

Essential Thrombocytosis

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ABSTRACT

Essential thrombocytosis [ET] is a nonreactive, chronic myeloproliferative disorder in which sustained megakaryocyte proliferation leads to an increase in the number of circulating platelets, splenomegaly, a clinical course characterized by thrombotic or haemorrhagic episodes or both¹. We report here three cases of Essential Thrombocytosis. The first two cases presented for the first time; the third case having complications caused by drugs used in its treatment.

Key Words : Essential Thrombocytosis , Splenomegaly, Erythromelalgia.

Introduction :

Essential thrombocytosis is a clonal proliferation of multipotent hematopoietic progenitor stem cells without a definable cause². It is found in 1-2 persons per 100,000 populations with a female preponderance and can occur in any age group². The majority of patients with essential thrombocytosis have mutations in one of three genes : Janus kinase 2 (JAK2) (50-60%), calreticulin (CALR) (25%), or myeloproliferative leukemia virus oncogene (MPL) (3-5%). Rare cases involve mutations in the thrombopoietin gene (THPO), which are associated with autosomal dominant hereditary thrombocytosis, and somatic mutations in tet methylcytosine dioxygenase 2 (TET2).

In 50 % cases, the disorder is asymptomatic. If symptomatic, it presents with either thrombotic episodes due to microvascular occlusion or hemorrhagic tendencies.

CASE 1

A 40 year old female patient (**Figure 1**) presented to us with chief complaint of left sided abdominal pain with dragging sensation off & on since one year. There was no history of easy fatigability, fever,

weight loss or bleeding tendencies. Examination did not reveal any pallor, icterus, lymphadenopathy, sternal tenderness or knuckle pigmentation. There was a 5 cm splenomegaly.

Laboratory investigations were as follows : Hemoglobin : 9 g/dL; White Blood Cell Count : 22,200 / mm³ with 88% Granulocytes & 8% Lymphocytes; Platelet Count : 11 lac / mm³ with Platelet Distribution Width of 13.1% and Plateletcrit of 1.10%; Kidney & Liver function tests were normal. CRP was negative. Serum Ferritin was 30 ng/ml. The peripheral blood smear showed Normocytic to Microcytic Anemia with Mild Hypochromia, Leucocytosis and abundant Platelets (**Figure 2**).

Ultrasonography of abdomen revealed heterogenous echotexture of liver with portal cavernoma formation and splenomegaly of 18.7cm. Her oesophago-gastro-duodenoscopy revealed small esophageal varices with duodenal ulcer in D1 segment.

Owing to high degree of thrombocytosis and splenomegaly, patient underwent bone marrow aspiration which showed hypercellularity with myeloid to erythroid ratio of 8:1; mild erythroid hyperplasia; severe hyperplasia of myeloid precursors with eosinophilia & basophilia without increase in myeloblasts and increased megakaryocytes with normal morphology (**Figure 3**).

At this stage two differential diagnosis were kept: CML with thrombocytosis and essential thrombocytosis. To confirm the diagnosis, patient

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underwent genetic studies as follows : BCR-ABL (Philadelphia) translocation tested by FISH technique was negative and JAK-2 mutation analysis done by PCR turned out to be positive for alteration of codon from GTC → TTC at position 617 of JAK 2 gene exon 14 (V617F).

Hence a final diagnosis of essential thrombocytosis was made and patient was discharged on hydroxyurea 500 mg tablet once a day. Owing to the duodenal ulcer, the patient was not started on aspirin. Four weeks post discharge her platelet count decreased to 5,42,000 /mm³.



Figure 1

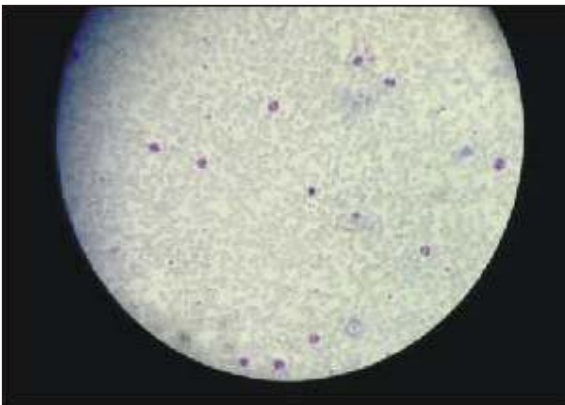


Figure 2 : Peripheral smear showing abundant platelets

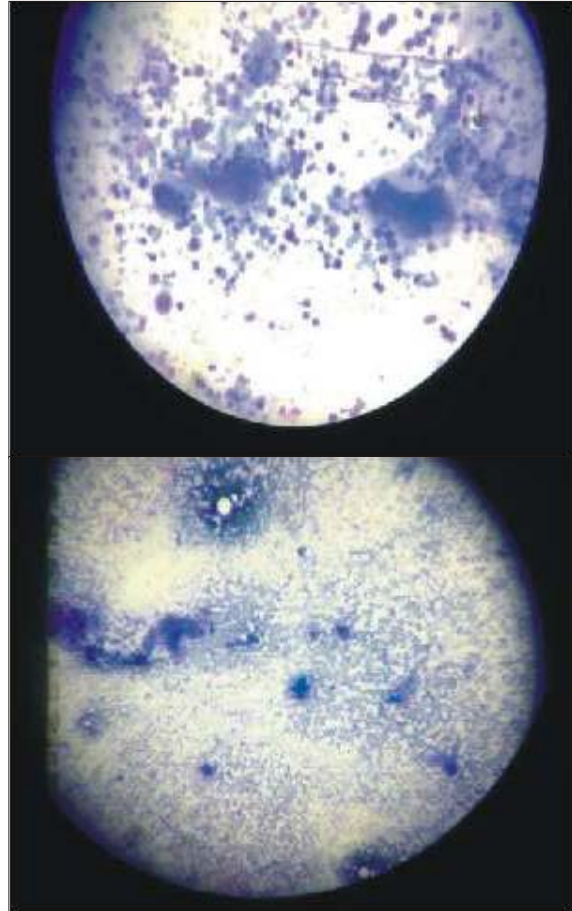


Figure 3 : Bone marrow aspirate showing increased megakaryocytes with normal morphology

CASE 2

A 52-year-old female patient (*Figure 4*) came with chief complaints of burning in hands and feet since one year and blackening of great toe and second digit of left foot since 6 months. General examination showed erythromelalgia of both feet along with trophic ulcers and blackish discoloration of great toe and second digit of left foot (*Figure 5*). Her systemic examination was unremarkable.

Her CBC showed a hemoglobin of 12.6 g/dL; white blood cell count : 20,100/mm³ with 83.3% granulocytes and 11.4 % lymphocytes; platelet count : 17,12,000 / mm³ with platelet distribution width of 13.3% and platelet crit of 1.420%; kidney

and liver function tests were normal. CRP was negative. Serum ferritin was 8.4 ng/ml. The peripheral blood smear showed normocytic normochromic, neutrophilic leucocytosis and abundant giant platelets (*Figure 6*). Ultrasonography of abdomen revealed mild splenomegaly of 13 cm. Bilateral arterio-venous doppler of lower limbs was normal. Her bone marrow biopsy (*Figure 7*) showed hypercellularity with myeloid to erythroid ratio of 4:1. Erythropoiesis showed normoplasia. Myelopoiesis showed mild hyperplasia of granulocyte precursors. Thrombopoiesis showed increased megakaryocytes with hyperlobated forms with no atypia.

Since the patient's ferritin reserves were low, patient was given intravenous iron sucrose and was discharged on low dose aspirin and hydroxyurea and was asked to follow up after 1 month.

After normalization of serum ferritin, she underwent genetic testing for BCR-ABL and JAK-2 mutations. She was negative for BCR-ABL fusion gene but turned out to be positive for JAK-2 Mutation.

Hence she was diagnosed as a case of essential thrombocytosis and was continued with low dose aspirin and hydroxyurea.



Figure 4



Figure 5 : showing erythromelalgia, trophic ulcer and gangrenous changes

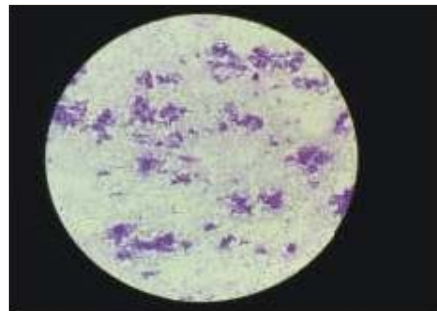


Figure 6 : Peripheral smear showing giant platelets

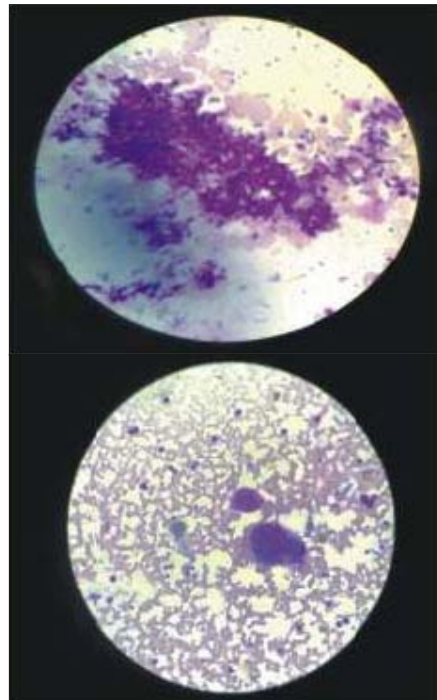


Figure 7 : Bone marrow biopsy showing increased megakaryocytes with hyperlobated forms

CASE 3

A 30 year old female patient presented with chief complaints of hyperpigmented brittle nails, skin bruises and bleeding per rectum.

The patient was a diagnosed case of essential thrombocytosis (JAK-2 positive) with past history of mesenteric vein thrombosis and deep vein thrombosis of left lower limb. She was on hydroxyurea, aspirin and warfarin.

On general examination, her vitals were stable; she was pale, with multiple skin bruises (**Figure 8**) and her nails showed onycholysis and hyperpigmentation (**Figure 9**). CBC showed Hemoglobin of 4.8 g/dl, total leucocyte count of 25000 /mm³, platelet count of 3,68,000 /mm³, MCV of 79.9 FL and RDW of 15%. Her INR was 3.47. Ascitic tap showed hemoperitoneum. Dermatologist opinion was taken for nail changes, which were attributed to hydroxyurea.

Hence the patient was having warfarin-induced ecchymosis as well as hydroxyurea induced nail changes. Warfarin was stopped and the patient was given vitamin K and transfused with fresh frozen plasma and whole blood.

The patient was later discharged on aspirin. Hydroxyurea was continued as nail changes were permanent.



Figure 8 : Warfarin induced skin ecchymosis



Figure 9 : Hydroxyurea induced nail changes

Discussion :

Essential thrombocytosis (ET), one of the myeloproliferative neoplasms, is a clonal hematopoietic stem cell disorder characterized by thrombocytosis and may be associated with thrombotic and hemorrhagic complications³. Epstein and Goedel first described it in 1934⁴. The etiology remains unknown. 50-60% of subjects show JAK-2 gene mutation³. Other mutations include acquired mutations in CALR gene and MPL oncogene.

The main pathophysiology behind essential thrombocytosis is increased production of platelets by megakaryocytes possibly due to autonomous production of platelets due to switching ON of thrombopoietin receptor, increased sensitivity to cytokines or decreased effect of plateletinhibiting factors (e.g. TGF-beta). Platelet survival & morphology is normal.

The course of essential thrombocytosis is complicated with episodes of microvascular occlusion and / or hemorrhage. Thrombosis occurs due to increased production of abnormal Thromboxane A₂^{5,6}. Bleeding diathesis occurs due to acquired VWF deficiency⁷.

Patients are mostly asymptomatic (**Case 1**) and diagnosed when their blood counts show persistent thrombocytosis. If symptomatic, patients present with symptoms of microvascular occlusion in the form of headache, blurring of vision, chest pain, abdominal pain, erythromelalgia (**Case 2**) and acral dysesthesia. Hemorrhagic complications are rare. The gastrointestinal tract is the primary site of bleeding. Approximately 40% of these patients have duodenal arcade thrombosis, resulting in sloughing of the duodenal mucosa, simulating a duodenal ulcer. (**Case 1**). The bleeding is generally associated with a platelet count > 10 lac.¹

Only 10% of patients present with mild splenomegaly; significant splenic enlargement should raise the possibility of another myeloproliferative neoplasm such as PMF or CML³. A small subset of subjects shows transformation to AML or PMF later on in life.

Diagnosis of essential thrombocytosis is made only after ruling out reactive thrombocytosis and other MPN / MDS and then using WHO-2016 criteria which is based on platelet count, bone marrow findings and genetic studies. The cut off point for platelet count is 4.5 lac / mm³.

The treatment of essential thrombocytosis includes stratifying the patients according to risk category. Patients are classified into

- Very-low risk** (Age < 60 years; no thrombosis history & absence of JAK2 mutation),
- Low risk** (Age < 60 years; no thrombosis history & presence of JAK2 mutation),
- Intermediate risk** (Age ≥ 60 years; no thrombosis history & absence of JAK2 mutation)
- High risk** (Age ≥ 60 years or thrombosis history & presence of JAK2 mutation)⁸.

All patients of essential thrombocytosis are started on low dose aspirin unless contraindicated. Cytoreductive agents are added if patient falls into high risk category.

Patients with essential thrombocytosis have a shortened life expectancy probably due to conversion to PMF or AML. Rates of conversion to myelofibrosis in the first decade after diagnosis is 3 to 10 percent; rising to 6 to 30 percent in the second decade³. Progression to AML occurs with a prevalence of 1 to 2.5 percent in the first decade after diagnosis, 5 to 8 percent in the second decade, and continuing to rise there after¹.

Conclusion :

Essential thrombocytosis has a varied spectrum of presentation in clinical setting. The diagnosis should always be made after ruling out causes of reactive thrombocytosis and other myelodysplastic syndromes.

Abbreviations :

- AML - Acute myeloid leukemia
 CALR - Calreticulin
 CML - Chronic myeloid leukemia
 MDS - Myelodysplastic syndrome
 MPL - Myeloproliferative leukemia virus
 MPN - Myeloproliferative neoplasia
 PMF - Primary myelofibrosis

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