Myeloproliferative disorders

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Normal hematopoiesis:

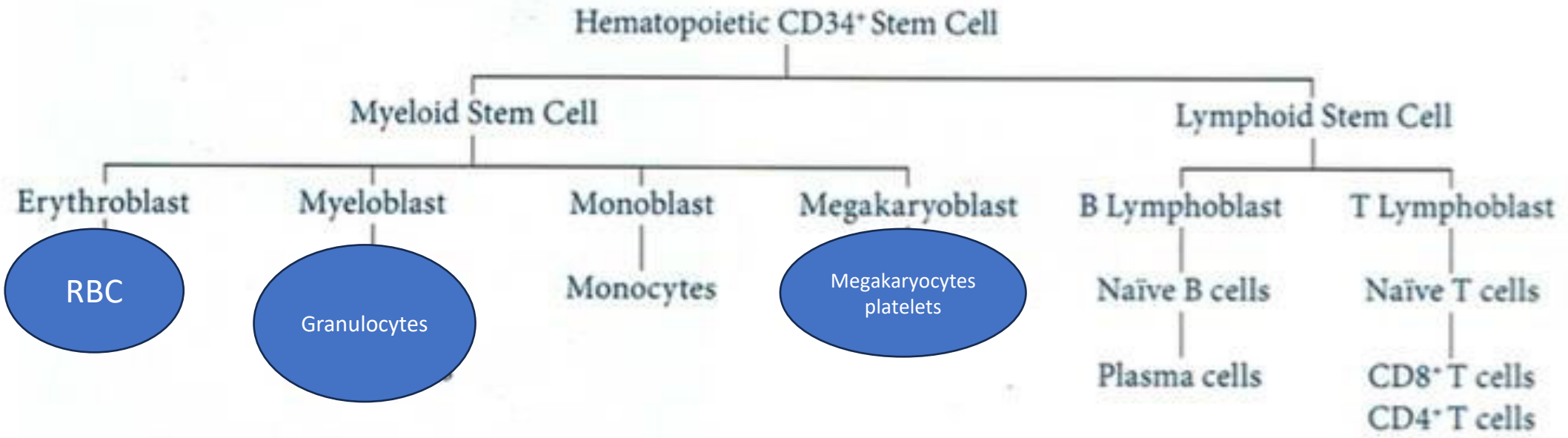


Fig. 6.1 Hematopoiesis.

Myeloproliferative disorders:

- Neoplastic proliferation of mature cells of the myeloid lineage.
- Could be:

1. Polycythemia vera
2. Essential thrombocythemia
3. Chronic myeloid leukemia (CML)
4. Myelofibrosis

- All types of myeloproliferative disorders have proliferation of all cell types, but it’s named after the predominant cell type.

All myeloproliferative disorders :

1. Hyperuricemia AND gout (except ET)
2. Progression to bone marrow fibrosis
3. Acute leukemia

Polycythemia:

- Neoplastic proliferation of all 3 cell lines, but red cell overproduction is the most prominent.
- Usually, secondary.

Polycythemia.

- Primary

Polycythemia vera

- Secondary

1. Relative (DEHYDRATION)
2. Hypoxia (smoking, high altitude, chronic cardiac or pulmonary disease)
3. EPO (paraneoplastic syndrome, RCC, HCC, ESA)

Polycythemia rubra vera

pathophysiology

- Mutation in the JAK2 protein which regulates marrow production.
- Normally, it needs erythropoietin(cytokine released in hypoxia to initiate erythrocyte production) to get activated but due to its mutation, it is activated all the time without needing erythropoietin.
- So erythropoietin levels are low due to negative feedback.

presentation

Patients present with symptoms of hyperviscosity from the increased red blood cell mass such as:

1-Headache.

2-Hypertension frequently occurs as a result of the expanded blood volume.

3-Pruritus often follows warm showers because of histamine release from increased numbers of basophils.

4-Physical examination often shows facial plethora and splenomegaly

Diagnosis

- 1-All 3 cell lines will be elevated:
- A-Hb > 19

  B-Hct > 60%

2-normal O2 sat (must exclude hypoxia as a cause of the erythrocytosis)

3-low EPO levels

4-low iron levels due to erythrocytosis

5- The most accurate test is the JAK2 mutation, found in 95% of patients

complications

- 1- increased risk of thrombosis.
- 2- gouty arthritis.
- Without treatment, death usually occurs within 1 year.

treatment

- 1-Serial phlebotomy: (target Hct is <45%)
- A-Every few months

B- can not be donated

2- aspirin to prevent thrombosis

3- hydroxyurea to lower the cell count

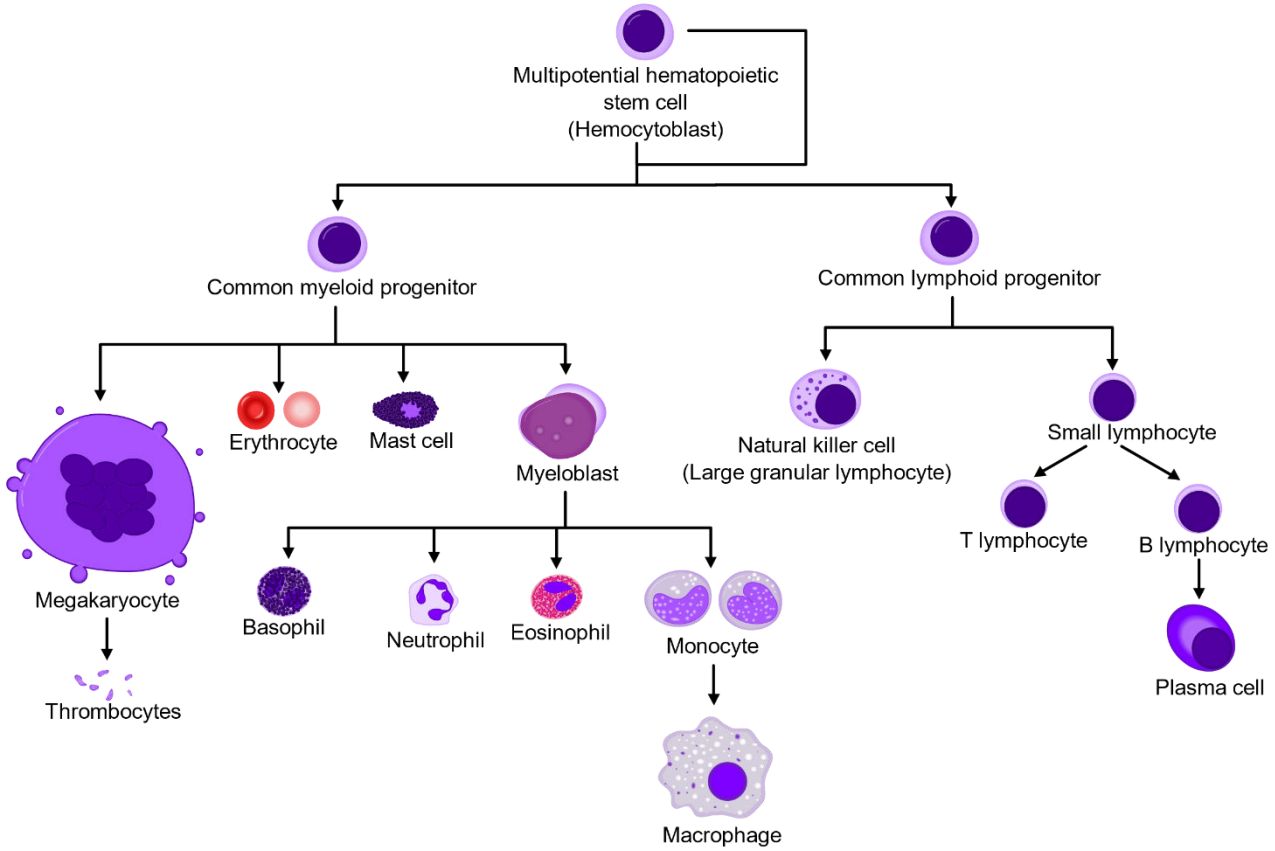
4- antihistamins

5- Ruxolitinib is an inhibitor of JAK

Chronic myeloid leukemia

Definition

- A neoplastic proliferation of mature myeloid cells, especially granulocytes and their precursors, basophils are characteristically increased.

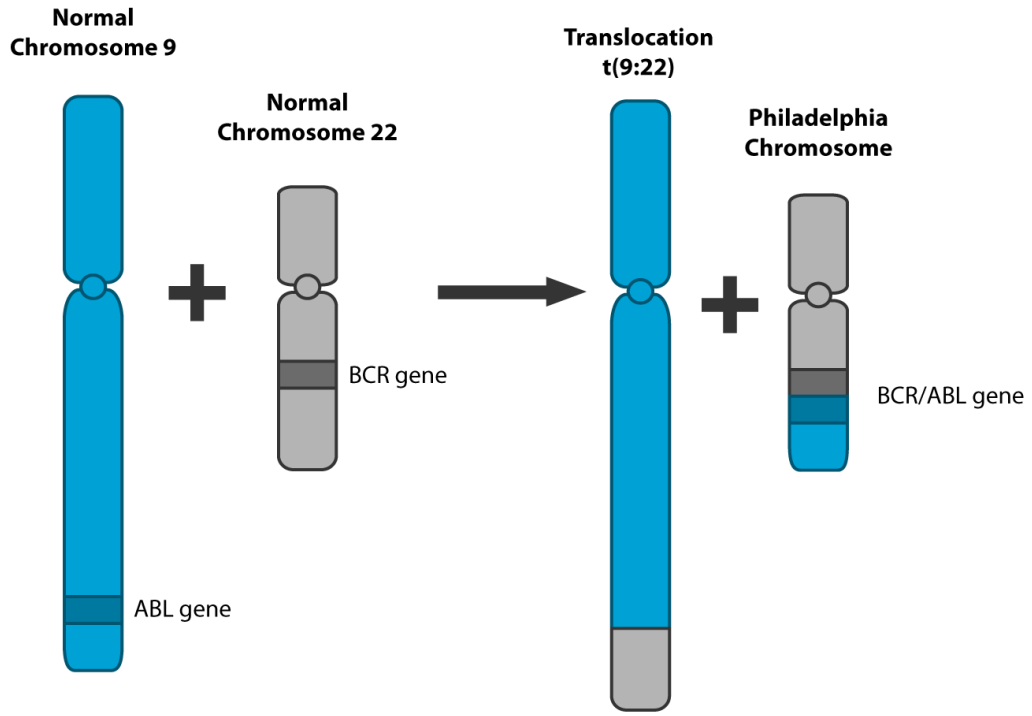


Epidemiology

- Occurs in any age group (mostly middle age to elderly) with a median age of 65 years

Pathophysiology

- Driven by t(9,22) (Philadelphia chromosome) which generates a BCR-ABL fusion protein with increased tyrosine kinase activity (an oncogene that expresses for the growth of the cell).



Clinical phases

- 1. Chronic phase: 85% of cases

  few blasts (20%) are shown in the peripheral blood or bone marrow biopsy.

2. Accelerated phase: impaired neutrophil differentiation

   circulating blasts (10-19%) appear on the bone marrow biopsy

3. Blast crisis: more aggressive course, blasts fail to differentiate

   blasts (>20%) in peripheral blood or bone marrow biopsy

Clinical presentation

1. Asymptomatic when diagnosed (20-50%)
2. Nonspecific symptoms (Fatigue, weight loss, fever, excessive sweating)
3. Secondary to splenic involvement
    a. Splenomegaly
    b. LUQ pain/fullness
    c. Shoulder tip pain (referred)
    d. Early satiety
4. Other
    a. Anemia
    b. Bleeding tendency (Due to low platelets)

Investigations

1. CBC
   a. High increase in WBC
   b. WBC differential: bimodal distribution, with predominance of myelocytes and neutrophils
2. Peripheral blood film
   a. Leukoerythroblastic picture
   b. Presence of different mid-stage progenitor cells differentiates it from AML
3. Bone marrow biopsy
   a. Myeloid hyperplasia with left shift
   b. Increased megakaryocytes
   c. Mild fibrosis
4. Molecular and cytogenetic studies: Philadelphia Chromosome

Treatment

- 1. Symptomatic
  a. Allopurinol (Decreases Uric Acid)
  b. Antihistamines

  2. Chronic phase
  a. Tyrosine Kinase Inhibitors (Imatinib, Dasatinib, or nilotinib)
  b. Interferon-α: may improve response to
  tyrosine kinase inhibitors
  c. Hydroxyurea in palliative setting
  d. Bone marrow transplantation (Curative)

- 3. Accelerated phase or blast phase
  a. Tyrosine Kinase Inhibitors
  b. AML Chemotherapy
  c. Stem cell transplantation (May be curative)

Essential thrombocythemia

Lujain alwlaidat

Definition

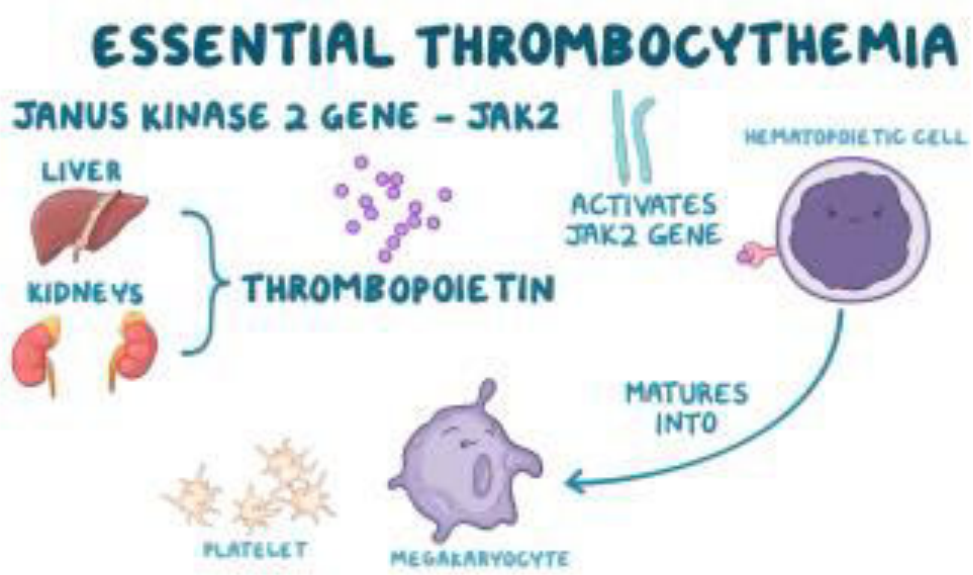
- Also known as Essential thrombocytosis.
- Overproduction of platelets in the absence of a secondary recognizable stimulus.
- Least aggressive of the Myeloproliferative disorders.
- To diagnose ET must rule out secondary thrombocythemia. More than 80% of cases are considered secondary (reactive), not essential.

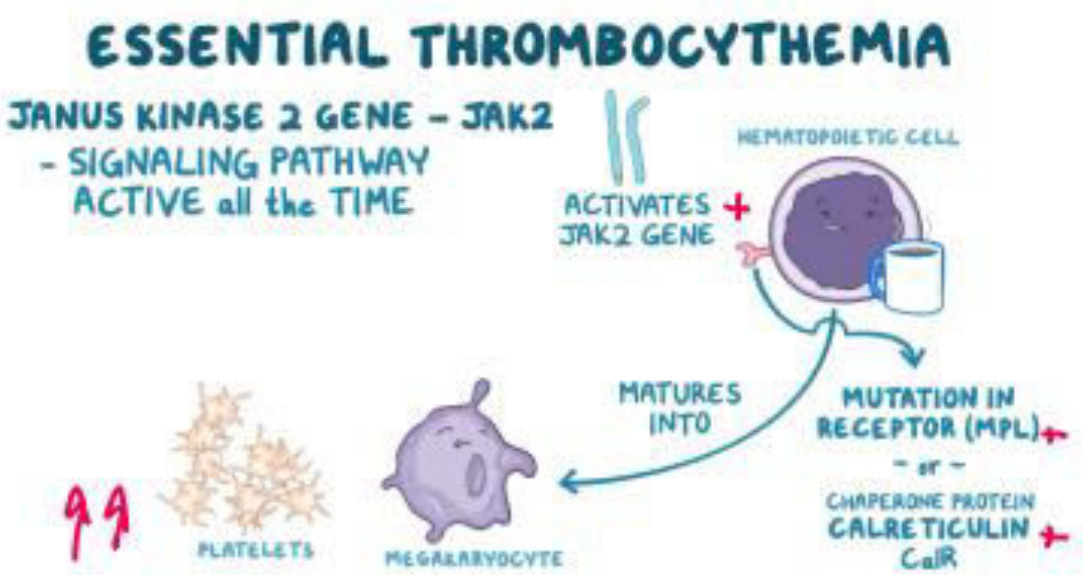
Epidemiology

- Incidence increases with age.
- 1 to 2.5 new cases/100,000 population per year.
- Median age is 55-65 years.
- Female:Male ratio is 2:1, at older ages become equal .

Pathogenesis

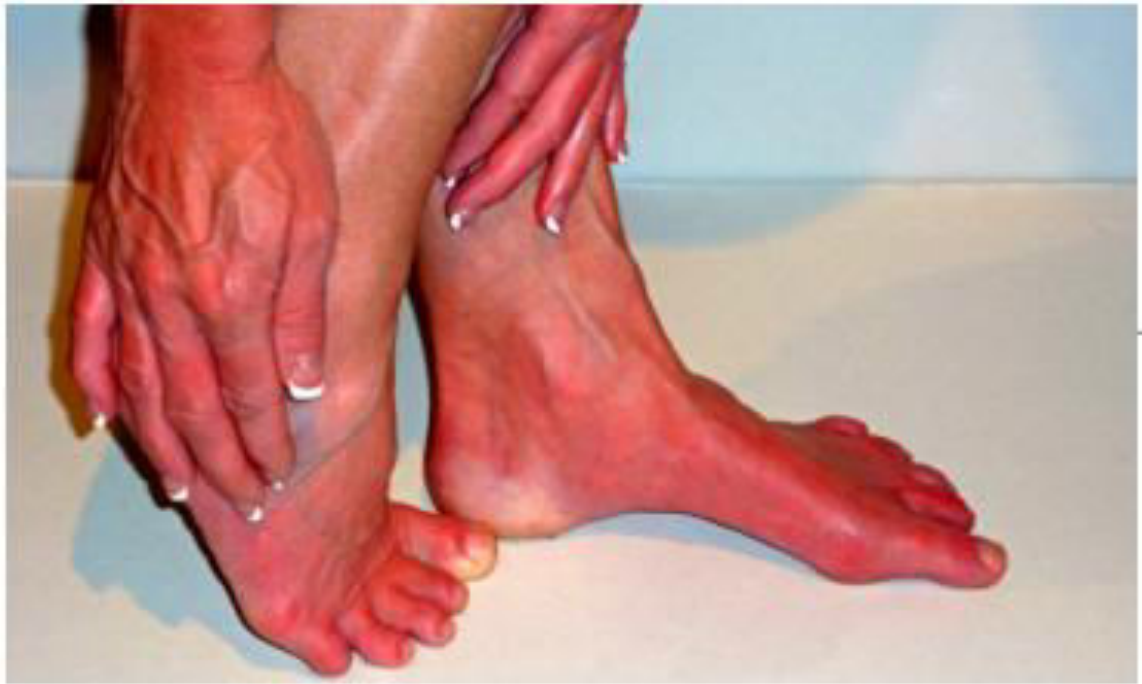
- Excessive platelet production by bone marrow without prolonged platelet survival in the peripheral blood. 90% of cases have a somatically acquired mutation in JAK2, CALR, or MPL genes





Signs and symptoms

- Often asymptomatic ,
- incidentally found on CBC ordered for other cause.
- Symptoms include : Vasomotor (40%) Headache (common), fatigue, nausea, dizziness, tinnitus, syncope
- Erythromelalgia (burning pain & numbness of hands and feet, dusky color,
- usually getting worse with heat
- Risk of thrombosis (arterial and venous).
- Risk of bleeding associated with platelets > 1.5 million/mm3 often GI bleeding
- Can develop splenomegaly.
- In pregnancy can ↑ risk of spontaneous abortion (Larger clots).
- Risk of transformation to Acute Myeloid Leukemia (0.6-5%), myelofibrosis



Erythromelalgia

Investigations

- CBC: platelet count , may have abnormal platelet aggregation test
- Hyperkalemia , hyperphosphatemia (secondary to release of platelet cytoplasmic contents).
- PCR testing of JAK2 V617F mutation gene
- Bone marrow Biopsy
- Exclude other myeloproliferative disorders and secondary thrombocytosis causes
- Secondary causes include : Iron deficiency ,infection, inflammation , tissue injury, trauma, ischemia, malignancy, surgery, post-splenectomy - Howell-Jolly bodies).

Diagnosis

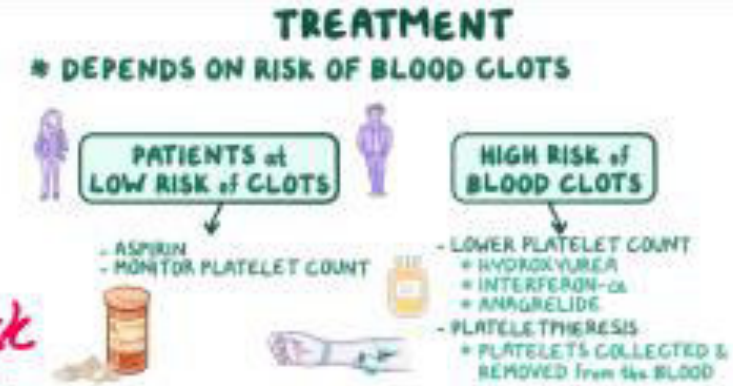
- Diagnosis of ET based on the 2016 WHO criteria ::

1. Platelet count > 450,000

2. Bone marrow biopsy showing megakaryocyte proliferation.

3. Not meeting WHO criteria for Chronic Myeloid Leukemia, polycythemia vera , primary myelofibrosis, myelodysplastic syndromes, or other myeloid neoplasms.

4.Presence of JAK2, CALR or MPL mutations



Diagnosis of ET*

* Low Risk

No thrombosis / major bleeding and age < 60 years

No cytoreduction
Re-consider if complications
Low-dose aspirin
if microvascular symptoms

* high Risk

History of / presentation with thrombosis
or major hemorrhagic complication
or age > 60 years

Cytoreductive treatment:
Hydroxyurea(HU) as first choice;
Interferon in special situations (pregnancy);
Anagrelide as second-line therapy in patients intolerant or refractory to HU
Low-dose aspirin if major thrombosis or microvascular symptoms

* according to WHO 2008[7]

Treatment

-Patients with significant erythromelagia but low risk of thrombosis (< 1,500,000 □ give low-dose aspirin

-Patients at high risk of thrombosis (> 60 Y.O, history of thrombosis, Cardiovascular risk or platelets >1,500,000) □ give cytoreductive therapy hydroxyurea (Goal is to reduce platelets to < 400,000). Anagrelide, busulfan and interferon alpha are 2nd line therapies

-Splenectomy not recommended (increased risk of bleeding episodes, thrombosis)

Prognosis

- Good prognosis in general.

- Can transform to Acute Myeloid Leukemia or myelofibrosis.

Myelofibrosis

Definition and Epidemiology

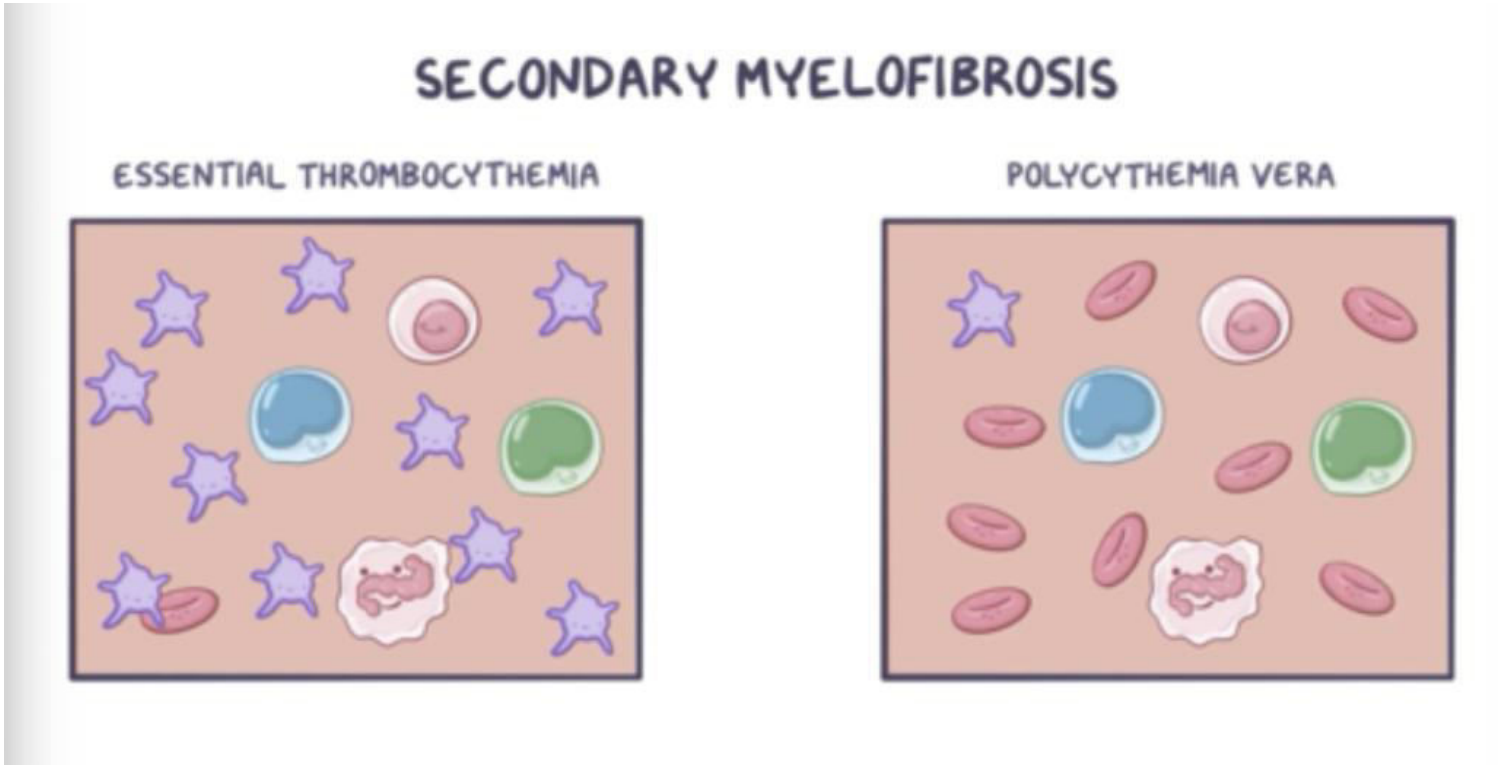
- Excessive bone marrow fibrosis leading to marrow failure

- Characteristics:
- 1. Anemia
- 2. Extramedullary hematopoiesis
- 3. leukoerythroblastosis
- 4. Teardrop red cells (Dacrocyte) in peripheral blood
- 5. Hepatosplenomegaly.
- Epidimiology
- A rare disorder.
- The prevalence of myelofibrosis is approximately 1 per 100,000 individuals worldwide.
- Most patients present over the age of 50 years
- Males are more commonly affected than females

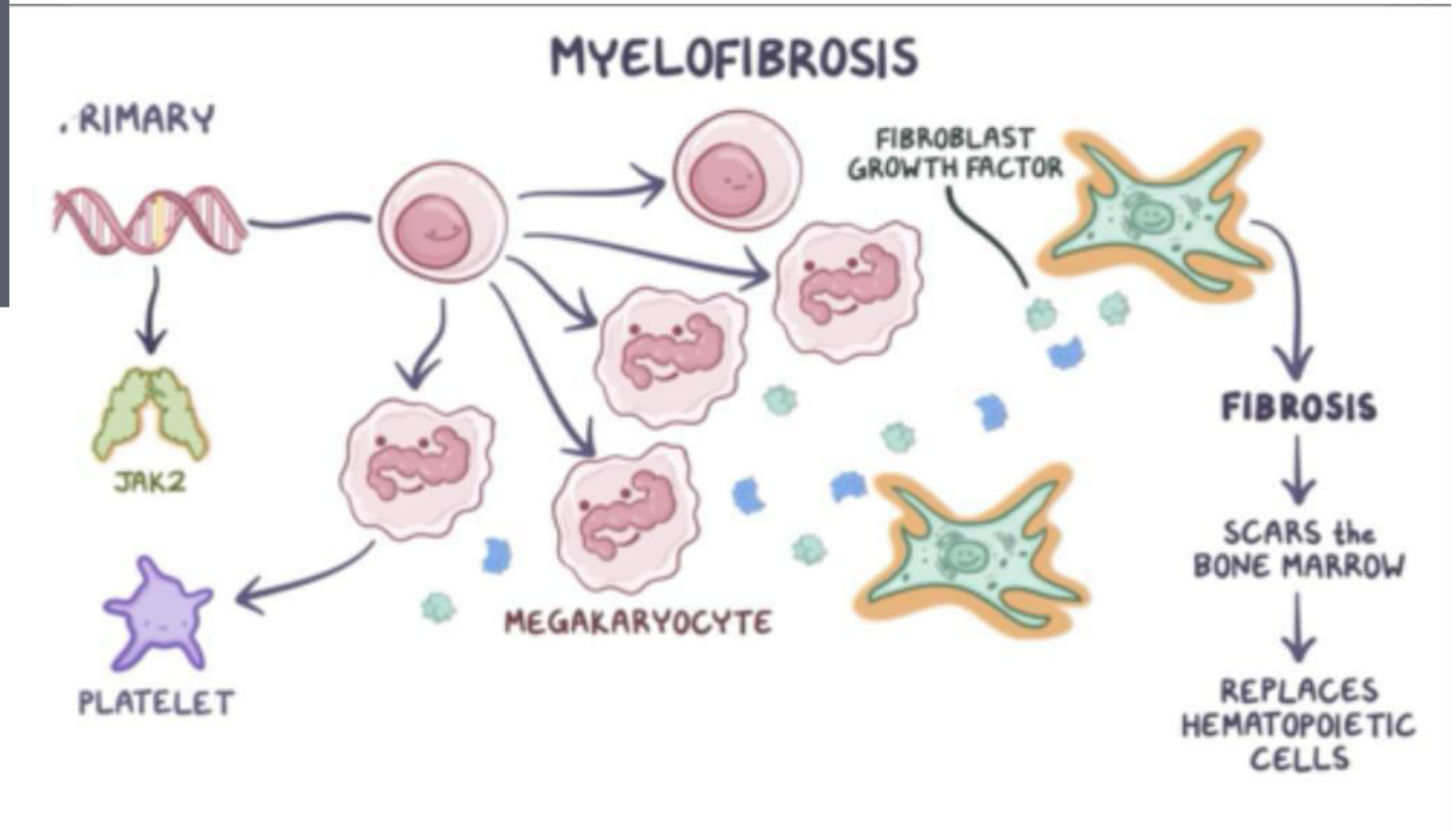
- Types

- primary

- secondary

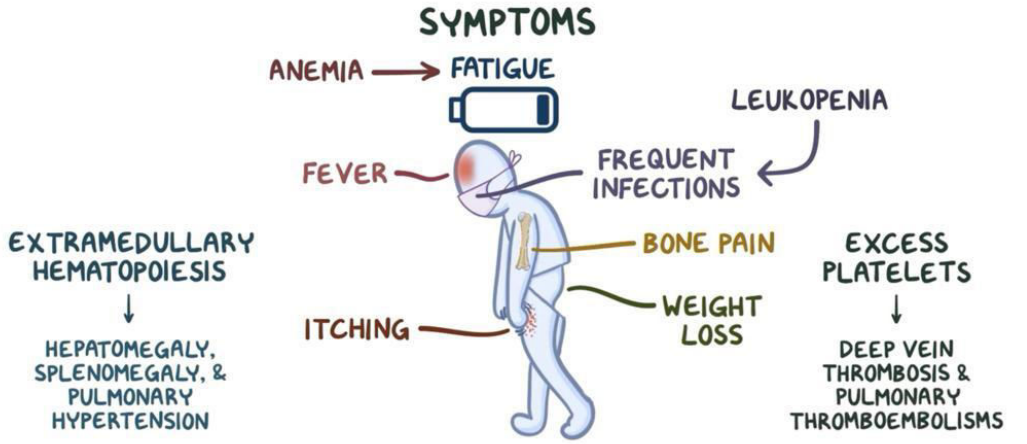


Pathophysiology of primary MF



Clinical Features

- 1. Anemia
- 2. Weight loss, fever, night sweats secondary to hypermetabolic state
  3. Splenomegaly (90%)
- 4. Hepatomegaly (70%)
- 5. Bone and joint pain
- 6. Signs of extramedullary hematopoiesis (depends on organ involved)



Investigations

- **1. CBC:**
  a. anemia
  b. variable platelets
  c. variable WBC
- **2. Biochemistry:**
  a. increased ALP (liver involvement, bone disease)
  b. increased LDH (2ry to ineffective hematopoiesis)
  c. increased uric acid (increased cell turnover)
  d. increased B12 (2o to increased neutrophil mass)

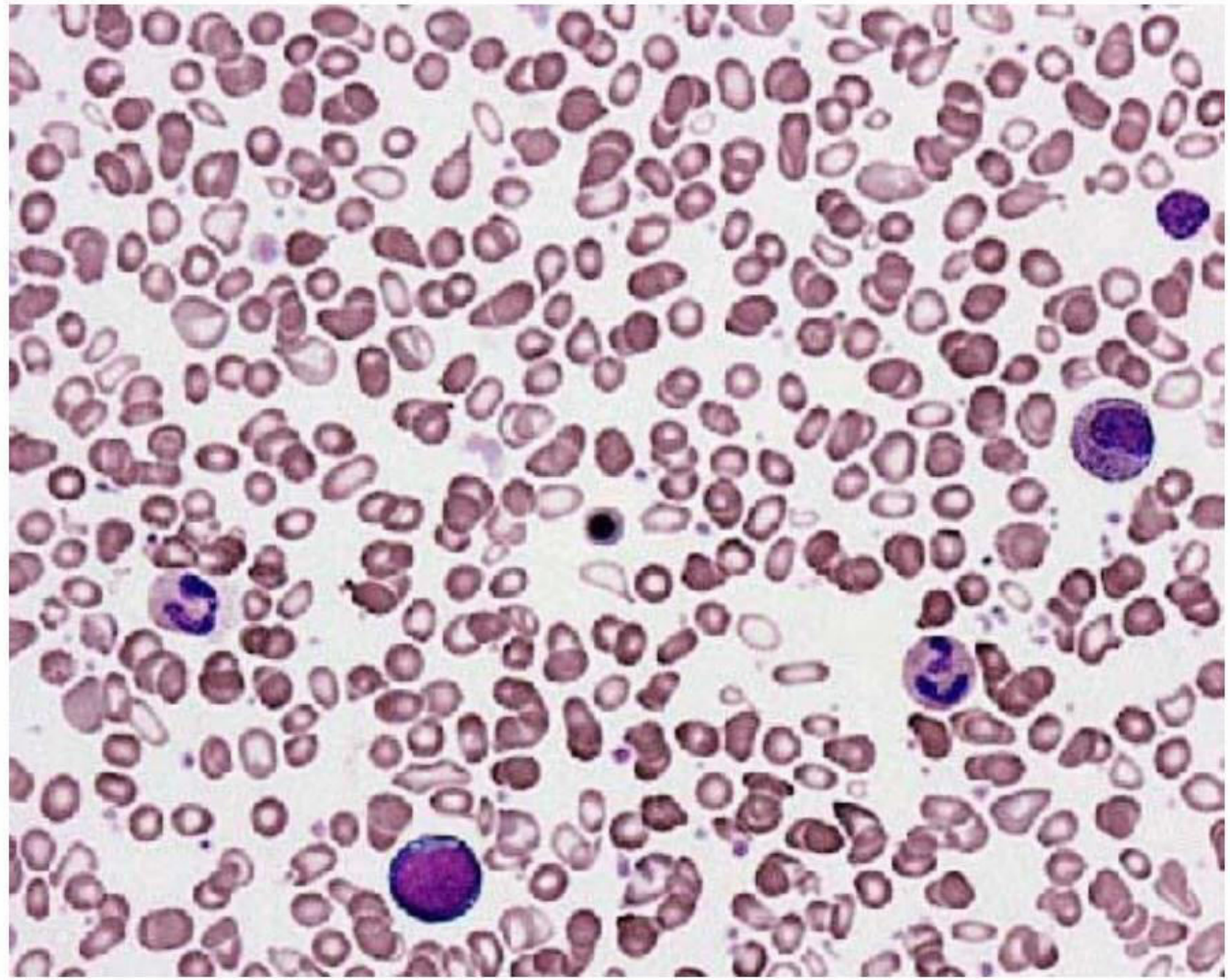
- **3. Blood film:**

a. leukoerythroblastosis with teardrop RBCs
b. nucleated RBCs
c. variable polychromasia (Multi colored RBCs)
d. large platelets
e. megakaryocyte fragments.

4. Bone marrow aspirate:

"dry tap" in as many as 50% of patients (no blood cells aspirated)

5. Bone marrow biopsy



Diagnosis

- Based on WHO criteria

- Primary Myelofibrosis (PMF)
- **Major criteriaa**

1. Megakaryocyte proliferation and atypia accompanied by either reticulin and/or collagen fibrosis (grade 2 to 3)

2. Not meeting WHO criteria for BCR-ABL1+ CML, PV, MDS, or other myeloid neoplasm

3. Presence of JAK2, CALR, or MPL mutation or in the absence, the presence of another clonal markerb or absence of evidence for reactive bone marrow fibrosis

- **Minor criteria**

1. Presence of one or more of the following, confirmed in two consecutive determinations

   a. Anemia not attributed to a comorbid condition

   b. Leukocytosis ≥11 × 109/L

   c. Palpable splenomegaly

   d. LDH level above the upper limit of the institutional reference range

   e. Leukoerythroblastosis

Diagnosis of overt PMF requires meeting all three major criteria and at least one minor criterion.

Treatment

- - Symptomatic treatment :

A. Anemia: Transfusion

B. Splenomegaly:

  Hydroxyurea

  Splenectom

- HSCT may be considered for younger patients.
- JAK2 inhibitors(Ruxolitinib)

Prognosis

- Median survival is 4 years from diagnosis

- **Poor prognostic factors :**

  -Advance age

  -Cytopenias

  -presence of circulating blast cells,

  -constitutional symptoms

Death occur mostly from infections , hemorrhage , cardiac failure postsplenectomy mortality and transformation into acute leukemia

- Dynamic International Prognostic Scoring System plus (DIPSS-plus) for IMF uses 8 factors to determine mean survival :

- Age older than 65 years
- Hemoglobin level less than 10 g/dl
- Leukocyte count higher than 25 $*10^9$ /L
- PLATLET COUNT LOWER THAN 100* 10^9 /L
- Circulating blasts of 1% or more
- Constitutional symptoms
- Red blood cell transfusion dependency
- Unfavorable karyotype

Classifications:
Low risk (0 adverse points) = 15.4
Intermediate 1 risk (1 adverse point) = 6.5
Intermediate 2 risk (2-3 adverse points)=2.9
High risk (4-6 adverse points)=1.3