

High Risk Essential Thrombocytemia with Coronary Arterial Disease and Arterial Thrombosis in Wangaya Hospital, Denpasar, Bali, Indonesia

Fanny Puspita Haryono¹, Made Suma Wirawan²

¹General Practitioner in Wangaya Hospital, Denpasar, Indonesia

²Internist in Wangaya Hospital, Denpasar, Indonesia

Abstract: We report a case of essential thrombocytemia in geriatric patient. The disease is uncommon in Indonesia and it makes difficulty to make the diagnosis. It involves an overproduction of megakaryocytes in bone marrow. The abnormal function of platelets and the amount of platelets can cause a blockage in blood vessel and make others complication. In the first stage of the disease is asymptomatic. The therapy of thrombocytemia is hydroxyurea at first line cytoreductive therapy at any age.

Keywords: Thrombocytemia, arterial thrombosis, coronary artery disease

1. Introduction

The classic myeloproliferative disorder includes polycythemia vera, primary myelofibrosis and essential thrombocytemia.¹ In the last few years, there have been significant advances in our understanding of the genetic basis, pathophysiology, and clinical course of ET.^{2,3} ET is neither a cytogenetically nor a morphological defined disease entity, but rather is a diagnosis of exclusion. Therefore the diagnosis of ET requires that both reactive thrombocytosis and other chronic myeloid disorder have been omitted.⁴

2. Case

70 years old female presented to emergency room in Wangaya District hospital, Denpasar, Indonesia with complaint black bluish in the top of her fingers on left hand since five days ago. She felt numbness in hands. Before the change of coloration in her finger, she hasn't injury. She hasn't hemorrhage. The stool and urinary is yellowish. She feels shortness of breath from three days ago and chest pain too. The shortness of breath reduced when sit down, and increased in lie down position. The chest pain likes strucked down heavy things but not referred to back. She hasn't cough and fever. She was known case of hypertension and cardiovascular disease for the last seven years ago. And transient ischemic attack three years ago, she never has high glucose blood level. Body weight was 55 kg and height 160 cm. Her blood pressure is 160/90 mmHg, her pulse rate is 72 times per minutes, the intensity is strength and regular, her respiratory rate is 26 times per minutes, the temperature is 36,7°C. In face-neck region: there was no pallor, no icteric, no cyanosis. There is increasing of jugular vein pressure and the using of breath muscle. In thoracal region examination, there is no rhonki and no wheezing in her lungs, there is midsistolic murmur on her apex of heart, the borderline of the heart enlarged. The under-left borderline of heart is in ICS seven linea anterior-axilla sinistra. The thrill is palpable in her apex. In abdominal region examination, we can palpate splenomegali. The spleen is enlarged in schuffner

one, but there isn't hepatomegaly. In extremity region examination, there is black bluish in top of second, third, and forth finger of left hand. Minimal swelling in her foot.



Figure 1: Gangrene of the left hand

Lab result shown the cell blood count hemoglobin 15,2; HCT: 48,2; PLT: $1,396 \times 10^6$ /cmm, WBC: $30,64 \times 10^3$ /cmm, neutrophile: 87,3%; liver function; SGOT: 70; SGPT :25, blood sugar ad random: 128mg/dl. Ureum: 100, creatinin: 2,5; electrolyte: sodium: 142; Kalium: 3,7; Chloride: 97. Blood smear: Leukocytosis with thrombocytosis moderate DD: reactive thrombocytosis with septicemia. Chest X-ray shown cardiomegaly, ECG: T inverted in V1-V4 (ischemic anteroseptal).



Figure 2: Electrocardiography

The diagnosis was suspect thrombocytopenia essential with arterial thrombosis and heart failure et causa coronary artery disease+hypertension was made. With the differential diagnosed is sepsis et causa gangrene digiti II-IV manus sinistra et causa arterial thrombosis with heart failure et causa coronary artery disease.

The patient was treated with aspirin 1x80mg and clopidogrel 1x75 mg. We plan to do bone marrow and give hydroxyurea (15mg/kg body weight) or Anagrelide (thromboreductant).

Cardiologist gives her diuretic(furosemide 2x20mg i.v.) and ARB (Valsartan 1x80mg), ISDN 3x5mg. We also treated by giving the antibiotic to cure secondary infection from the arterial thrombosis. We consult the patient to surgeon and decided to necrotomy her fingers, but the patient and family reject. Patient condition getting worse day by day, and she was died at fifth days after the treatment.

3. Discussion

On the anamnesis we found data that black bluish in the top of her fingers on left hand from five days before admission. There wasn't injury. She hasn't high blood glucose level or past illness with high glucose level, there isn't another bleeding. She is never smoking tobacco. There is not hematological disorder in her family. From the physical examination, there were necrotic tissue in her digiti II-IV in left hand. From the laboratory examination there was increased of leukocytes and thrombocytes. The leukocyte is more than 10.000/cmm and the thrombocyte is more than 1.000.000/cmm. From the blood smear, leukocytosis with thrombocytosis moderate. So we diagnosed this patient with suspect thrombocytopenia essential with arterial thrombosis. Maybe the arterial thrombosis causes secondary infection .

And the differential diagnosis is sepsis et causa gangrene manus digiti II-IV with reactive thrombocytosis. For the treatment, we give her aspirin 1x80mg and clopidogrel 1x75 mg to her thrombosis and give antibiotics to prevention infection secunder and reduced leukocytosis. Surgery will do necrotomy, but the patient rejected. We plan to do bone marrow puncture to see the possibility the increasing of megakaryocyte and to make that thrombocytopenia essential beco could become definite assessment.

The patient also feel shortness of breath 3 days prior to admission. Orthopneu, she also felt chest pain like strucked down in her chest. Her past illness were hypertension and cardiology disease without regular control and treatment. From the physical examination, she had high blood pressure, increased of JVP, used of breath muscle, and minimally swelling in her foot. From the laboratory examination, cardiomegaly in her chest X ray and ischemic anteroseptal in her electrocardiography. So, the assesment for these are heart failure caused by coronary artery disease and hypertension. The treatment for this case are diuretics(furosemide 2x20mg i.v) to balance the liquid of the body and reduced shortness of breath, clopidogrel 1x75mg, ISDN 3x5mg and aspirin 1x80mg to reduce the ischemic which caused chest pain.

Thrombocytosis is defined as platelet count >450.000/cmm. The major types of thrombocytosis include reactive (or secondary thrombocytosis, clonal myeloid neoplasm, and familial or hereditary thrombocytosis.⁷ As the most common cause is reactive process, at the time of the first visit we always consider secondary thrombocytosis through a complete interview, physical examination, laboratory examination.

Table 1: 2016 WHO diagnostic criteria for ET compared with those for prefibrictic myelofibrosis.^{2,5}

<i>Diagnostic criteria</i>	<i>Major criteria</i>	<i>Minor criteria</i>
For ET (Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria, and the minor criterion)	<ol style="list-style-type: none"> 1. PLT count>450x10⁹/L 2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers 3. Not meeting WHO criteria for BCR-ABL1⁺ chronic myeloid leukemia, PV, PMF, MDSs, or other myeloid neoplasms. 4. Presence of JAK2, CALR, or MPL mutation 	Presence of a clonal marker or absence of evidence for reactive thrombocytosis
For prefibrictic myelofibrosis (Diagnosis of prefibrictic myelofibrosis requires meeting all 3 major criteria, and at least 1 minor criterion)	<ol style="list-style-type: none"> 1. Megakaryocytic proliferation and atypia, without reticulin fibrosis>grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting WHO criteria for BCR-ABL1⁺, chronic myeloid leukemia, PV, ET, MDSs, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutation, presence of another clonal marker, or absence of minor reactive bone marrow reticulin fibrosis 	Presence of at least 1 of the following, confirmed in 2 consecutive determinations: <ol style="list-style-type: none"> a. Anemia not attributed to a comorbid condition b. Leukocytosis (WBC count>11x10⁹/L) c. Palpable splenomegaly d. Lactate dehydrogenase level increased to above upper normal limit of institutional range
Diagnostic criteria	Major criteria	Minor criteria
For ET (Diagnosis of ET requires meeting all 4 major criteria or the	<ol style="list-style-type: none"> 5. PLT count>450x10⁹/L 6. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No 	Presence of a clonal marker or absence of evidence for reactive thrombocytosis

first 3 major criteria, and the minor criterion)	significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers 7. Not meeting WHO criteria for BCR-ABL1 ⁺ chronic myeloid leukemia, PV, PMF, MDSs, or other myeloid neoplasms. 8. Presence of JAK2, CALR, or MPL mutation	
For prefibrotic myelofibrosis (Diagnosis of prefibrotic myelofibrosis requires meeting all 3 major criteria, and at least 1 minor criterion	4. Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis 5. Not meeting WHO criteria for BCR-ABL1 ⁺ , chronic myeloid leukemia, PV, ET, MDSs, or other myeloid neoplasms 6. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutation, presence of another clonal marker, or absence of minor reactive bone marrow reticulin fibrosis	Presence of at least 1 of the following, confirmed in 2 consecutive determinations: e. Anemia not attributed to a comorbid condition f. Leukocytosis (WBC count > 11 x 10 ⁹ /L g. Palpable splenomegaly h. Lactate dehydrogenase level increased to above upper normal limit of institutional range

Table 2: Diagnostic Workup of Patients with Thrombocytosis.⁸

Fields/investigations	Questions and/or assessments
Familial history	Relatives with thrombocytosis or other known hematologic disorder
Medical history	Diseases or conditions that can be associated with thrombocytosis (eg malignancy, inflammatory bowel disease, iron deficiency, splenectomy, bleeding) Vascular complication (thrombosis or bleeding) Comorbidities like diabetes, hypertension, or dyslipidemia
Lifestyle	Smoking, physical activity, dietary habits
Medications	Regular and/or recent use of drugs
Symptoms	Headache, vertigo, dizziness, tinnitus, erythromelalgia
Physical examination	Presence of splenomegaly and/or hepatomegaly
First level tests*	CBC count and evaluation of peripheral blood smear Evaluation of body iron status (serum iron, TIBC, transferrin saturation, and serum ferritin) CRP Screening for BCR-ABL1 rearrangement Test for JAK2(V617F), CALR exon 9 indels, and MPL exon 10 mutations, to be performed sequentially on granulocyte DNA
Second level test	Bone marrow evaluation through bone marrow aspirate and biopsy (H&E or Giemsa, Gomori and Perls Staining) Further laboratory tests (eg, von Willebrand factor when platelet count is > 1000 x 10 ⁹ /L or when an acquired von Willebrand syndrome is anyhow suspected) and radiological /ultrasound examination

According to the European Leukemia Net (ELN) recommendation,⁹ all ET patients should be managed with low dose aspirin if microvascular disturbances are present. A study conducted on low risk venous thrombosis in JAK2-mutated patients and the rate of arterial thrombosis in those with cardiovascular risk factors.¹⁰ In the remaining low risk patient, antiplatelet therapy was not effective as primary prophylaxis thrombosis. Subsequent studies have confirmed that cardiovascular risk factors and JAK2 (V617F) represent independent risk factor for thrombosis in ET.^{11,12,13} In JAK2 (V617F) plays a major role in the pathogenesis of thrombosis, whereas CALR or MPL mutation and triple negativity identify patient with lower thromboembolic risk. Although cytoreductive treatment is not indicated in low risk ET patients who have an incidence of thrombosis similar to that of healthy control population.¹⁴ It is definitely indicated in high risk patients.^{15,16} The ELN recommended hydroxyurea at first line cytoreductive therapy at any age, although they also underlined that its use should be carefully considered in patients younger than 40 years of age.⁹ In our current practice, we start hydroxyurea at a dose 1 g/day, and then modify the dose according to the hematologic response. The objective of treatment is dual, that is: (1) to lower PLT count below 450 x 10⁹ /L and (2) to correct leukocytosis (WBC count > 11.000/cmm), if present. We consider correcting leukocytosis very important, whereas we are relatively flexible with respect to the PLT

count: actually, we consider acceptable also values between 450.000 and 600.000/cmm, especially if these values can be achieved with lower doses of hydroxyurea (eg, 500 mg per day). Our clinical practice is supported by a number of studies showing that the actuarial probability of thrombosis is influenced by leukocytosis and not by PLT count.¹⁷⁻²⁰ In the prospective Thrombocytopenia 1 Trial (PT-1) cohort, PLT count outside of the normal range during follow up was not associated with a risk of thrombosis, but rather with a risk of bleeding.²⁰

References

- [1] Tefferi, A the Philadelphia chromosome negative chronic myeloproliferative disorders: a practical overview. *Mayo Clinic Proc* 1998; 73:1177
- [2] Passamonti F, Thiele J, Girodon F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by international working group on myelofibrosis research and treatment. *Blood*. 2012; 120(6):1197-1201
- [3] Cazzola M. Mutant calreticulin: when a chaperone becomes intrusive. *Blood*. 2016;127(10): 1219-1221
- [4] Harrison, CN. Current trends in Essential Thrombocythemia. *BRJ Haematology* 2002;117:196

- [5] Bakta, Made. Hematologi Klinik Ringkas. Diagnostic Criteria for Essential Trombocytomia. 2006:155
- [6] Arber D.A., Orazi, et al. The 2016 Revision to the WHO classification of myeloid neoplasm and acute leukimia. Blood. 2016; 127(20):2391-2405
- [7] Schaffer Al. Thrombocytosis. N Engl J Med. 2004; 350(12):1211-1219
- [8] Elisa R, Mario C. How I treat essential thrombocytomia. Blood.2017;128:120
- [9] Barbui T, Barosi, et al. Differential clinical effect of different mutation subtypesin CALR-mutant myeloproliferative neoplasm leukimia. 2016;30(2):431-438
- [10] Alvarez, Larran A, et al. Observation vs anti PLTtherapy as primary prophylaxis for thrombosis in low risk essential thrombocytomia . Blood.2014;124(16:2611-2612)
- [11] Barbui, Finazzi, et al. Development and validation of an international prognostic score of thrombosis in essential thrombocytomia(IPSET-thrombosis). Blood. 2012 :120-126: 5128-5133
- [12] Finazzi, Carroblo,et al. Calreticulin mutation does not modify the IPSET score for predicting the risk of thrombosis
- [13] Barbui, Vannucchi,et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocytomia. Blood Cancer J.2015; 5:e369
- [14] Ruggeri, Finazzi, et all. No treatment for low risk thrombocytomia: results from a prospective study. Br J Haematol.1998;103(3):772-777
- [15] Cortelazzo, Finazzi, et al. Hydroxyurea for patients with essential thrombocytomia and a high risk of thrombosis. N. Engl J. Med.1995;332 (17):1132-1136
- [16] Barbui, Finazzi. When and how to treat essential thrombocytomia. N Engl J Med. 2005; 353(1):85-86
- [17] Carobbio, Antonioli, et al.Leukocytosis and risk stratification assesment in essential thrombocytomia. J Clin Oncol. 2008; 26(16):2372-2736
- [18] Carrobio, Finazzi, et al. Hydroxyurea in essential thrombocytomia:rate and clinical relevance of response by European Leukemia Net criteria. Blood: 2010;116(7):1051-1065
- [19] Carobbio, Thiele, et al. Risk factors for arterial and venous thrombosis in WHO defined essential thrombocytomia: an international study of 891 patients. Blood.2011; 117(22):5857-5859
- [20] Campbell, MacLean,et al. Correlation of Blood counts with vascularcomplications in essential thrombocytomia: analysis of the prospective PT1 cohort. Blood:2012;120(7):1409-1411
- [21]