

## **Case History: A 45 Year Old Female Presenting with Fatigue, High Platelets and Splenomegaly. Clinical Approach, Investigations and Management**

**Saad Hussain Gillani<sup>1\*</sup> and Qurratulain Maroof<sup>2</sup>**

<sup>1</sup>*Classified Medical Specialist, Fauji Foundation Hospital, Pakistan*

<sup>2</sup>*Medical Officer Fauji Foundation Hospital, Pakistan*

**\*Corresponding Author:** Saad Hussain Gillani, Classified Medical Specialist, Fauji Foundation Hospital, Pakistan.

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A 45 year old female presents with a 9 months history of fatigue & 6 months history of weakness and burning of hands upper abdominal discomfort and headaches.

She has been complaining of low appetite and steady weight loss as well.

On examination, she is 5 feet 3 inches tall. Her weight is 55 kilograms.

She has apale appearance suggestive of anaemia.

There is no lymphadenopathy in cervical region or axillary region.

Abdomen exam reveals splenomegaly palpable up to 2 finger breadths below the left costal margin.

Liver is not palpable.

She is afebrile and chest is clear with normal vesicular breathing.

Heart sounds are normal and Neurological examination reveals no focal neurological deficit or otherwise any other pathology.

Investigations are ordered which include

FBC Full Blood Count

LFTs/ Liver Function Tests

RBS/Random blood sugar and Urea

Pregnancy test was negative.

FBC reveals a

Hb of 12 g/L

Platelet count of  $1300 \times 10^9/L$

WCC of  $7 \times 10^3/L$

What is the most likely diagnosis you would like to consider in this patient?

**Essential thrombocytosis:** Essential thrombocytosis (primary thrombocythemia) is a nonreactive, chronic myeloproliferative disorder in which sustained megakaryocyte proliferation leads to an increase in the number of circulating platelets.

**What are the clinical features and characteristics of this disease?**

Majority (25 - 33%) of patients with essential thrombocytosis (primary thrombocythemia) are asymptomatic at diagnosis. The rest of them display vasomotor symptoms or complications from thrombosis or bleeding. Most of the symptoms are related to small- or large-vessel thrombosis.

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Microvascular occlusion of the toes and fingers causes digital pain; gangrene; or erythromelalgia, which is characterized by burning pain and dusky extremity congestion.

The pain increases with exposure to heat and improves with cold; a single dose of aspirin may provide relief for several days.

Headache is the most common neurologic symptom. Patients also report paresthesias and episodic transient ischemic attacks; transient neurologic symptoms include the following:

- Unsteadiness
- Dysarthria
- Dysphoria
- Vertigo
- Dizziness
- Migraine
- Syncope
- Scotoma
- Seizures

Thrombosis of large veins and arteries is common and may result in occlusion of the leg, coronary, and renal arteries. Retinal artery involvement is also possible.

Other complications include venous thrombosis of the splenic, hepatic, pelvic veins & veins of legs. Priapism can occur very rarely as well.

Pulmonary vasculature occlusion can lead to Pulmonary hypertension.

**Bleeding complications are as follows:**

The gastrointestinal tract is the primary site of bleeding complications; approximately 40% of these patients have duodenal arcade thrombosis, resulting in sloughing of the duodenal mucosa, simulating a duodenal ulcer other sites of bleeding include the skin, eyes, gums, urinary tract, joints, and brain.

Bleeding is usually not severe and only rarely requires transfusion.

The bleeding is generally associated with a platelet count greater than 1 million/ $\mu\text{L}$ .

Constitutional symptoms occur in 20-30% of patients. Weight loss is uncommon.

Other symptoms include sweating, fever, and itching.

Pregnancy complications are as follows:

Spontaneous abortions increase.

Placental infarctions may occur, resulting in intrauterine growth retardation and fetal death.

In most cases, fetal loss occurs during the first trimester.

A patient history of spontaneous abortion is the greatest risk factor for subsequent spontaneous abortions.

Excessive bleeding during delivery is rare.

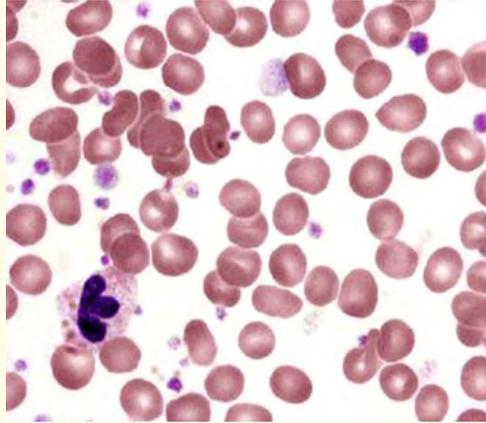
Patients with successful pregnancies show a decrease in platelet count.

**What are the main characteristics of this disease?**

Essential thrombocytosis is characterized by the following:

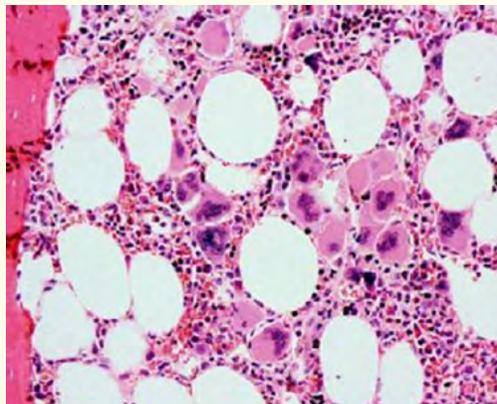
- A persistently elevated platelet count greater than 450,000/ $\mu\text{L}$
- Megakaryocytic hyperplasia

- Splenomegaly
- A clinical course complicated by thrombotic or hemorrhagic episodes or both.



**Figure 1**

Peripheral blood smear in essential thrombocytosis showing increased platelet numbers. Courtesy Wei Wang, MD Department of Pathology, Medical University of South Carolina.



**Figure 2**

Bone marrow biopsy showing increased megakaryocytes in a patient with essential thrombocythemia. Courtesy Wei Wang, MD, Department of Pathology, Medical University of South Carolina.

**Risk factors include the following:**

- Age 60 years or older
- History of thrombosis
- Platelet count greater than  $1500 \times 10^9/L$  which is paradoxically associated with an increased risk of gastrointestinal tract bleeding in young women.
- Increased BMI

- Cardiac risk factors such as smoking, hypertension and hypercholesterolemia.
- Markers of increased thrombosis such as factor V Leiden and antiphospholipid antibodies.
- JAK2 Mutation.

**What are the British Society for Haematology Diagnostic Criteria for this condition?**

British Society for Haematology proposes the following five criteria for diagnosis of essential thrombocytosis:

- Sustained platelet count of  $> 450 \times 10^9 /L$
- Presence of an acquired pathogenic mutation (eg in the JAK2, CALR or MPL genes)
- No other myeloid malignancies
- No reactive cause for raised platelets.
- Bone marrow aspirate and trephine biopsy showing increases megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm.
- Normal iron stores.

Diagnosis requires the presence of criteria 1 -3 or criterion 1 plus 3 – 5

**What is the differential Diagnosis for this condition?**

1. The main differential diagnosis are
2. Chronic Myelogenous Leukemia (CML)
3. Myelodysplastic Syndromes
4. Polycythemia Rubra Vera
5. Primary Myelofibrosis
6. Secondary Thrombocytosis

**What further investigations would you advise**

Tests and procedures used in the workup for essential thrombocytosis include the following:

Complete Blood Count (CBC)

This shows a sustained unexplained elevation in platelet count.

Leukocytosis, erythrocytosis and mild anemia maybe found

Bone Marrow aspirate and biopsy

Genetic studies – For JAK 2 V617F, CALR and MPL mutation

Blood film

Coagulation Studies

Platelet aggregation studies

Serum chemistry

Cytogenic studies are usually normal.

Molecular studies eg PCR Polymerase chain reaction, Southern /genomic blotting may be used as a sensitive means of excluding chronic myelogenous leukemia.

Uric acid levels are elevated in 25 % of patients at diagnosis.

Pseudohyperkalemia may occur and falsely elevated phosphorus and acid phosphatase levels maybe noted.

Vitamin B 12 levels are elevated in 25 % of patients.

Elevation of CRP, fibrinogen and interleukin -6 levels suggest secondary thrombocytosis.

Computed Tomography or Ultrasonography of the abdomen may reveal splenomegaly in patients with essential thrombocytosis even when the spleen is not physically palpable.

**What is the Pathophysiology of this condition?**

Platelet life is normal in essential thrombocytosis.

The elevated counts result from increased production of platelets by megakaryocytes.

The cause of this increase in platelet production remains unclear, but possibilities include the following:

Autonomous production

Increased sensitivities to cytokines (eg, interleukin-3 [IL-3])

Decreased effect of platelet-inhibiting factors (eg, transforming growth factor [TGF] beta)

Defects in the accessory cell microenvironment

The majority of patients with essential thrombocytosis have mutations in one of three genes: Janus kinase 2 (JAK2), calreticulin (CALR), or myeloproliferative leukemia virus oncogene (MPL).

MPL mutations have been associated with only about 3-5% of essential thrombocytosis cases.

JAK2 mutation occurs in around 50 - 60% of patients.

Somatic mutations in CALR are found in approximately 25% of essential thrombocytosis cases.

**What is the 10 years survival rate in these patients?**

Patients with essential thrombocytosis (primary thrombocythemia) have a 10-year survival rate of 64-80%, which may not be significantly different from that of the age-matched general population.

Death mainly occurs due to thrombotic complications.

Most of the clinical manifestations of disease in patients with essential thrombocythemia occur due to involvement of large-vessel or microvascular thrombosis and bleeding.

**What are the main complications of this disease?**

Progression to Acute myelogenous leukemia occurs in 0.6 - 5% of patients during the first ten years and increases significantly in subsequent decades.

Risk factors include anemia (hemoglobin less than 12 g/dL in women and less than 13.5 g/dL in men), platelet count of greater than 1,000,000/ $\mu$ L, and increased age.

**What is the incidence of this disease with respect to gender and age?**

In elderly patients with essential thrombocytosis, the frequency is similar in both genders.

In younger patients, the incidence of essential thrombocytosis is higher in women.

Essential thrombocythemia occurs more frequently in older patients, although younger patients may also develop the disease.

The median age at diagnosis is around 60 years & the disease is rare in children.

**How would you manage this patient**

**Medical Management:**

Treatment in patients with essential thrombocytosis / primary thrombocythemia should be individualized on the basis of risk factors for thrombohaemorrhagic complications.

Observation maybe appropriate for low risk patients i.e. the ones lacking the above risk factors.

Low risk patients experience low rates of thrombosis or bleeding.

Patients with JAK 2 mutations can be treated with daily low dose aspirin twice daily and is also useful for treating symptoms of microvascular occlusion i.e. erythromelalgia.

In emergencies plateletpheresis may be useful to achieve a rapid decrease in platelets counts in the setting of acute thrombosis or marked thrombocytosis.

Cytoreductive therapy is used to decrease the platelet count in High Risk patients. Ie those over 60 years of age, those with history of thrombosis or platelets count greater than 1.5 million/micro litre.

Low dose aspirin with cytoreductive therapy or observation may help treat intermediate risk patients

Lifestyle modification should be recommended for all patients with reversible risk factors. These include balanced diet and regular exercise to promote weight loss for obese patients and smoking cessation for smokers.

### **Cytoreductive Therapy**

Cytoreductive Therapy is used to reduce the risk of haemorrhage for patients with platelet counts above 1 million per microliter.

Extreme thrombocytosis may promote the abnormal adsorption of large Von Willebrand Factor multimers VWF. These patients should be screened for the presence of Von Willebrand Disease / VWD.

Low dose aspirin therapy eg less than 100 mg / day is acceptable if the ristocetin cofactor level is at least 30 %. If it is less than 30% aspirin should be avoided.

Hydroxyurea is considered the first line cytoreductive therapy drug of choice in essential thrombocythemia.

### **Second line agents include the following:**

Busulfan

Anagrelide

Interferon alfa

### **Ruxolitinib**

This is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases. Jakavi directly targets the underlying mechanism of the disease significantly reducing the size of the spleen.

A combination of cytoreductive agents may be needed in cases difficult to manage by single agent therapy

**Interferon alpha** produces high rates of clinical and molecular responses in patients with JAK2 or CALR mutations.

Italian guideline recommend using interferon alfa as a first line platelet lowering therapy for patients younger than 40 years male or female who have no child bearing potential.

Interferon alpha may also be used as a second line therapy in older patients.

In emergencies plateletpheresis may be useful to achieve a rapid decrease in platelet counts.

**Plateletpheresis** maybe indicated in the setting of acute thrombosis and / or marked thrombocytosis.

Another drug Imetelstat which is a telomerase inhibitor is under trial and has shown promise [1-3].

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