

# Acute Stroke as Initial Manifestation of Essential Thrombocytosis in a 77-Year-Old Filipino Female: A Case Report



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## ABSTRACT

Essential thrombocytosis (ET) is one of the myeloproliferative neoplasms (MPNs) which increase the probability of thrombosis and bleeding. ET is usually discovered as an incidental finding on blood workup and in rare cases, will present as vascular events such as stroke. Our patient, a 77-year-old female, a case of acute cerebral infarct presented with numbness and severe weakness of left upper and lower extremity. Serial complete blood count showed an elevated platelet count. Bone marrow aspiration studies showed increased number of enlarged megakaryocytes. She was diagnosed as a case of ET and maintained on Aspirin 80 mg per tablet once a day and Hydroxyurea 500 mg per tablet once a day.

**Keywords:** Essential thrombocytosis, Myeloproliferative neoplasms, Acute cerebral infarct, Aspirin, Hydroxyurea

## INTRODUCTION

Essential thrombocytosis (ET) is characterized by elevation of platelet count with associated hyperplasia of megakaryocytes in the bone marrow. The thrombocytosis increases the probability of thrombosis and can even cause bleeding.[1] Hematologic disorders were determined to be the underlying cause of cerebrovascular disease in 1.27% of patients diagnosed with such blood-related conditions.[2]

ET is one of the myeloproliferative neoplasms or MPNs which also includes chronic myeloid leukemia (CML), polycythemia vera (PV) and primary myelofibrosis (PMF). The World Health Organization (WHO) classification also included chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL) and MPN-unclassifiable.[3] Patients with JAK (Janus Kinase) 2 mutations are associated with the risk of developing MPNs.[4]

In a retrospective study by Rose, et.al. in 2012 involving patients with thrombocytosis in a tertiary care hospital, primary thrombocytosis was observed in 5% of cases.[5] The estimated yearly incidence in the United States is 2.5 per 100,000, whereas the prevalence is estimated to be 24 per 100,000.[6] Moreover, the incidence is higher in female than in male patients, female to male ratio of 2:1.3.3.[7] The median age at diagnosis is 60 years.[8]

JAK2 mutation is present in 90% of patients with PV and 60% of patients with ET and PMF. JAK2 functions to activate intracellular signaling pathways that eventually lead to increased expression of

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cytokines such as key hematopoietic cytokines, such as erythropoietin, thrombopoietin (TPO) and granulocyte colony-stimulating-factor.[9]

In 2008, the World Health Organization set the criteria for ET with the diagnosis requiring four criteria: (a) sustained platelet count  $>450 \times 10^9/L$ , (b) bone marrow biopsy showing increased number of enlarged, mature megakaryocytes; no significant increase or left shift of granulopoiesis or erythropoiesis, (c) not meeting WHO criteria for PV, PMF, BCR-ABL (Fusion of the break point cluster (BCR) gene at chromosome 22 and Abelson (ABL) tyrosine kinase gene at chromosome 9) positive CML, MDS (myelodysplastic syndrome) or other myeloid neoplasm and (d) demonstration of JAK2 V617F or other clonal marker or in the absence of JAK2 V617F, no evidence of reactive thrombocytosis.[10]

According to the British Committee for Standards in Hematology, diagnosis of ET requires three out of

the following five (A1 to A3 or A1 + A3 to A5)[11] criteria:

(A1) Sustained platelet count  $>450 \times 10^9/L$

(A2) Presence of an acquired pathogenic mutation (JAK2, CALR, or MPL)

(A3) No other myeloid malignancy, especially polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome

(A4) No reactive cause for thrombocytosis and normal iron stores

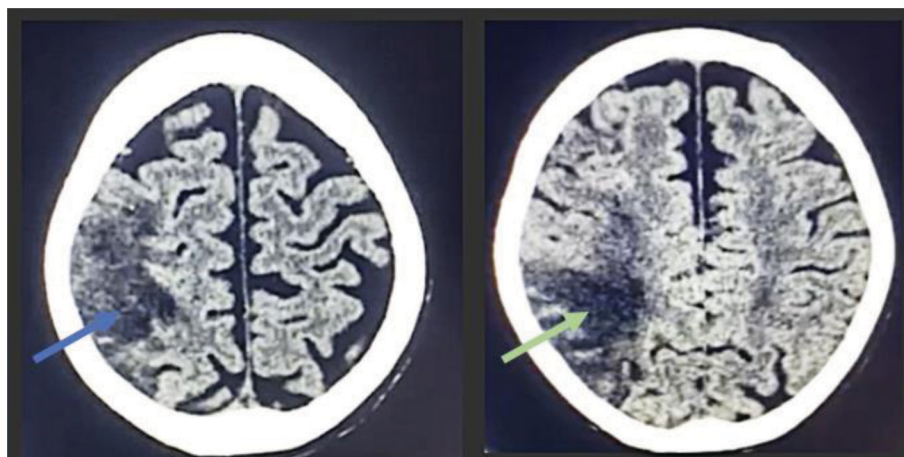
(A5) Marrow studies showing increased megakaryocytes displaying a spectrum of morphology with prominent large hyperlobulated forms; reticulin is generally not increased

## CASE PRESENTATION

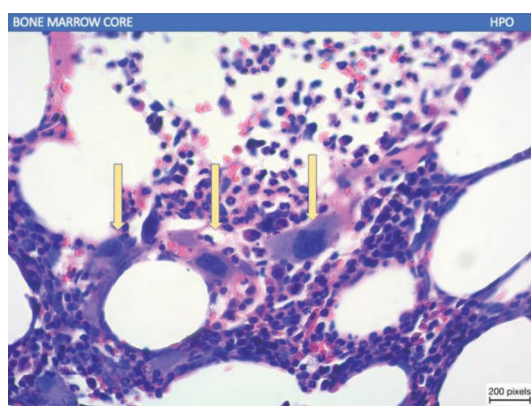
A 77-year-old female initially presented with numbness of the left upper extremity. After nine



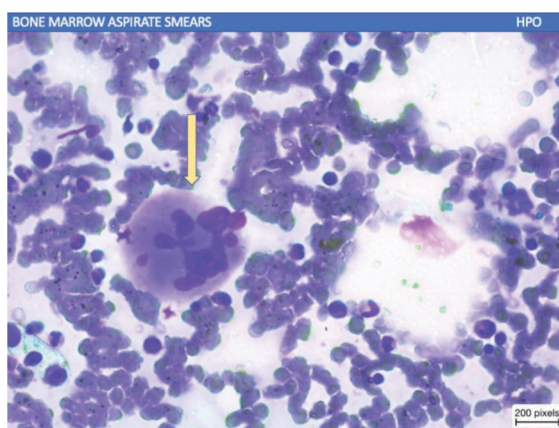
**Figure 1:** Erythematous appearance of both dorsal and palmar aspects of both hands



**Figure 2:** Areas of hypodensity are noted in the cortical and subcortical regions of the right frontal, parietal, temporal and occipital lobes seen in plain cranial computerized tomography as indicated by the arrows.



**Figure 3:** Increased number of megakaryocytes, with hyperlobulation (multiple overlapping lobes) as indicated by yellow arrow (high power field)



**Figure 4:** An image of enlarged megakaryocyte on bone marrow aspiration as indicated by yellow arrow (high power field)

days, the patient presented with severe weakness of left upper and lower extremity. This patient was diagnosed with hypertension for five years with no known other comorbidities. She was a non-smoker, non-alcoholic beverage drinker and denies illicit drug use.

The patient came in hypertensive with her blood pressure elevated at 170/90 mmHg. On physical examination, the patient had erythematous palms with noted macules on both dorsal and palmar aspects of both hands. She reported having a burning-like sensation in her palms for the past five years. There were no carotid bruits or murmurs which are all physical examination findings pointing to risk factors for developing stroke. Neurologic findings during admission included left central facial palsy, weakness on the left and upper extremity with manual muscle testing score of 1/5, and 50% hemisensory deficit in both left upper and lower extremities. NIHSS (National Institute for Health Stroke Score) was at 13 which indicated a moderate severity of stroke.

Cranial computed tomography showed areas of hypodensity in the cortical and subcortical regions of the right frontal, parietal, temporal and occipital lobes. There was loss of grey-white matter differentiation as well as effacement of the adjacent cortical sulci which was interpreted as acute infarction.

Her post-imaging assessment was acute cerebral infarct, right frontoparieto-occipital area, right middle cerebral artery in territory, NIHSS score of 13. She was immediately given Clopidogrel 75 mg/tab one tablet once a day, atorvastatin 40 mg/tab one tablet once a day and was started on intravenous plain 0.9% saline at a rate of 120 cc per hour for mean arterial pressure maintenance.

Echocardiogram showed normal ejection fraction at 62% with aortic sclerosis, mild mitral regurgitation, mild tricuspid regurgitation and normal pulmonic pressure at 21 mmHg. Carotid evaluation showed atherosclerosis and non-hemodynamically significant (<50%) stenoses in the bilateral internal, common and external carotid arteries with normal bilateral

vertebral arterial flow. No episodes of atrial and ventricular fibrillation were noted on Holter studies.

Basic laboratories were done which showed normal fasting blood sugar, lipid profile, liver function tests and creatinine. Initial complete blood count showed hemoglobin at 125, hematocrit 0.3 and white blood cell count at 9.5 mg/dL; however, the platelet count was elevated at 651 mg/dL  $\times 10^9/L$ .

Secondary causes of thrombocytosis were investigated including iron deficiency anemia. Iron was 23.45 ug/dL, ferritin was 330.30 ng/mL and total iron binding capacity 149.85 ug/dL (148.60-491.60). Repeat complete blood count showed reduced platelet count from baseline at 578  $\times 10^9/L$ . After three days, the platelet count was elevated at 629  $\times 10^9/L$ .

Bone marrow aspiration was done which showed normocellular bone marrow (20%-30%) with megakaryocytic hyperplasia with large forms with intact erythropoiesis and granulopoiesis. Myeloid erythroid ratio was 2.4:1. The findings were suggestive of MPN which was compatible with ET.

Clopidogrel was discontinued and Aspirin 80 mg per tablet once a day and Hydroxyurea 500 mg per tablet once a day were started since the patient was diagnosed with ET. The patient underwent daily physical rehabilitation and was eventually discharged with an MRS (Modified Rankin Scale) score of 5 and with the same neurological deficits.

## DISCUSSION

ET is usually discovered as an incidental finding on blood workup. In symptomatic patients, the most frequently reported are just constitutional symptoms including fatigue (90.3%) and numbness (58.8%). [12] Hence, the diagnosis of ET is usually missed. Other classical findings of ET include "erythromelalgia" which is a result of occlusion of small blood vessels and manifests as discomfort and burning sensations in the fingers or toes, sometimes accompanied by mottling or discoloration of the skin, which is present in this case. Increased thrombotic risk can cause vascular events like cerebrovascular accidents and can also cause thrombosis in hepatic, portal and mesenteric circulations. [13] The thrombotic risk event increases over time after

the diagnosis. The strongest predictive factors for thrombotic complications are age older than 60 years or a history of previous thrombosis. [14]

In a study made by Arboix, et.al., they studied 1099 patients with first acute cerebrovascular accident and found six cases of ET (0.54%) in whom cerebrovascular disease was the first manifestation of ET. The mean platelet count was  $597 \times 10^9/L$  (range, 414 to  $760 \times 10^9/L$ ). All patients had circulating erythroid progenitors, megakaryocytic progenitors, or both. [15]

The vascular complication of ET affects a patient's quality of life which includes cerebrovascular accidents in the form of ischemic stroke and transient ischemic attacks. [16]

In patients with thrombocytosis, the bleeding time, platelet glass retention and clot retraction are normal, but evidence of platelet hyperaggregability is present which posits risk to develop vascular events. [17] The patient was diagnosed as a case of ET since she was able to fulfill the criteria of the British Committee for Standards in Hematology which includes: (1) No other myeloid malignancy, especially PV, PMF, CML, or myelodysplastic syndrome; (2) No reactive cause for thrombocytosis and normal iron stores and (3) Marrow studies showing increased megakaryocytes displaying a spectrum of morphology with prominent large hyperlobulated forms; reticulin is generally not increased. JAK2 mutation was not done for this case due to financial limitations. However, in a study conducted by Karkucak, et.al. in 2012, JAK2 mutation was reported to be positive only in 61% of ET cases. [18]

She was classified as high risk due to her age (>60 years) and history of thrombotic event as seen in her stroke. Another risk factor was having a platelet count of greater than or equal to  $1,500 \times 10^9/L$ . According to the current treatment algorithm for ET by Tefferi, et.al. in 2018, patients who are at high risk with history of arterial thrombosis should be started on Hydroxyurea and Aspirin twice daily. [19]

Aside from Aspirin which is an anti-platelet that can significantly reduce thrombosis, Hydroxyurea was included in treatment since it also produced a significant reduction in thrombotic events in patients with ET. Hydroxyurea is a hydroxylated analog of urea, inhibiting DNA synthesis by inhibiting ribonucleotide diphosphatase reductase and blocking the conversion of ribonucleotides to

deoxyribonucleotides.[20] In PT-1 trial, a randomized study that compared Hydroxyurea plus Aspirin versus anagrelide plus Aspirin, it demonstrated the superiority of Hydroxyurea plus low-dose Aspirin in preventing vascular events overall and transformation to myelofibrosis, although anagrelide proved to be superior in prevention of venous occlusive events.[21]

The reported life expectancy of patients with ET were as high as 33 years in patients younger than 60 years.[19]

## CONCLUSION

Complete blood count including platelet count is a valuable examination, yet most of the times, overlooked by physicians. Increased platelet count should be further investigated, especially in thrombotic diseases since this is a risk factor for developing vascular events such as stroke. This low-cost laboratory examination may also serve as a hint to less common diseases like MPNs such as ET.

## Ethical Considerations

This study complies with the ethical principles set out in relevant guidelines as specified in the Certificate

of Agreement and Compliance in this research; as well the National Ethical Guidelines 2017 edition.

## Informed Consent Process

A clearly written informed consent form was obtained, understood and signed by the patient and a legally acceptable representative, securing their consent for presentation, publication of the case, taking of photographs and videos, including other diagnostic results and images. The primary investigator, not the primary physician of the patient, obtained consent.

## Vulnerability

The subject in this research was a patient of the secondary investigator of this research. Nevertheless, vulnerability was reduced with the primary investigator obtaining the consent for the patient.

## Privacy and Confidentiality

Patients' confidentiality is protected by removing patient identifiers in the case report, with full compliance to the Data Privacy Act of 2012 and its implementing rules and regulations in 2016.

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