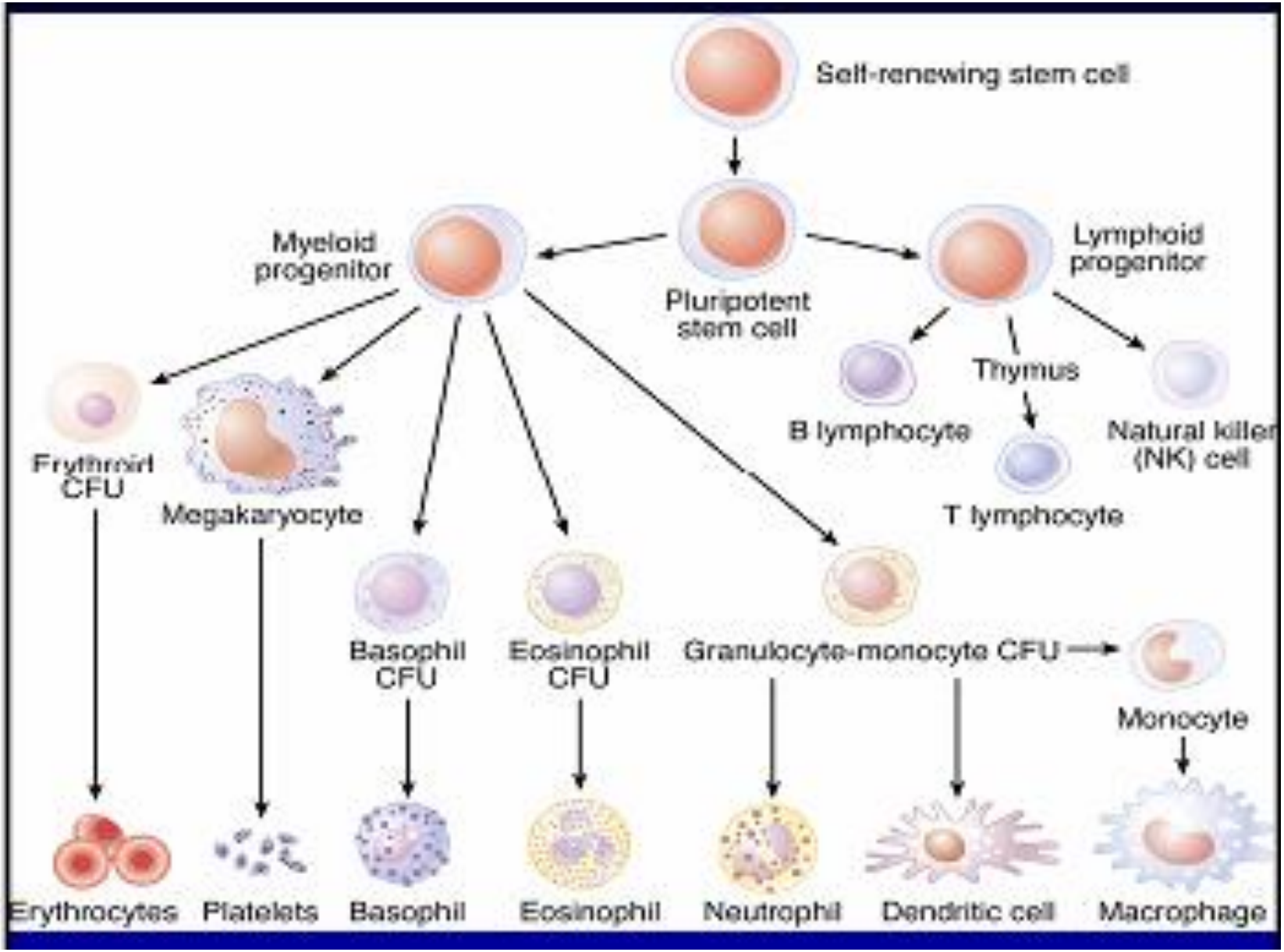
Myeloprolifirative Disorders

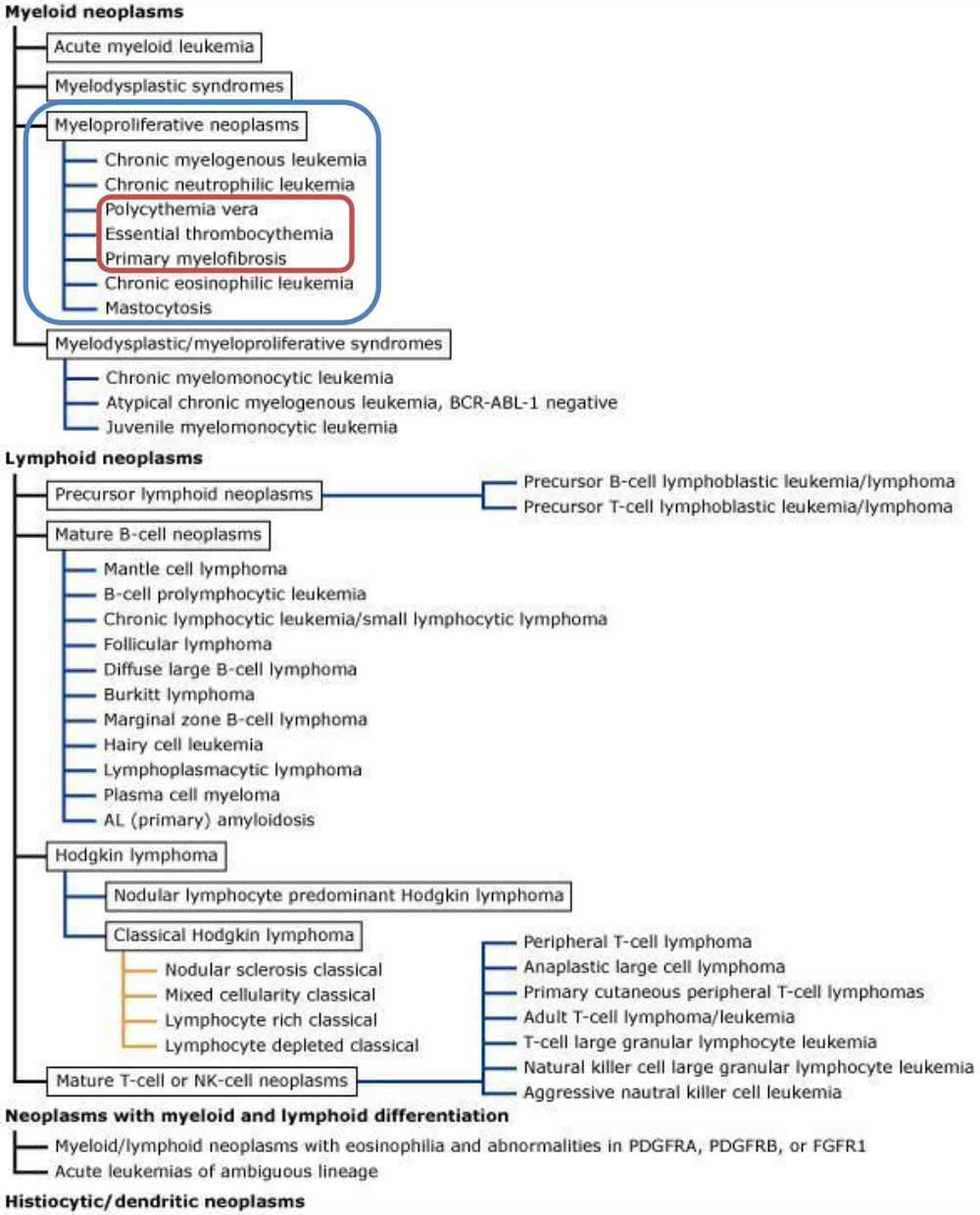
(MPD)

המצגת הוכנה ע"י: אלעד בן מאיר
סטודנט שנה 4
בית הספר לרפואה
אוניברסיטת תל-אביב

מחלקה פנימית ג'
המרכז הרפואי שיבא
טיוטור: דר' חוסם קאסם


Self-renewing stem cell
Pluripotent stem cell
Myeloid progenitor
Lymphoid progenitor
Thymus
B lymphocyte
T lymphocyte
Natural killer (NK) cell
Frythroirl CFU
Megakaryocyte
Basophil CFU
Eosinophil CFU
Granulocyte-monocyte CFU
Monocyte
Erythrocytes
Platelets
Basophil
Eosinophil
Neutrophil
Dendritic cell
Macrophage

Conceptual organization of hematologic malignancies



Organization of tumors of the hematopoietic and lymphoid tissues as described by the World Health Classification 2008.

Table 103-1 WHO Classification of Chronic Myeloproliferative Disorders
Chronic myelogenous leukemia, [Ph chromosome t(9;22)(q34;11), BCR/ABL-positive]
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia (and the hypereosinophilic syndrome)
Polycythemia vera
Chronic idiopathic myelofibrosis (with extramedullary hematopoiesis)
Essential thrombocythemia
Chronic myeloproliferative disease, unclassifiable

MPD - Common Features

- Origin in a multipotent hematopoietic progenitor cell
- Overproduction of one or more blood element without significant dysplasia
- Predilection to extramedullary hematopoiesis
- Myelofibrosis
- Transformation to AML (varying rate)

CML\CEL\CNL vs PV\ET\IMF

	CML\CEL\CNL	PV\ET\IMF
phenotype	primarily **myeloid**	Primarily **erythroid** or **megakaryocytic** hyperplasia
genotype	CML – t(9;22)(q34;11) CNL – t(15;19) CEL – PDGFRα mutation	JAK2 V617F
Transformatiom into each other	-	+
Natural history	• Measured in years • High transformation into AML	• Measured in decades • Low transformation into AML

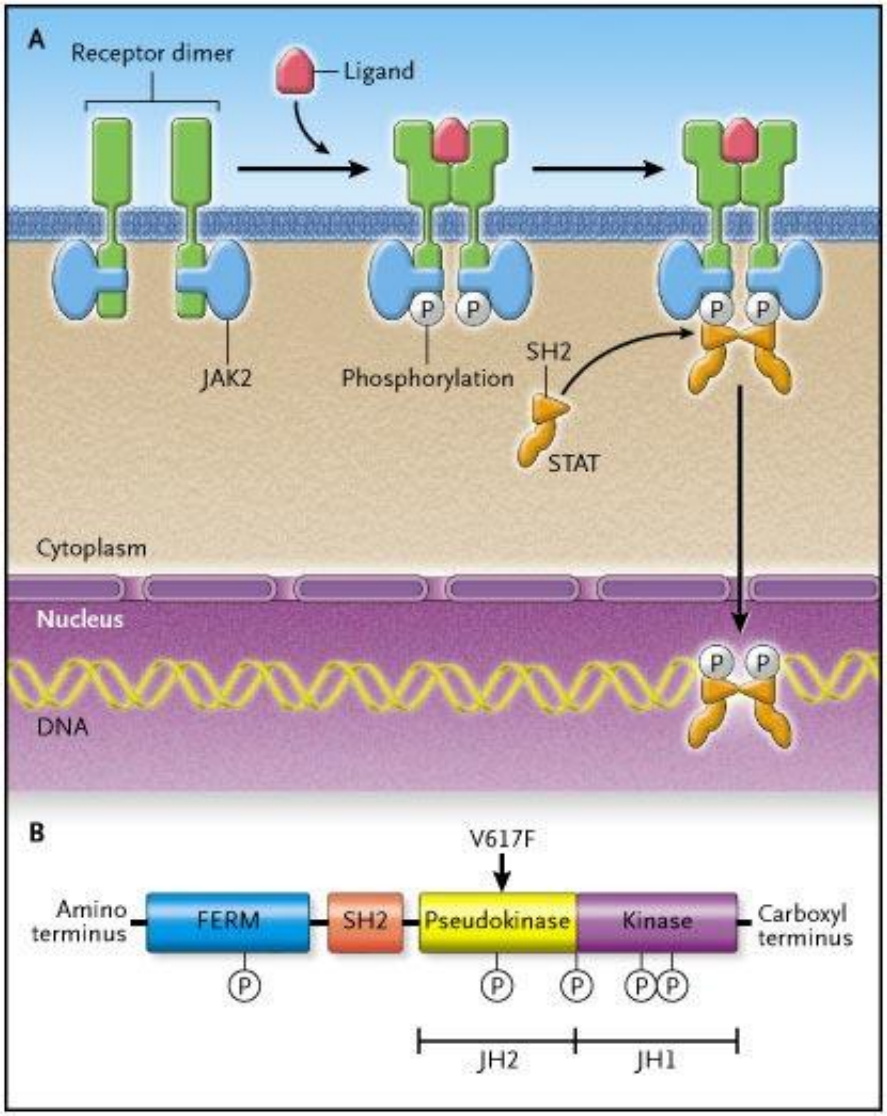
PV\ET\IMF - Common Features

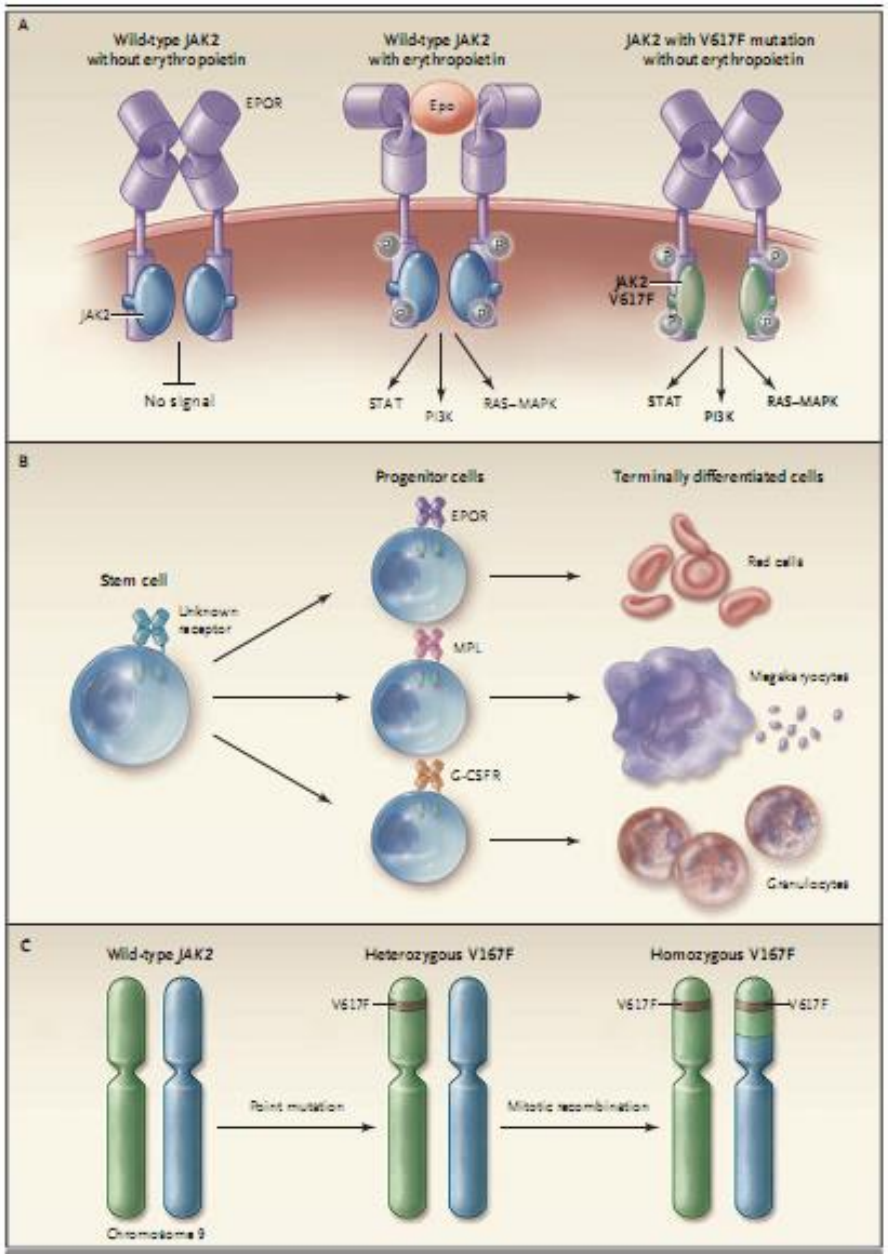
- Variable degrees of BM **hypercellularity**
- Atypical **megakaryocytic** hyperplasia and clustering
- Splenomegaly
- Leukocytosis
- Thrombocytosis
- Clonal **cytogenetic abnormalities**
- **JAK2**

JAK2

- Janus kinase (JAK, “Just another kinase”) is a family of intracellular tyrosine kinases that transduce cytokine-mediated signals via the JAK/STAT pathway.
- In the Janus family (JAK 1,2,3, TYK2) each has a kinase domain (JAK homology 1) and a catalytically inactive pseudokinase domain (JAK homology 2).
- These 2 similar domains in the protein reminds of the **Roman God Janus** who looked simultaneously in 2 directions.

- The JAK/STAT signal transduction pathway plays a major role in cellular proliferation, differentiation and survival.
- Abnormalities affecting members of this pathway are associated with hematological malignancies.
- Sequencing of the JAK2 in patients with 9pLOH revealed a G to T transversion that changed a valine to phenylalanine at position 617**: V617F**
- The mutant **JAK2 V617F** protein resulted in better transduction of the signals induced by GF and gain of function involves loss of control and overproduction of mature cells.





JAK2 V617F

PV	>90%
ET	50%
IMF	45%

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Milestones in the History of Philadelphia-Negative Myeloproliferative Disorders and Their Relationship with the V617F Mutation in JAK2.*

Year	Historical Milestone	Relationship Later Established with V617F Mutation in JAK2
1892	First description of polycythemia vera[4]	
1951	Polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis linked as related conditions[1]	Mutation found in all three disorders[6-9]
1974	Identification of erythropoietin-independent erythroid colonies[10]	Mutation associated with cytokine independence of primary erythroid progenitors and cell lines[6-9]
1976	Stem-cell origin of polycythemia vera[11]	Mutation found in multipotent progenitors and hematopoietic stem cells[6,12]
1983–2003	Dysregulated tyrosine kinases found in chronic myeloid leukemia,[13,14] mastocytosis,[15] chronic myelomonocytic leukemia,[16,17] and chronic eosinophilic leukemia[18]	Tyrosine kinase function of JAK2 constitutively activated by mutation[7-9,19]
2002	Description of mitotic recombination involving chromosome 9p as the most common cytogenetic lesion in polycythemia vera[20]	Homozygosity of the mutation caused by mitotic recombination of chromosome 9p[6-9]
2001–2004	Erythropoietin-independent growth in polycythemia vera dependent on JAK–STAT signaling[21,22]	STAT proteins constitutively activated by mutation[7-9,19]
2005	Description of the JAK2 V617F mutation[7-9,19]	

* STAT denotes signal transducers and activators of transcription.

Polycitemia Vera

(PV)

General

- A clonal disorder involving a multipotent hematopoietic progenitor cell in which phenotypically **normal RBC**, **Leukocytes** and **platelets** accumulate in the absence of recognizable physiologic stimulus
- The most common MPD
- 2 per 100,000
- Occurrence increasing with age
- Familial transmission occurs but infrequent
- Slight M>W
- Median survival 9-12 y

Etiology

- Unknown
- cytogenetic abnormalities (9p, 20q, trisomy 8) – 30% of pts.
- JAK2 V617F – >90% express mutation, 30% homozygotes
- JAK2 V617F is the basis for many phenotipic characteristic of PV pts. but not solely.
- No clinical difference between WT\hetrozygotes\homosygotes PV pts.

Clinical features

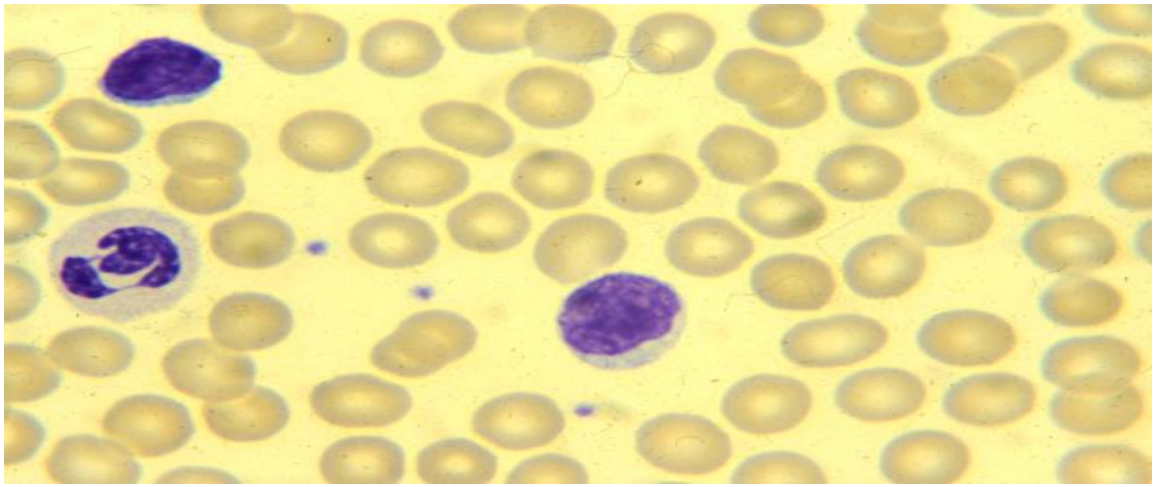
- **Blood count**:
  - RBC ↑ (**Polycytosis**)
  - Platlets ↑ (**Thrombocytosis**)
  - WBC↑ (**Leukocytosis)**
- **Splenomegaly**
- **Venus\Arterial thrombosis** (Cerebral, Cardiac, mesenteric vessels)
  - Budd chiari syndrome
  - Digital ischemia
  - Easy bruising
  - Epistaxis
  - Acid-peptic disease
  - Gastrointestinal hemorrhage

- **Systolic hypertension**

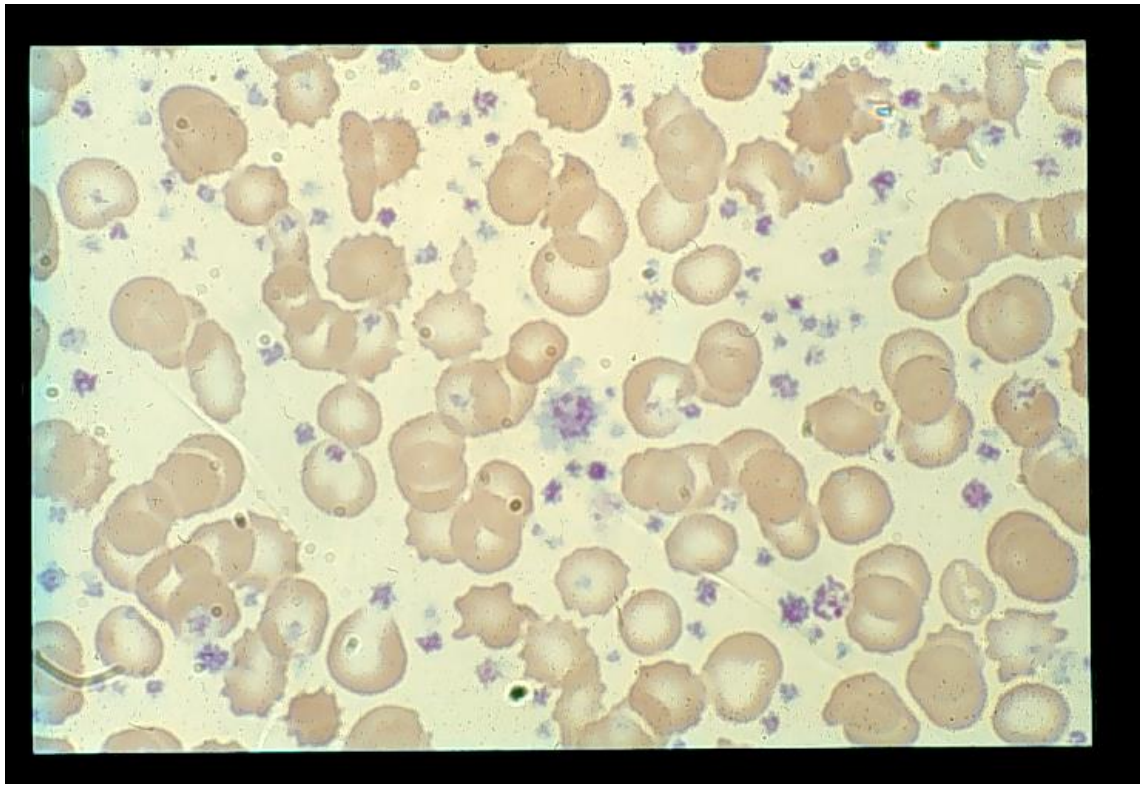
Clinical features

- **Erythromelalgia** (Erythema, burning and pain in the extrimities)
- **Aquagenic pruritus**
- **Neurologic symptoms**
  - Vertigo
  - Tinnitus
  - Headache
  - visual disturbances
  - TIA
- **Hyperuricemia** (secondary gout, uric acid stones)

Normal



PV



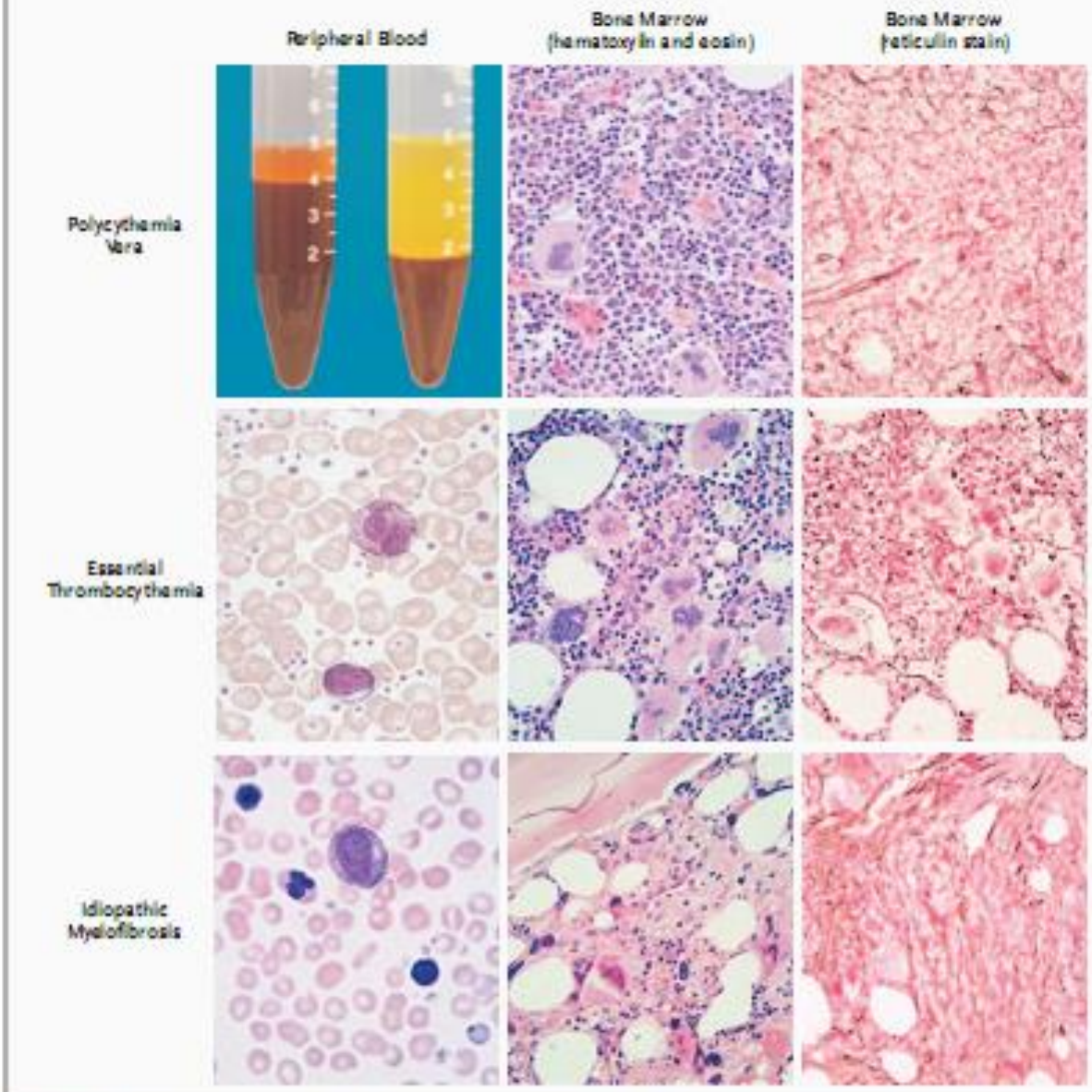


Figure 1. Laboratory Features of Polycythemia Vera, Essential Thrombocythemia, and Idiopathic Myelofibrosis.

Polycythemia vera is characterized by an increased hematocrit in the peripheral blood (test tube on left); a hypercellular marrow with increased numbers of erythroid, megakaryocytic, and granulocytic precursor cells; and a variable increase in the number of reticulin fibers. Essential thrombocythemia is characterized by an increase in the number of platelets in the peripheral blood and an increased number of megakaryocytes in the marrow, which tend to cluster together and have hyperlobated nuclei. Idiopathic myelofibrosis is characterized by the presence of immature red and white cells (a so-called leukoerythroblastic blood film) and "teardrop" red cells, disordered cellular architecture

Complications

1. Increase in blood viscosity
2. Increased RBC, leukocytes and platelets turnover (increased uric acid & cytokine production)

- **Thrombosis & infarctions in vital organs**
- **Peptic ulcer disease**
- **Myelofibrosis** (mostly reversible, may cause hepatosplenomegaly)
- **Transformation into AML (2%)**

Diagnosis

- **Absolute erythrocytosis** (RBC mass & plasma volume)
- RBC count, MCV, RDW – **microcytic erythrocytosis with ↑RDW**
- **Leukocytosis** & **thrombocytosis**
- **JAK2 V617F**
- **Erythropoietin levels**
- uric acid ↑
- BM biopsy & cytogenetic abnormality – non specific!!

Table 103-2 Causes of Erythrocytosis

Relative erythrocytosis: Hemoconcentration secondary to dehydration, androgens, or tobacco abuse

Absolute erythrocytosis

Hypoxia

- Carbon monoxide intoxication
- High affinity hemoglobin
- High altitude
- Pulmonary disease
- Right-to-left shunts
- Sleep-apnea syndrome
- Neurologic disease

Renal disease

- Renal artery stenosis
- Focal sclerosing or membranous glomerulonephritis
- Renal transplantation

Tumors

- Hypernephroma
- Hepatoma
- Cerebellar hemangioblastoma
- Uterine fibromyoma
- Adrenal tumors
- Meningioma
- Pheochromocytoma

Drugs

- Androgens
- Recombinant erythropoietin

Familial (with normal hemoglobin function, Chuvash, erythropoietin receptor mutations)

WHO criteria for PV 2007

Major criteria

1. Hemoglobin **18.5 g/dL** in men, **16.5 g/dL** in women or other evidence of increased red cell volume
2. Presence of ***JAK2* 617VF** or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor criteria

1. BM biopsy showing **hypercellularity** for age with trilineage growth (**Panmyelosis**) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. **Serum Epo level** < the reference range for normal
3. **Endogenous erythroid colony formation** in vitro

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the first major criterion together with 2 minor criteria

Rx.

- **PHLEBOTOMY** –
  - The mainstay of treatment.
  - Goal: to keep Hct < 45%\Hb<14 g/dL in men, and Hct<42%\Hb<12 g/dL in women.
  - Maintain RBC mass within normal range and induce a state of iron deficiency.
  - Once an iron deficiency state is achieved – phlebotomy at 3-month intervals
- **Aspirin** –
  - Potentially harmful if the RBC mass is uncontrolled by phlebotomy
  - Indicated only when thrombosis has occurred
- **Cytotoxic agents** - their use should be avoided. If must be used:
  - In younger pts. – **IFNα**, **Angrelide** (PDEi), **HU** or **Allogenic BM trans.**
  - In older pts. – **HU** start 1 g daily or **busulfan** start 4mg daily
  - In elderly pts. with life expectancy < 10 yrs. – **^{32}P** every 3 months

- Rx. of pruritus - antihistamines \ paroxetine (SSRI) \ IFNα
- Rx. of erythromelalgia (microvascular disturbances) - aspirin → if non responsive - Cytotoxic agents (HU)
- Rx of hyperuricemia - Allopurinol

Rx.

Risk		Rx.
Low	**no history of thrombosis and Age<60 and Plt ct. < 1.5 million**	***Phlebotomy + Aspirin***
High	**history of thrombosis or age ≥ 60 years**	***Phlebotomy + Aspirin + HU***
Intermediate	**Neither low- nor high-risk**	***Phlebotomy + Aspirin (depends) + HU?***

Essential Thrombtosisocy (ET)

General

- A clonal disorder involving a multipotent hematopoietic progenitor cell of unknown ethiology characterised by over production of **platelets** without a definable cause
- 1-2 per 100,000
- F > M
- Occur at any age
- No clonal marker is available

Table 103-5 Causes of Thrombocytosis
Malignancy
Infection
Myeloproliferative disorders: polycythemia vera, idiopathic myelofibrosis, essential thrombocytosis, chronic myelogenous leukemia
Myelodysplastic disorders: 5q-syndrome, idiopathic refractory sideroblastic anemia
Postsplenectomy or hyposplenism
Hemorrhage
Iron deficiency anemia
Surgery
Rebound: Correction of vitamin B_{12} or folate deficiency, post-ethanol abuse
Hemolysis

Etiology

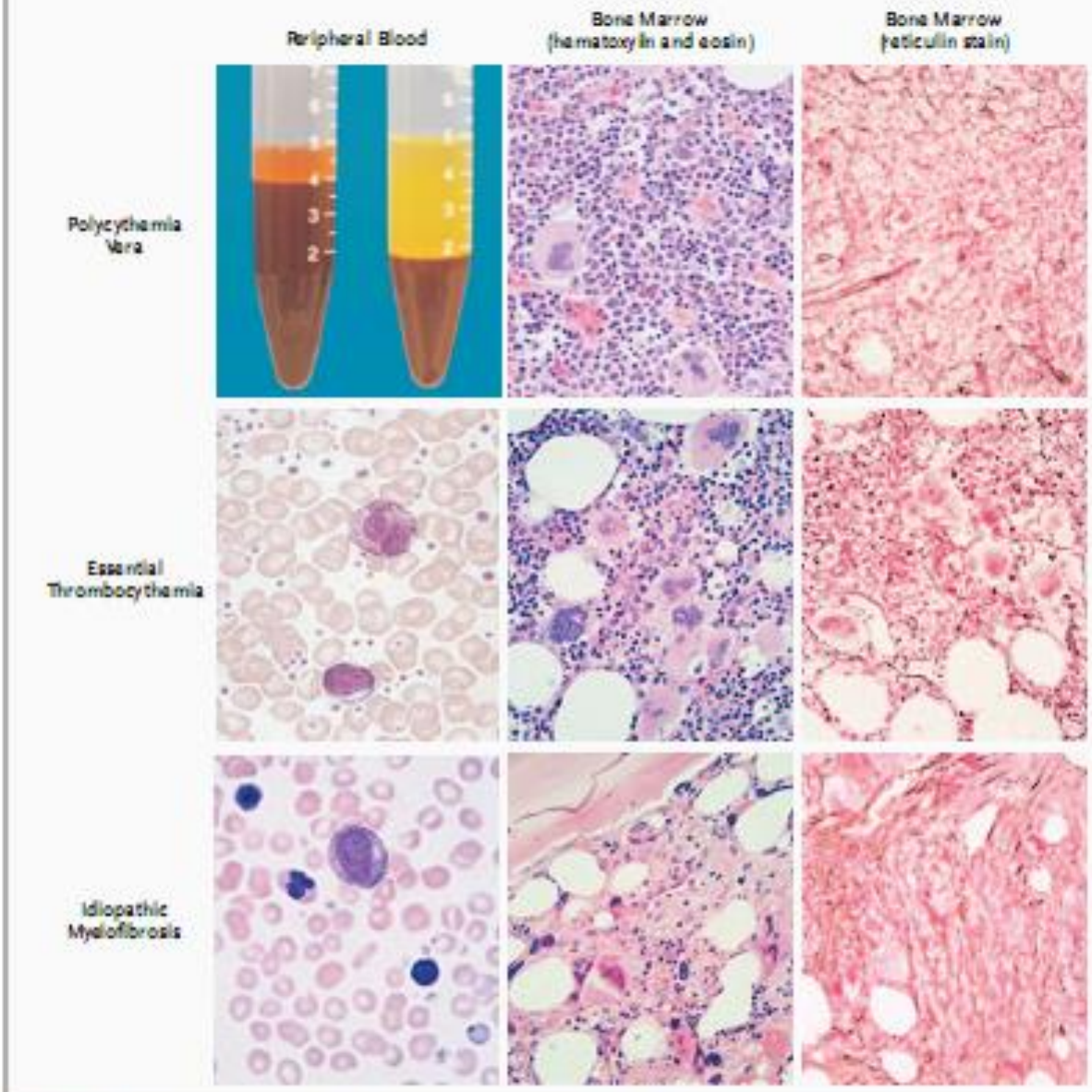
- Unknown
- cytogenetic abnormalities (20q, trisomy 8) – 5% of pts.
- JAK2 V617F – 50% express mutation, 60% homozygotes
- Neither TPO nor c-Mpl has been implicated in the pathogenesis of ET

Clinial features

- A significant number of pts. are **asymptomatic**
- Blood count:
  - **Platelets ↑** ($>10^6$)
  - Mild WBC↑
  - Hb N
- Blood film: **many large and abnormal platelets**

Clinial features

- **Thrombosis**
  - microvascular occlusions (erythromelalgia, ocular migrane, TIA)
- **Hemorrhage tendency** – acquired vWD
- **Mild Splenomegaly**
- **Marrow biopsy** :
  - Megakaryocyte hyperplasia & hypertrophy
  - Hypercellularity
- **Transformation into PV, MF and AML**



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Diagnosis

- ET is diagnosed by exclusion –

  R/O reactive or clonal causes of thrombocytosis

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Myelodysplastic disorders: 5q-syndrome, idiopathic refractory sideroblastic anemia
Postsplenectomy or hyposplenism
Hemorrhage
Iron deficiency anemia
Surgery
Rebound: Correction of vitamin B_{12} or folate deficiency, post-ethanol abuse
Hemolysis

Proposed revised WHO criteria for ET 2007

1. Sustained **platelet count > 450 x 10^9/L**
2. Bone marrow biopsy specimen showing **proliferation mainly of the megakaryocytic lineage** with increased numbers of enlarged, mature megakaryocytes; no significant increase or left-shift of neutrophil, granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for PV, IMF, CML, MDS, or other myeloid neoplasm
4. Demonstration of *JAK2* 617VF or other clonal marker, or in the absence of a clonal marker, no evidence for reactive thrombocytosis

Diagnosis requires meeting all 4 criteria

Rx.

- Survival of ET pts. is not different than of general population.
- Elevated platelets count in asymptomatic ET patient without cardiovascular risk factors requires no therapy.
- Therapy required only to alleviate microvascular symptoms (50%) and prevent thrombosis (20%) and major bleeding (5%).

Rx.

- **Aspirin** - low dose aspirin (40-80 mg/day) safe and reduces thrombotic complications
- **Cytotoxic agents**
  - **Hydroxyurea** as first line Rx at any age
  - **IFNα** in hydroxyurea failures or for child-bearing age females
  - **Anagrelide** if you can not use the above

Rx.

Risk		Rx.
Low	**no history of thrombosis and Age<60 and Plt ct. < 1.5 million**	***Aspirin***
High	**history of thrombosis or age ≥ 60 years**	***Aspirin + HU***
Intermediate	**Neither low- nor high-risk**	***Aspirin (depends) + HU?***

Idiopathic Myelofibrosis

(IMF)

General

- A clonal disorder involving a multipotent hematopoietic progenitor cell of unknown ethiology characterised by **marrow fibrosis**, **extramedullary hematopoiesis** and **splenomegaly**.
- The least common MPD
- Most common in 6th decade or later
- Median survival 5 y
- Myelofibrosis and splenomegaly are common features of PV, CML and variety of other disorders.

Table 103-3 Disorders Causing Myelofibrosis	
Malignant	**Nonmalignant**
Acute leukemia (lymphocytic, myelogenous, megakaryocytic)	HIV infection
Chronic myelogenous leukemia	Hyperparathyroidism
Hairy cell leukemia	Renal osteodystrophy
Hodgkin disease	Systemic lupus erythematosus
Idiopathic myelofibrosis	Tuberculosis
Lymphoma	Vitamin D deficiency
Multiple myeloma	Thorium dioxide exposure
Myelodysplasia	Gray platelet syndrome
Polycythemia vera	
Systemic mastocytosis	

Etiology

- Unknown
- cytogenetic abnormalities (9p, 20q-, trisomy 8 or 9 or 1q) – common, non specific.
- JAK2 V617F – 45% express mutation, almost non homozygotes
- Fibrosis\osteosclerosis\angiogenesis caused by overproduction of TGFβ\osteoprotegerin\VEGF respectively.
- Fibroblasts involved are polyclonal

Clinical features

- No specific signs or symptoms, many are asymptomatic at presentation

- **Splenomegaly**
- **Blood count**:
  - **Anemia** - Hb ↓, MCV →
  - Platlets ↑, ↓
  - WBC↑, ↓
- **Hepatomegaly**
- **Non-hepatosplenic EMH**

Clinial features

- **Leukoerythroblastic smear**:
  - Teardrop poikilocytes
  - Nucleated RBC
  - Myeloblasts, myelocytes and promyelocytes
- **Marrow biopsy**:
  - Reactive\cellular phase – rare
  - Myelofibrosis – fibrosis & megakariocyte atypia, inaspirable
- **Bone pain**

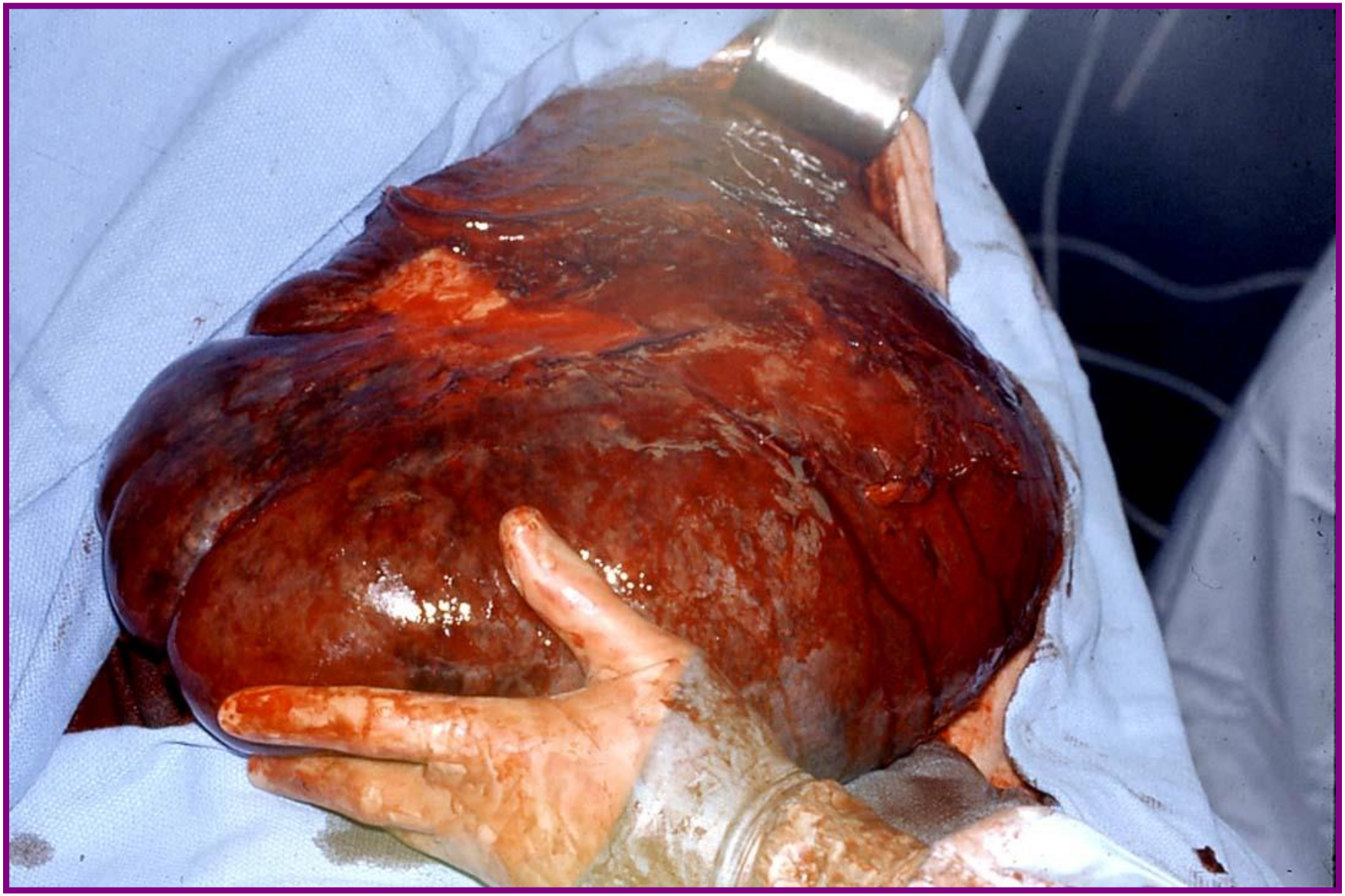
Clinial features

- **Constitutinal symptoms**:
  - Night sweat
  - Fatigue
  - low-grade fever
  - weight loss (cachexia)

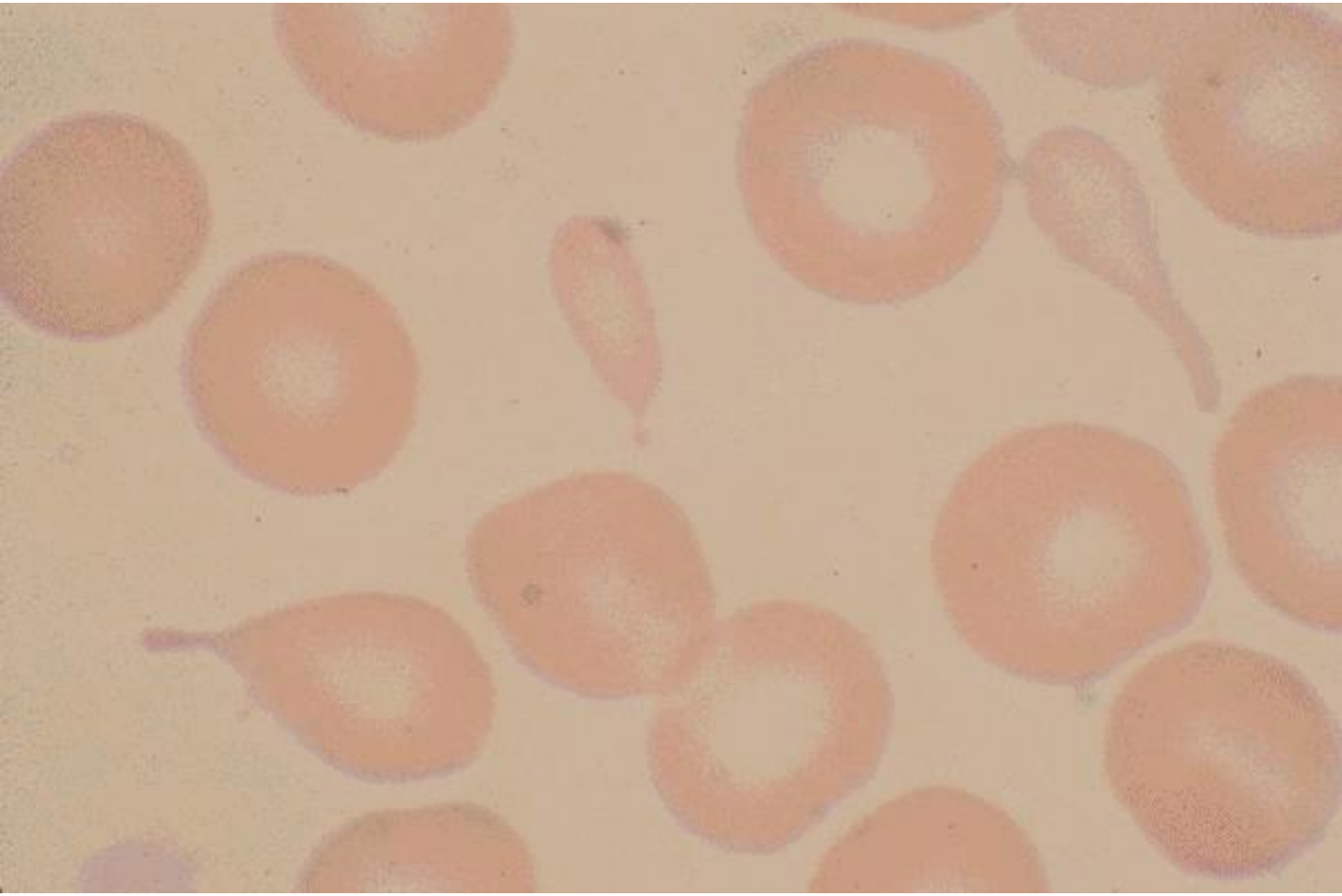
Table 1. Clinical features at presentation of myelofibrosis with myeloid metaplasia.

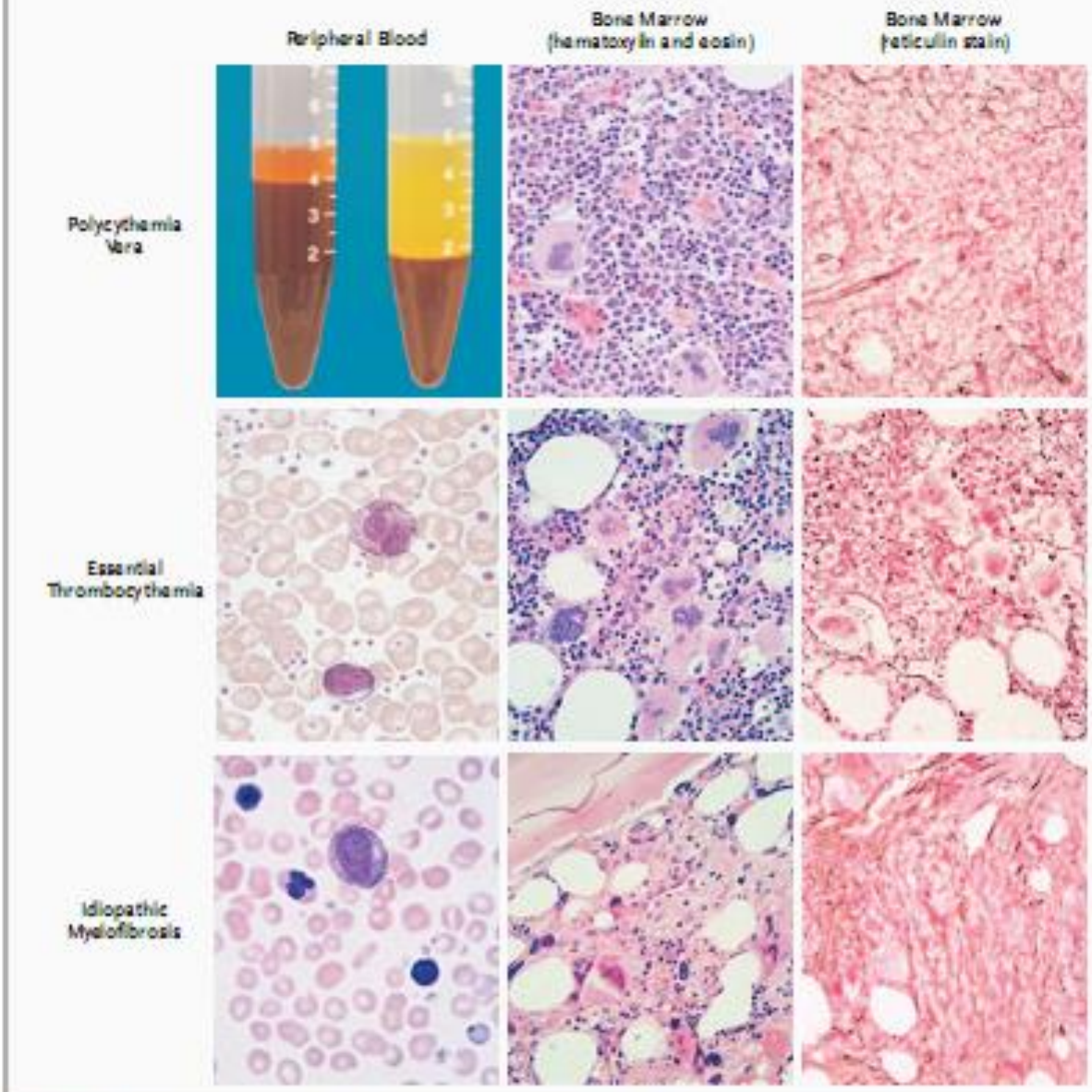
Symptom/sign	Clinical feature
Myeloproliferation	Splenomegaly
	Hepatomegaly
	Extramedullary hematopoiesis[a]
	Bone pain
	Thrombosis
Cytopenias	Fatigue
	Dyspnea
	Ischemia
	Infection
	Bleeding
Constitutional	Fatigue
	Night sweats
	Fever
	Weight loss

[a] May occur in any location including lung, epidural space, pericardium, intraperitoneal cavity.



Tefferi et al: Blood 95:2226, 2000





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Complications

- Survival varies according to specific clinical features, but shorter than PV or ET pts.
- Natural history:
  - Increasing marrow failure
  - Transfusion-dependent anemia
  - Increasing organomegaly
- Chronic phase → accelerated phase
- Transformation into aggressive AML (10%)

WHO criteria for MF 2007

Major

1. **Megakaryocyte proliferation and atypia** accompatined by either reticulin or collagen **fibrosis**, or in the absence of reticulin fibrosis the megkaryocyte changes must be accompanied by **increased marrow cellularity**, granulocytic proliferation and often decreased erytropoiesis
2. Not meeting WHO criteria for PV, PMF, CML, MDS, or other myeloid neoplasm
3. Demonstration of *JAK2 V*617F or other clonal marker, or in the absence of a clonal marker, no evidence for reactive myelofibrosis

Minor

1. Leukoerythroblastosis
2. Increased LDH
3. Anemia
4. Palpable splenomegaly

Diagnosis requires the presence of all major criteria and 2 minor criteria

Prognostic factors

Table 2. Agnogenic myeloid metaplasia: prognostic summary.

Feature	All MMM patients (Dupriez score)[7]	Young MMM patients (Cervantes score)[44]
Anemia (hemoglobin <10 g/dL)		
Leukocytes (<4 or $>30\times10^9$/L)		
Blood blasts ($>1\%$)		
Constitutional symptoms		
Low risk	0 Factors (median survival: 93 months)	0–1 factor (median survival: 176 months)
Intermediate risk	1 Factor (median survival: 26 months)	
High risk	2 factors (median survival: 13 months)	2–3 factors (median survival: 33 months)

Rx.

- **Allogenic BM transplantation** - the only curative treatment, but very hard for pts.

- **Non-transplant therapy**

- **Experimental therapy**

Transplant vs. Other treatments

Low risk
(life-expectancy > 10 years)

Observation

Intermediate risk
(life-expectancy 5-10 years)

- Age < 50 years

  Transplant is Reasonable

- Age > 50 years

  Non-transplant\ Experimental drugs

High risk
(life-expectancy < 5 years)

- Age < 50 years

  Transplant is preferred

- Age 50-60 years

  Transplant is reasonable

- Age > 60 years

  Non-transplant\ Experimental drugs

Tefferi and Deeg.
Mayo Clin Proc, in press

Rx.

- **Transplant option**
  - **Myeloablative**
  - **Reduced-intensity conditioning (RIC)**
- **Non-transplant options**
  - **Treatment for anemia**
    - **Erythropoietin**
    - **Corticosteroids**
    - **Androgen + Prednisone**
    - **Danasol**
    - **Thalidomide + Prednisone**
    - **Lenalidomide**
  - **Treatment for splenomegaly**
    - **Hydroxyurea (HU)**
    - **splenectomy**
  - **Treatment for extramedullary hematopoiesis**
    - **Low dose irradiation**
  - **Supportive care**

Experimental therapy

Table 3. Current therapeutic strategies undergoing evaluation for the treatment of primary myelofibrosis.

- Small-molecule inhibitors of JAK2V617F
- TGF-β inhibitors
- NFκB inhibitors
- Chromatin-modifying agents
- Protease inhibitors
- Bcl-xL inhibitors
- VEGF inhibitors

Future therapy for MPD

Therapeutic potential of JAK2 inhibitors

Srdan Verstovsek[1]

[1]*The University of Texas M. D. Anderson Cancer Center, Houston, TX*

Table 1. Preliminary clinical observations in selected JAK2 inhibitor trials.

Agent	Company	Target(s)	JAK IC_{50} (nM)	Current phase	Preliminary clinical observations in myelofibrosis studies
INCB018424	Incyte	JAK1, JAK2	JAK1 = 2.7* JAK2 = 4.5* JAK3 = 322*	III	Decreased spleen size irrespective of JAK2 mutational status; improved quality of life, weight and performance; decreased inflammatory cytokine levels. Myelosuppression.
TG101348	TargeGen	JAK2	JAK1 = 105 JAK2 = 3 JAK3 = 996	II	Decreased spleen size; decrease in WBC. Myelosuppression; gastrointestinal disturbance.
XL019	Exelixis	JAK2	JAK1 = 132 JAK2 = 2 JAK3 = 250	discontinued	Decreased spleen size only in patients with JAK2 V617F or MPL mutation; decreased pruritis and improved fatigue. Neurotoxicity.
CEP701 (lestaurtinib)	Cephalon	JAK2, FLT3	JAK2 = 1	I/II	Decreased spleen size, improvement in blood cell count. Myelosuppression; gastrointestinal disturbance.

*Assays performed at 1 mM ATP concentration.

Thank You!!