in an adolescent with concurrent hemoglobin H-Constant Spring disease and polycythemia vera

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## Abstract

Thrombosis is a major complication of polycythemia vera (PV) and also a well-known complication of thalassemia. We reported a case of non-atherosclerotic ST-segment elevation myocardial infarction (STEMI) in a 17-year-old man with concurrent post-splenectomized hemoglobin H-Constant Spring disease and *JAK2* V617F mutation-positive PV. The patient initially presented with extreme thrombocytosis (platelet counts greater than 1,000,000/ $\mu$ L) and three months later developed an acute STEMI. Coronary artery angiography revealed an acute clot in the right coronary artery without atherosclerotic plaque. He was treated with plateletpheresis, hydroxyurea and antiplatelet agents. The platelet count decreased and his symptoms improved. This case represents the importance of early diagnosis, awareness of the increased risk for thrombotic complications, and early treatment of PV in patients who have underlying thalassemia with marked thrombocytosis.

## Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) which is characterized by the proliferation of red blood cells independent of a normal control mechanism. The majority of patients have a mutation of the Janus Kinase 2 (*JAK2*) gene. Diagnosis can be obtained by the examination of a complete blood count (CBC) that reveals polycythemia and other laboratory support as follows: demonstration of *JAK2* mutation, panmyelosis

or proliferation of all myeloid lineages (including erythroids, granulocytes, and megakaryocytes) from bone marrow (BM) biopsy, subnormal serum erythropoietin, and endogenous erythroid colony formation *in vitro*.<sup>1</sup> Both arterial and venous thromboses are major complications of PV that occur in newly diagnosed patients at 16% and 7.4%, respectively.<sup>2</sup> The proposed mechanisms of thrombosis include abnormalities of red blood cells, white blood cells, platelets, endothelial cells, coagulation factors as well as patient risk factors.<sup>3</sup>

Thalassemia is a group of inherited red blood cell disorders that results from a defect in the globin chain synthesis leading to chronic hemolytic anemia. It has a wide range of severity, from asymptomatic to transfusion-dependent anemia.<sup>4</sup> Thalassemia remains a major health problem in Southeast Asia. Gene defects in alpha globin were found in 30-40% of people in Northern Thailand and Laos, whereas beta globin gene defects were present in 1-9% and hemoglobin E (Hb E) was more prevalent in the Thai-Laos-Cambodia border area, with the Hb E carrier prevalence around 50-60%.<sup>5</sup> The thalassemia syndromes that have clinical significance include Hb Bart's hydrops fetalis, homozygous beta-thalassemia, Hb E/beta-thalassemia, and Hb H disease. Hb H-Constant Spring (Hb H-CS) disease is the most common nondeletional type of Hb H disease in Southeast Asia that appeared to have more clinical severity than deletional Hb H disease.<sup>5</sup> Thalassemia disease also increases the risk of thrombosis. The incidence of thrombosis in thalassemia major and thalassemia intermedia were 0.9-4% and 3.9-29%, respectively. Abnormalities in red blood cells, platelets, endothelial cells, coagulation factors as well as individual risk factors also contribute to the pathogenesis of thrombosis in thalassemia.<sup>6</sup>

There are only a few case reports of PV in beta-thalassemia traits,<sup>7,8</sup> but no reports regarding thalassemia intermedia or major. We report a young man who had concurrent post-splenectomized Hb H-CS disease and *JAK2* V617F mutation-positive PV and developed acute non-atherosclerotic ST-elevation myocardial infarction (STEMI) early in the course of the disease. This study was approved by the Institutional Review Board of Faculty of Medicine, Chiang Mai University, Thailand.

## Case Report

A 17-year-old man was referred from a regional hospital to our institute for evaluation of his elevated platelet counts. He had an underlying disease of Hb H disease that required a splenectomy due to transfusion dependency when he was 5 years-old. The

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physical examination revealed no anemia, no jaundice, an enlarged liver to two centimeters below the right costal margin, and a splenectomy scar on his abdominal wall. The CBC showed a Hb of 11.5 g/dL, hematocrit (Hct) of 36.5%, corrected white blood cells (WBC) of 29,200/ $\mu$ L (neutrophils 66%, lymphocytes 16%, monocytes 8%, eosinophils 9%, basophils 1%), nucleated red cells (NRCs) 9/100 WBC, platelets 2,206,000/ $\mu$ L. Two months prior to his referral the patient's medical record from the regional hospital showed a platelet count of 976,000/ $\mu$ L. His blood smear revealed marked thrombocytosis with variations in size and staining of the platelets, in addition to hypochromic microcytic red blood cells, NRCs and leukocytosis as shown in Figure 1A.

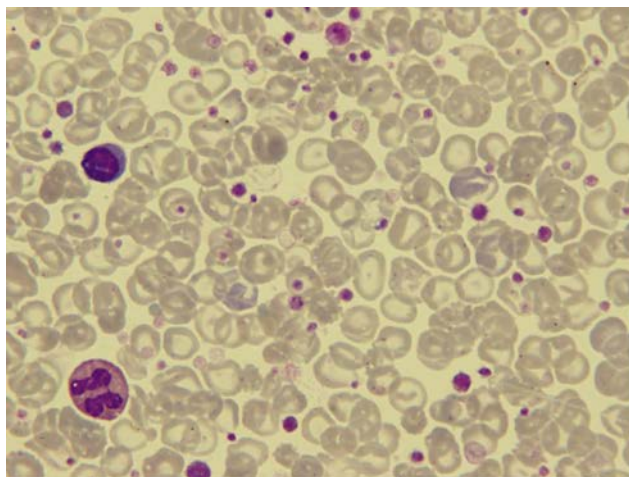
Initially, reactive thrombocytosis associated with splenectomy was suspected. However, MPN such as essential thrombocythemia (ET) and PV could not be excluded because of the extreme thrombocytosis and abnormal platelet morphology. The patient underwent a bone marrow aspiration and a biopsy that revealed hypercellularity with an increase in megakaryocytes, erythroid cells and myeloid precursors with normal maturation, the myeloid to erythroid ratio was 1:2, compatible with panmyelosis as shown in Figure 1B. Chromosome analysis from the bone marrow showed 46, XY. *JAK2* V617F mutation analysis by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) was positive. The Hb

analysis by high performance liquid chromatography (HPLC) demonstrated AA<sub>2</sub>HbA<sub>2</sub>'sCS: HbA<sub>2</sub> 1.7%, Hb Bart's and Hb H 12.3% that confirmed the diagnosis of Hb H-CS disease. Alpha-globin gene analysis showed the termination codon mutation leading to Hb Constant Spring but did not find common alpha-globin gene deletions in Thailand including Southeast Asian deletion (-<sup>SEA</sup>), Thai deletion (-<sup>THAI</sup>), 3.7-kb deletion (- $\alpha^{3.7}$ ), and 4.2-kb (- $\alpha^{4.2}$ ) deletion. Because red cell inclusion bodies were found after staining red cells with methylene blue, it still supported the diagnosis of Hb H-CS disease. Although, the baseline Hb from the regional hospital was not available, it was likely to be around 8.1±1.18 g/dL according to data of non-deletional HbH disease in Thailand.<sup>9</sup> Since his Hb levels were more than the 99<sup>th</sup> percentile of this reference range to the level of 12-12.9 g/dL during the follow up, this supported the diagnosis of PV with Hb H-CS disease. Low dose aspirin was given for the prevention of thrombosis. He did not receive cytoreductive treatment due to his young age and no history of thrombosis.

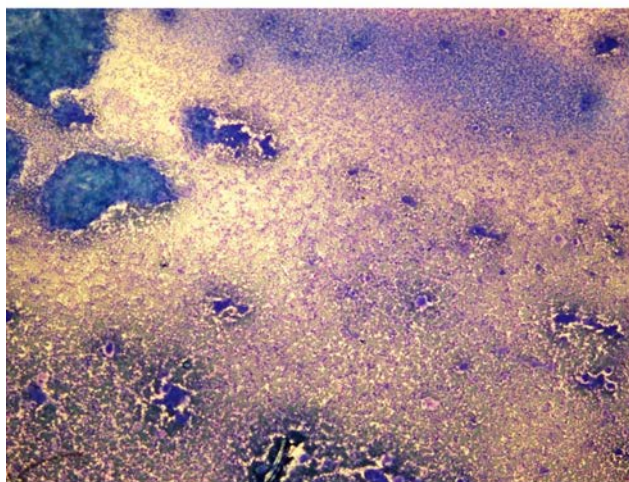
Three months later, the patient was admitted to the hospital due to chest pain. His electrocardiogram (ECG) showed an ST elevation in leads II, III, aVF and ST depression in leads V1-V6 as shown in Figure 2. Cardiac enzymes were elevated as follows: total CK of 2298 U/L (normal range 0-195), CK-MB of 209 ng/mL (normal range 0.63-5.1), and troponin T of 2.34 ng/mL (normal <0.01). Acute STEMI was diagnosed. Coronary artery angiography revealed an acute clot in mid right coronary artery (RCA) and irregular surface of proximal RCA suspected white clot. The findings showed that he was unlikely to have atherosclerotic plaque. His CBC still showed marked thrombocytosis with platelet of 2,278,000/ $\mu$ L, Hb of 9.5 g/dL, and WBC of 29,200/ $\mu$ L (neutrophils 66%, lymphocytes 16%). Echocardiography revealed good left ventricular systolic function with an ejection fraction of 61.6%. The patient was a non-smoker and laboratory testing for other cardiovascular risk factors were negative as follows: fasting blood sugar (FBS) of 74 mg/dL, total cholesterol of 121 mg/dL, low density lipoprotein (LDL) cholesterol of 54 mg/dL, high density lipoprotein (HDL) cholesterol of 24 mg/dL, triglyceride of 141 mg/dL, blood urea nitrogen (BUN) of 13 mg/dL, creatinine of 0.7 mg/dL, and uric acid of 6.5 mg/dL.

Plateletpheresis was administered to rapidly reduce platelets, together with hydroxyurea 3000 mg/day for cytoreduction. Medical treatment for acute MI including aspirin and ticlopidine were also given without thrombolytic therapy or percutaneous coronary intervention. After two weeks of treatment, his platelet count and WBC count decreased to 949,000/ $\mu$ L and 12,700/ $\mu$ L, respectively without any chest pain. However, his follow-up ECG showed Q

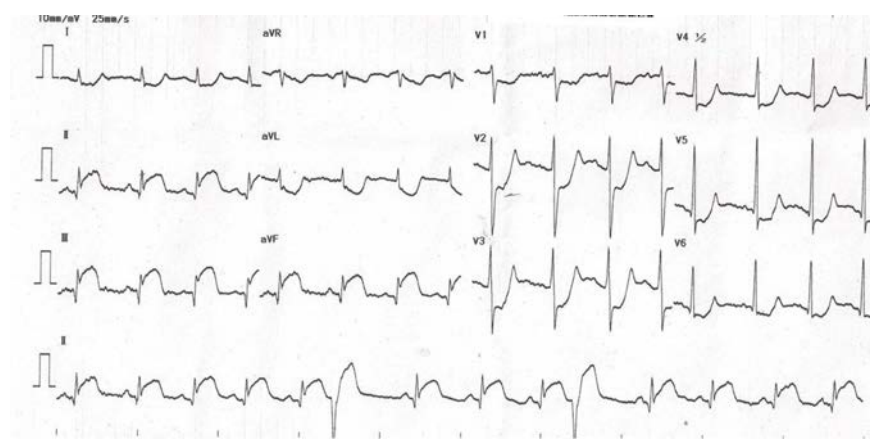
A



B



**Figure 1. A) Blood smear of the patient showing hypochromic microcytic red blood cells with anisocytosis and poikilocytosis compatible with thalassemia. Platelets were markedly increased with a variation in size and staining, including agranular platelets. B) Bone marrow aspirate revealing hypercellular marrow of 90%. There was panmyelosis or a proliferation of erythroid, granulocytic and megakaryocytic lineages with effective maturation. Megakaryocytes were increased in size with pleomorphism, and also nuclear lobulation. Significant platelet clumping was also seen.**



**Figure 2. Electrocardiogram (ECG) of the patient showing normal sinus rhythm with occasional premature ventricular contractions (PVC). ST elevation in leads II, III, aVF with ST depression in leads I, aVL, and V1-V6 were noted. These findings were compatible with an acute ST-elevation myocardial infarction (STEMI) of the inferior wall.**



wave and inverted T in lead II, III, aVF that was compatible with inferior wall infarction. The patient was discharged from the hospital and had a follow-up appointment at a hematology clinic without any recurrent thromboembolic events. His Hb levels were maintained at 8.1-12.9 g/dL, WBC count at 4,720-16,100/ $\mu$ L, and his platelet count was around 367,000-784,000/ $\mu$ L by 2000-2500 mg/day of hydroxyurea. Antiplatelet treatment was reduced from dual agents to low dose aspirin alone after the platelet count was controlled.

## Discussion

We report a case of acute STEMI in a young patient with Hb H-CS disease and PV. The diagnosis of PV in this case was based on the bone marrow findings of panmyelosis, an increased red cell volume, and a presence of *JAK2* V617F mutation. From the World Health Organization (WHO) 2008 diagnostic criteria, the level of Hb should be greater than 18.5 g/dL in males or more than 17 g/dL if associated with a documented and sustained increase of at least 2 g/dL from the baseline value.<sup>1</sup> These criteria as well as the newly proposed criteria that reduce cut-off levels of Hb to 16.5 g/dL<sup>10</sup> may be not applicable for the diagnosis of PV in thalassemia since patients may have very low baseline Hb levels. However, the evidence of increase red cell volume in this patient was made by applying the criteria of a Hb more than the 99<sup>th</sup> percentile of reference range of thalassemia patients in Thailand.<sup>9</sup> ET was a possible differential diagnosis because his platelets were greater than 450,000/ $\mu$ L, the presence of *JAK2* mutation, and basically did not meet the WHO criteria for other myeloid neoplasms.<sup>11</sup> However, his bone marrow findings supported the diagnosis of PV more than ET. Extreme thrombocytosis or platelet counts more than 1,000,000/ $\mu$ L can be found not only in MPN, but also in many reactive causes. Post-splenectomized Hb E/ $\beta$ -thalassemia accounted for 15% of the cases of extreme thrombocytosis in Thailand.<sup>12</sup> It is important to note that abnormal platelet morphology and staining is very helpful when considering MPN in addition to reactive thrombocytosis.<sup>11</sup> *JAK2* mutation analysis is also helpful when investigating MPN since it is mainly positive in MPN,<sup>1,11</sup> but absent in thalassemia major patients with thrombocytosis due to splenectomy.<sup>13</sup> This case report illustrates the serious thrombotic complications of PV found in a splenectomized thalassemic patient. Acute myocardial infarction events were reported in both PV and  $\beta$ -thalassemia major.<sup>2,14</sup> The mechanisms of thrombosis in both PV and thalassemia are complex. In this case, findings from a coronary artery angiogram suggest that

marked thrombocytosis from PV in addition to post-splenectomy seems to be the most important factor that contributes to thrombus formation. Platelets are not only increased, but also have enhanced activation in PV.<sup>3</sup> Evidence of platelet activation and abnormal platelet aggregation were also found in thalassemia, especially in a post-splenectomy state.<sup>6</sup>

Although no polycythemia was observed in this patient due to underlying thalassemia, red blood cells in both thalassemia and PV can aggravate thrombosis due to enhanced exposure of negatively charged phosphatidylserine as well as increased cohesiveness and aggregability.<sup>6,15</sup> As a result, non-transfusion dependent thalassemia, like in this patient, had a higher incidence of thrombotic events compared to patients who received regular transfusions.

The other factors that enhance thrombus formation include leukocytosis, vascular defect, and coagulation factor abnormalities. Leukocytosis that occurred in this patient is a risk factor of thrombosis in PV.<sup>16</sup> It was hypothesized that proteolytic enzymes released from neutrophils both damage and activate endothelial cells and platelets.<sup>3</sup> Consequently, endothelial cell activation, increased endothelial-derived microparticles, and a decreased level of nitric oxide in both PV and thalassemia can promote thrombosis.<sup>3,6</sup> Finally, many abnormalities of procoagulation factors and inhibitors that promote a prothrombotic state were also reported in both PV and thalassemia.<sup>3,6</sup>

The age of onset of PV in this patient was slightly under the minimum age, in the range between 18-95 years, in the large international PV cohort.<sup>2</sup> However, the younger age of onset is not a negative prognostic factor for survival.<sup>2</sup> For acute management of extreme thrombocytosis with acute MI in this patient, we used plateletpheresis to rapidly reduce platelets before attaining the effects of the platelet-lowering agent. Although therapeutic plateletpheresis was only a weak recommendation according to current apheresis guidelines,<sup>17</sup> this strategy was effective in ameliorating symptoms due to thrombocytosis in PV and ET in the previous case series<sup>18</sup> and possibly had benefits in terms of prevention of early recurrent MI in this case report. For long-term management of PV, phlebotomy was omitted due to the fact that the hematocrit in this case was already less than 45%, which is the current target that was confirmed in the randomized trial.<sup>19</sup> Cytoreductive treatment was definitely indicated after he had an MI as a thrombotic event. However, this scenario suggests that it may have a role in the primary prevention of thrombosis in low cardiovascular risk PV patients with extreme thrombocytosis. Hydroxyurea is an effective drug but it should be used with caution in young patients,<sup>20</sup> even

its leukemogenic potential was not clearly demonstrated.<sup>2</sup> Finally, an antiplatelet agent was given for the treatment of coronary artery disease and also for the prevention of other cardiovascular events in PV.<sup>20</sup>

## Conclusions

This case report represents the importance of early diagnosis and treatment of PV in patients who have underlying inherited anemia such as thalassemia. PV can occur in young patients and also in patients who have reactive thrombocytosis that may result in a delayed diagnosis. Careful evaluation of the baseline CBC and a peripheral blood smear are simple and effective steps before proceeding with further investigations. Prompt diagnosis and management are critical for preventing thrombotic complications in PV.

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