Approaches in Hematology

Hematology Made Easy

Essential thrombocythemia

- ✓ **Essential thrombocythemia (ET)** is an uncommon myeloproliferative neoplasm (MPN) characterized by excessive clonal platelet production with a tendency for thrombosis and hemorrhage.

- ✓ **Age of onset:** ET usually presents in middle-aged and older adults.

- ✓ **Pathogenesis**: Approximately 90 percent of cases have a somatically acquired mutation in JAK2, CALR, or MPL.
  - JAK2 mutation – 60 to 65 % (اللي دايماً بيتطلب)
  - CALR mutation – 20 to 25 %
  - MPL mutation – 5 %
  - No JAK2, CALR, or MPL mutation ("triple negative") – 10 to 15 %

- ✓ **Clinical presentation:**
  - Up to one-half of patients with ET are discovered incidentally when thrombocytosis is noted on a complete blood count.
  - Others present with disease-related symptoms (e.g., headache, dizziness, visual changes) or complications (e.g., thrombosis, bleeding, first-trimester fetal loss)

  - Vasomotor symptoms: They are thought to be related to microvascular disturbances.
    - Headache
    - Lightheadedness
    - Syncope
    - Atypical chest pain
    - Acral paresthesia
    - Livedo reticularis
    - Erythromelalgia (burning pain of the hands or feet associated with erythema and warmth)
    - Transient visual disturbances (e.g., amaurosis fugax, scintillating scotomata, ophthalmic migraine.

  - Thrombosis and hemorrhage:
    - Risk of Thrombosis: Patients with ET have an increased risk of thrombosis (e.g., cerebrovascular event, myocardial infarction, superficial thrombophlebitis, deep vein thrombosis, pulmonary embolus) and hemorrhage, likely due to qualitative and quantitative platelet alterations.

- N.B1: An assessment of thrombotic and hemorrhagic risk is an essential part of determining the appropriate management for an individual patient and is discussed in more detail separately.

- N.B2: Importantly, some patients with platelet counts >1 million/microL will have bleeding associated with an acquired von Willebrand disease.

- Predictors of arterial thrombosis include:
  - Age >60.
  - History of thrombosis.
  - Presence of cardiovascular risk factors (e.g., tobacco use, hypertension, diabetes mellitus).
  - White blood cell count >11,000/microL.
  - Presence of the JAK2 V617F mutation.

- Of interest, the presence of a platelet count >1 million/microL was associated with a significantly decreased risk for arterial thrombosis, presumably because of the occurrence of acquired von Willebrand disease in this group of patients.

- Only the male gender is predicted for venous thrombosis.

- Thrombotic events in ET include:
  - Stroke
  - Transient ischemic attacks
  - Retinal artery or venous occlusions
  - Coronary artery ischemia
  - Pulmonary embolism
  - Hepatic or portal vein thrombosis
  - Deep vein thrombosis
  - Digital ischemia: it may start as the Raynaud phenomenon with pallor and/or cyanosis of the digits and dysesthesia and may progress to ischemic necrosis of the terminal phalanges.

- Risk of Bleeding: Bleeding manifestations at the initial presentation of ET are relatively frequent; the risk is significantly associated with extreme thrombocytosis:
  - Platelet count >1 million/microL and >1.5million/microL and >2 million/microL.
  - The use of aspirin in doses >325 mg/day
  - Following treatment with nonsteroidal anti-inflammatory drugs (NSAID)

- However, the risk of major bleeding, as well as thrombosis, may be high post-surgery even in patients with well-controlled disease, or who are receiving thromboprophylaxis.
- Pregnancy loss: Patients with ET have an increased risk of first-trimester pregnancy loss.

✓ **Investigations**:

A. Blood film:

- ET is characterized by marked thrombocytosis in the peripheral blood. The platelets vary in size (platelet anisocytosis), ranging from very small to giant platelets.
- N.B: A leucoerythroblastic picture with teardrop-shaped red blood cells (dacryocytes), poikilocytosis, and circulating nucleated red cells suggests transformation to a post-Essential Thrombocythemia (ET) myelofibrosis stage.

B. Bone marrow aspiration and biopsy: (بذل النخاع وعينة النخاع هتبين الاتى)

- Bone marrow biopsy classically shows normocellularity or moderate hypercellularity for age and trilineage growth with prominent large to giant megakaryocytes with abundant mature cytoplasm, and deeply lobulated and hyperlobulated nuclei.
- The megakaryocytes are located throughout the bone marrow but may occur in loose clusters.
- N.B: If you find one of the following, think of other than ET:
  - Megakaryocytes with highly atypical morphology
  - Increased myeloblasts
  - Myelodysplastic features
  - Significant (> grade 1) reticulin fibrosis or collagen fibrosis

C. Test for mutations:

- Most patients with ET demonstrate mutually exclusive mutations in JAK2, MPL, or CALR. Rough estimates for the frequency at which these genes are mutated in ET are as follows:
  - JAK2 mutation – 60 to 65 percent
  - CALR mutation – 20 to 25 percent
  - MPL mutation – 5 percent
  - No JAK2, CALR, or MPL mutation ("triple negative") – 10 to 15 percent

- N.B: The available test in lab centers is often JAK2 617f.

✓ **Diagnosis**:

- ET is suspected in patients with unexplained persistent thrombocytosis. Several criteria have been proposed for making the diagnosis of ET:

1. Diagnostic evaluation: It is our practice to include the following in the initial evaluation of a patient with suspected ET:

- Focused history including an assessment of
  - Constitutional symptoms,
  - Disease tempo (with prior blood counts when available)
  - Vasomotor symptoms.
  - Thrombotic/ hemorrhagic events, and cardiovascular risk factors.
  - Patients are queried about diseases or conditions that can be associated with thrombosis (e.g., splenectomy, inflammatory bowel disease, malignancies, collagen

vascular diseases) and whether the patient has relatives with thrombocytosis or other hematologic disorders.

- Physical examination should include an assessment of spleen size by palpation.
- Laboratory studies include:
  - A complete blood count with differential and review of the peripheral smear
  - Chemistries with liver and renal function and electrolytes, lactate dehydrogenase (LDH), uric acid, and serum iron studies.
  - Peripheral blood fluorescence in situ hybridization (FISH) or reverse transcription polymerase chain reaction (RT-PCR) forBCR-ABL1 is sent to exclude chronic myeloid leukemia.
  - Patients with a platelet count >1 million/microL are also evaluated for acquired von Willebrand disease, Do Ristocetin Cofactor Assay
  - Bone marrow aspirate and biopsy. This sample should be sent for pathologic review with trichrome and reticulin stains, cytogenetics, and molecular testing for JAK2 mutations.
  - If JAK2 testing is negative, molecular testing is performed for CALR and MPL mutations, if they are negative also --> demonstrate recent clonal markers.

2. WHO criteria: Diagnosis of ET by the 2016 World Health Organization (WHO) criteria requires all four of the following major criteria or the first three major criteria plus the minor criterion.

   ❖ Major criteria

   i. Platelet count ≥450 x 10 /L (≥450,000/microL)
   ii. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage within 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.
   iii. WHO criteria for BCR-ABL1-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, myelodysplastic syndrome, or other myeloid neoplasms not met.
   iv. Demonstration of a JAK2, CALR, or MPL mutation

   ❖ Minor criterion

   i. Demonstration of another clonal marker (ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, or SRF3B1mutation). {Unfortunately, they are not available)
   ii. No identifiable cause of thrombocytosis (e.g., infection, inflammation, iron deficiency anemia)

3. British guidelines propose the following five criteria for the diagnosis of essential thrombocytosis:
   1) Sustained platelet count ≥450 × 109/L
   2) Presence of an acquired pathogenetic mutation (e.g., in the JAK2, CALR or MPL genes)
   3) No other myeloid malignancy, especially polycythemia vera, primary myelofibrosis, chronic myeloid leukemia, or myelodysplastic syndrome

4) No reactive cause for thrombocytosis and normal iron stores
5) Bone marrow aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominant large megakaryocytes with hyperlobated nuclei and abundant cytoplasm; reticulin is generally not increased (grades 0–2/4 or grade 0/3)

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

✓ **Differential diagnosis:** Conditions which must be distinguished from ET include:

- Reactive thrombocytosis
- Chronic myeloid leukemia
- Polycythemia vera.
- Primary myelofibrosis
- Myelodysplastic syndrome.

- Reactive thrombocytosis: A variety of medical and surgical conditions can result in reactive thrombocytosis. These include:
  - Iron deficiency anemia
  - Surgical or functional asplenia, metastatic cancer.
  - Trauma (surgical or otherwise).
  - Acute bleeding or hemolysis, and a variety of infectious or inflammatory processes
    - When a cause for reactive thrombocytosis is not readily apparent, the demonstration of elevated acute-phase reactants (C-reactive protein [CRP], fibrinogen, erythrocyte sedimentation rate, ferritin) may be used as evidence for the presence of an occult inflammatory process.

- Chronic myeloid leukemia: Demonstration of the BCR/ABL translocation between chromosomes 9 and 22 mandates a diagnosis of chronic myeloid leukemia (CML). This is particularly relevant to patients with CML who may present with either isolated thrombocytosis or substantial bone marrow fibrosis, and who otherwise might have been diagnosed as having ET or primary myelofibrosis, respectively.

- Polycythemia vera: A clonal JAK2 mutation-positive chronic myeloproliferative disorder associated with an increased red cell mass defines polycythemia vera.

- Primary myelofibrosis and prefibrotic myelofibrosis: Primary myelofibrosis (PMF) is characterized by bone marrow reticulin fibrosis along with leucoerythroblastic blood picture with teardrop-shaped red blood cells (dacryocytes), poikilocytosis, and circulating nucleated red cells. The differentiation between PMF and ET is dependent primarily on the presence of megakaryocyte proliferation and atypia, the degree of bone marrow fibrosis and splenomegaly, and the presence of peripheral blood leucoerythroblastic in PMF. Distinguishing between these two conditions is important because of the major differences in survival and complication rates between them. Patients with prefibrotic myelofibrosis have a survival that is better than that of patients with overt PMF, but worse than that of patients with ET.

- Myelodysplastic syndrome (MDS) is a series of related diseases with varying degrees of disordered hematopoietic maturation. Although most are associated with thrombocytopenia, a few, such as the 5q– syndrome, the 3q21q26 syndrome, and myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis are associated with thrombocytosis.

✓ **Treatment**

- Pretreatment evaluation
  - ❖ Clinical – History and examination for venous or arterial thrombosis, hemorrhage, vasomotor symptoms (e.g., headache, dizziness, visual disturbances, erythromelalgia, acrocyanosis), hepatosplenomegaly, and cardiovascular (CV) risk factors (e.g., hypertension, diabetes mellitus, tobacco use, hyperlipidemia).
  - ❖ Laboratory – Pretreatment studies include complete blood count (CBC) with differential count, review of a blood smear, liver and kidney function tests.

- For platelet count >1 million/microL on CBC or clinical bleeding, we measure Ristocetin cofactor (RCo) activity; RCo <30 percent is considered acquired von Willebrand syndrome (VWS).
- JAK2 V617F; if no JAK2 mutation is found, we test for mutations of CALR exon 9 and MPL exon 10.
- Risk stratification: Calculate International Prognostic Score of Thrombosis (IPSET).
  1) High risk: History of thrombosis or age >60 years with JAK2 V617F mutation
  2) Intermediate risk: No prior thrombosis, age >60, and no JAK2 mutation
  3) Low risk: No prior thrombosis, age ≤60, JAK2 V617F detected.
  4) Very low risk: No prior thrombosis, age ≤60 years, and no JAK2 mutation.

- Management:

$\mathcal{R}$ All patients should discontinue smoking, control overweight, and modify other CV risk factors.

$\mathcal{R}$ We recommend treatment with a cytoreductive agent for patients with a history of venous or arterial thrombosis or acquired VWS (i.e., RCo <30 percent).

$\mathcal{R}$ We favor hydroxyurea, rather than anagrelide or interferon, and adjust the dose to maintain the platelet count of 100,000 to 400,000/microL.

- Our approach follows:

➢ Venous thrombosis – Treat with hydroxyurea plus life-long systemic anticoagulation.

➢ Arterial thrombosis – Treat with hydroxyurea plus life-long low-dose aspirin.

➢ Acquired VWS – Treat with hydroxyurea alone (i.e., no aspirin or anticoagulation).

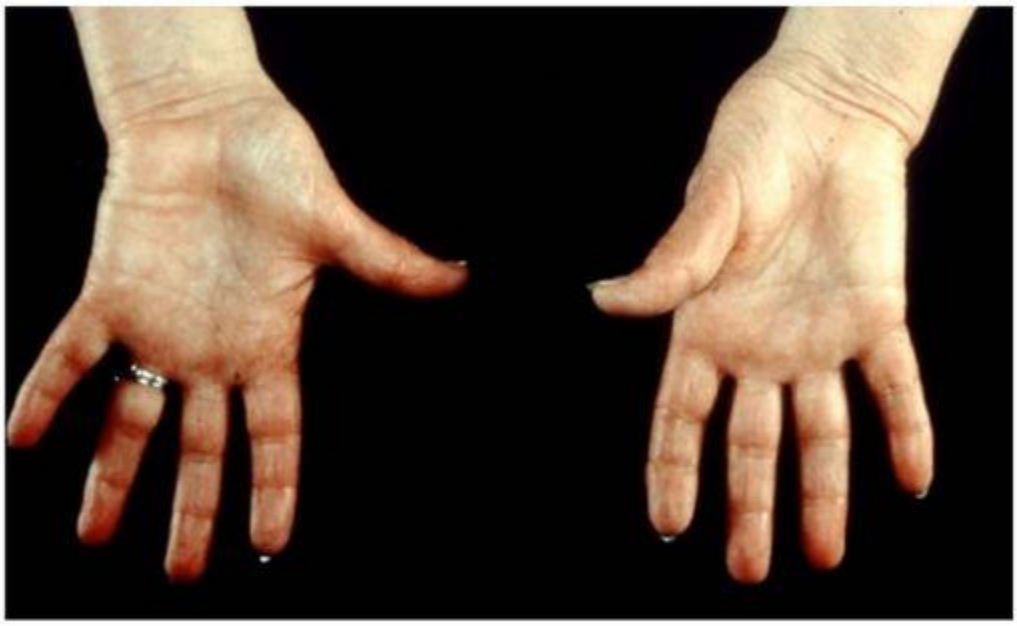
➢ No prior thrombosis with high- or intermediate-risk IPSET score: We suggest treatment with hydroxyurea plus low-dose aspirin, rather than other approaches.

- No prior thrombosis with low- or very low-risk IPSET score; We suggest observation alone or aspirin, rather than cytoreductive therapy.
- We manage these patients as follows:
  - JAK2 V617F mutation plus CV risk factors -->Twice daily low-dose aspirin.
  - Either JAK2 V617F or CV risk factors Once daily low-dose aspirin.
  - For no JAK2 mutation and no CV risk factors --> We observe without initial treatment.

- Pregnancy: For pregnant patients (or those who desire to become pregnant) who require cytoreductive agents, we recommend interferon (IFN) rather than hydroxyurea or other cytoreductive agents

- Hydroxyurea resistance/intolerance: For hydroxyurea resistance/intolerance, we suggest IFN rather than anagrelide or other agents.

Erythromelalgia involving the hands in essential thrombocythemia



This photograph shows the presence of erythromelalgia of the hands in a woman with essential thrombocythemia. This condition is associated with burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis, in the presence of palpable pulses, and is common in both essential thrombocythemia and polycythemia vera.