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CHRONIC MYELOID LEUKEMIA
IDIOPATHIC MYELOFIBROSIS
POLYCYTHEMIA VERA

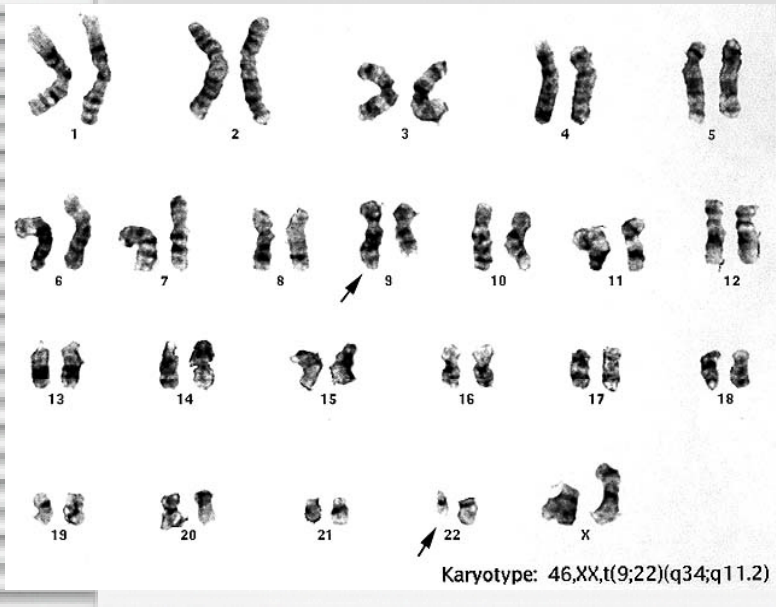
CHISINAU - 2020

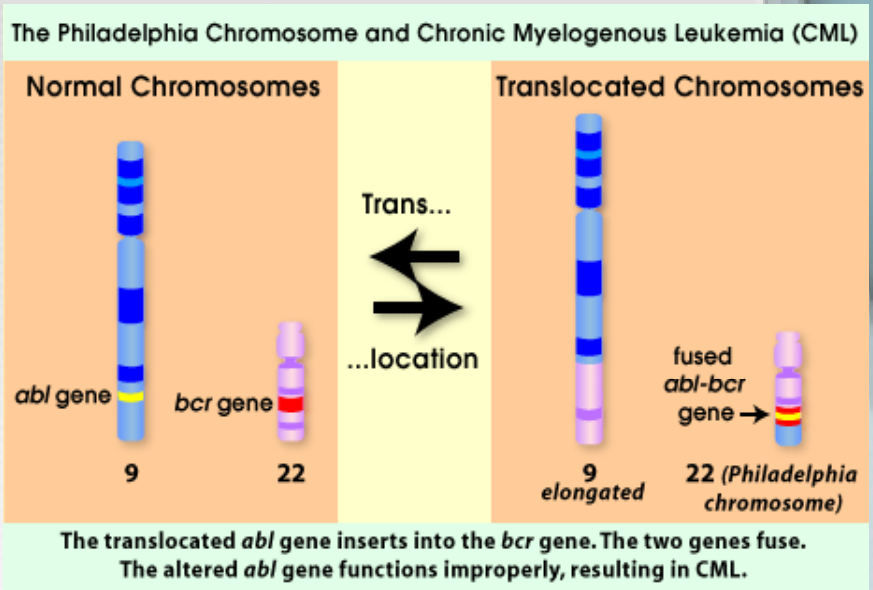
CHRONIC MYELOID LEUKEMIA (CML) **is a clonal myeloproliferative disorder resulting from the stem cell neoplastic transformation caused by translocation between the long arms of chromosomes 22 and 9. The annual incidence of CML ranges between 0.6 – 1.6 cases per 100.000 population. CML accounts 15 – 20% of leukemias in adults. This myeloproliferative malignancy occurs mostly in workable population with the age of 40 – 50 years old. Male : female ratio may reach 1.4 : 1.**

ETIOLOGY: **A higher incidence of CML is registered among persons heavily exposed to radiation, including survivors of the atomic bomb blasts in Japan and patients undergoing radiotherapy, and in those with obesity.**

PATHOGENESIS: **The tyrosine kinase activity and BCR functional domains of the p210 chimeric protein act on a number of signaling pathways and intermediate the promotion of leukemogenesis by changing proliferation, apoptosis, and altered interaction with the cellular matrix.**

PHILADELPHIA CHROMOSOME – CYTOGENETIC MARKER OF CHRONIC MYELOID LEUKEMIA



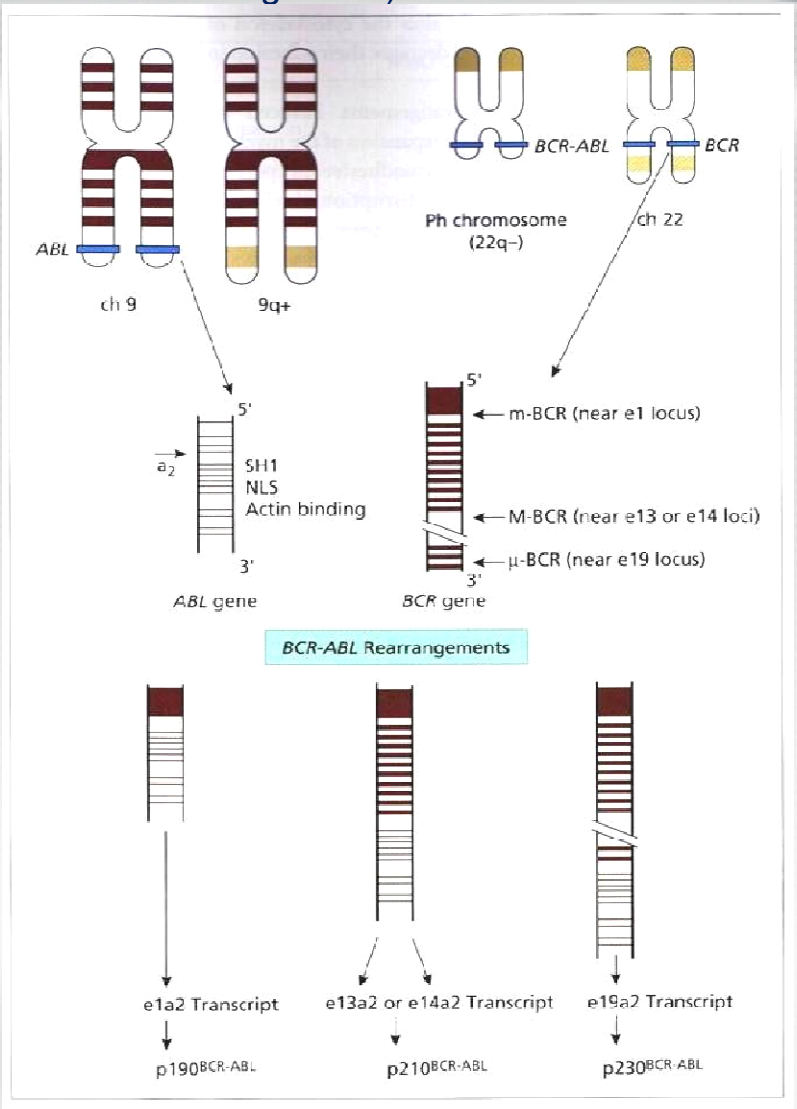


The discovery of Philadelphia chromosome, and the subsequent finding of BCR-ABL chimeric gene, led to an unique understanding of the biology of the disease that spurred the development of targeted therapy, as well as the methods for the molecular monitoring of the disease. Ph chromosome is absent in 2 – 3% of cases of CML. In Ph-negative CML or atypical CML the prognosis is less favorable.

MOLECULAR PATHOGENESIS OF CHRONIC MYELOID LEUKEMIA

(Williams M.E., Kahn M.J., American Society of Hematology Self-Assessment Program. Blackwell Publishing: 2005)

The 3′ portion of the *ABL* gene on the distal tip of chromosome 9 is translocated to the *BCR* gene on chromosome 22 to form the 22q- abnormality referred to as the Ph chromosome. The breakpoints within the *ABL* gene occur within introns 1b or 2, both of which are 5′ (upstream) to the a2 exon. The a2 and downstream exons encode the Src homology (SH) domains, including the SH1/tyrosine kinase domain, DNA binding domain, nuclear localization signal (NLS) and actin binding site. The breakpoints on chromosome 22 occur at one of three different locations within *BCR*, yielding hybrid oncogenes of varying length consisting of 5′ *BCR* sequences and 3′ *ABL* sequences. Each hybrid oncogene gives rise to a chimeric transcript and fusion protein with variable oncogenic activity. These include $p190^{BCR-ABL}$ (resulting from fusion at the m-BCR site), $p210^{BCR-ABL}$ gene product (resulting from fusion at the M-BCR site) and $p230^{BCR-ABL}$ (resulting from fusion at the μ-BCR site). See the text for discussion of disease-associated features.



CLINICAL AND HEMATOLOGIC SUMMARY

The clinico-evolutional and hematologic patterns of CML comprise splenomegaly, myeloid hyperplasia of the bone marrow, hypercatabolic symptoms and progression to the acute leukemia in the majority of cases.

The clinical course of the disease consists of 3 consecutive phases: chronic, accelerated and acute, and may be associated with life-threatening emergencies, especially thrombotic and infectious complications, splenic infarcts, bleeding, etc.

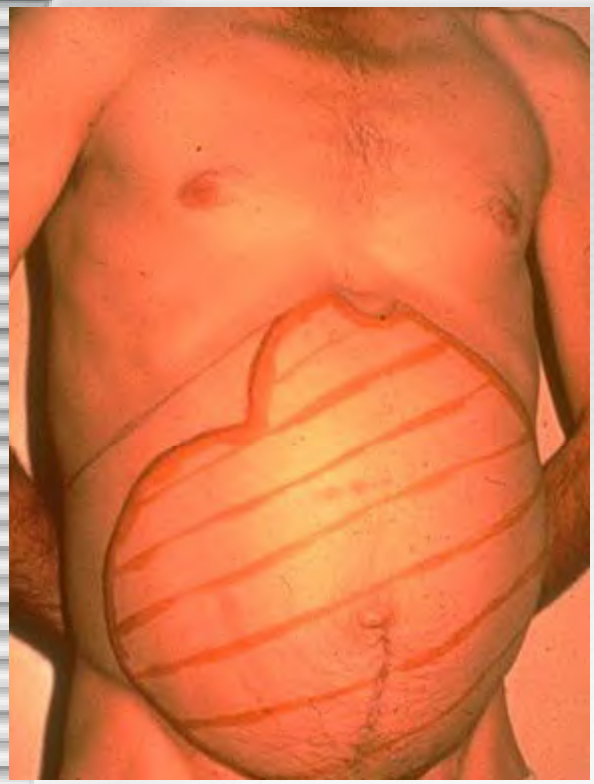
Early chronic (initial) phase: **Asymptomatic phase. Leukocyte count doesn't exceed 30 x 10^9/l. CML may be diagnosed occasionally in virtue of peripheral blood findings: neutrophilic leukocytosis, with all stages of maturation, and basophilia. Hemoglobin level and thrombocyte count usually are within the normal limits. Platelets may be slightly increased. This stage is usually overseen.**

Late chronic phase: **The majority of patients show symptoms of vigorous hematopoiesis (fever, sweat, bone pain, weight loss, and fatigue) or signs of extramedullary hematopoiesis (splenomegaly and left upper quadrant discomfort). The spleen varies in size from just a palpable tip to a mass filling the abdomen. Spleen size correlates reasonably well with the magnitude of the leukocyte count. Approximately 50% of patients have hepatomegaly. Leukocytosis ranges from 40.0 x 10^9/l to more than 500.0 x 109/l. The increased leukocyte and platelet counts may lead to some complications: splenic infraction, thromboses in small vessels (retinal, those of cavernous body with priapism), retinal edema, stupor. Splenomegaly is absent in 10% of cases with CML.**

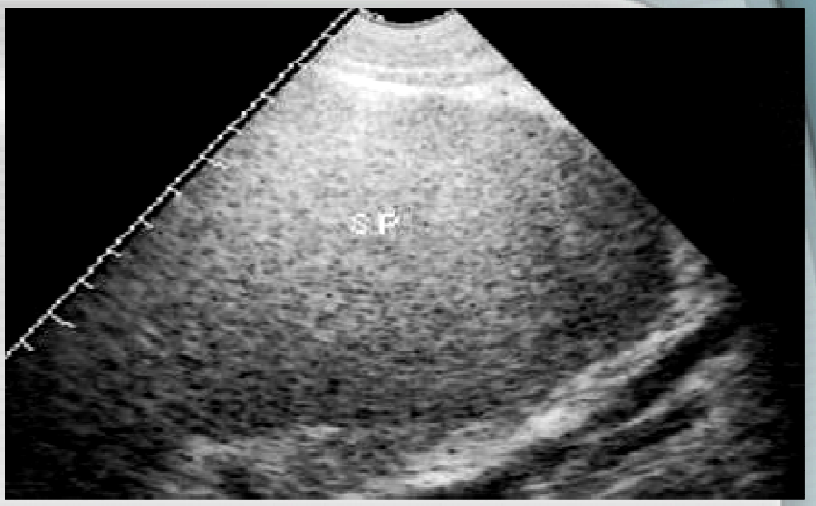
Accelerated phase: **Fever regardless to infection, bone pain, extending splenomegaly, leukemic infiltration in sites such as the skin, soft tissues, bones, with spinal cord compression, decreased effectiveness of cytotoxic agents. Peripheral blood blasts are more common and usually exceed 15% of the total white blood. These symptoms usually appear 6 – 12 months before the blast crisis develops.**

Acute phase: **In 20% of patients the blast crisis can occur rather abruptly and without being preceded by the accelerated phase. Compared to accelerated phase, blast phase is more easily defined as meeting the strict definition of acute leukemia. The increased genetic instability leads to additional chromosomal abnormalities, leading to the development of malignant subclones. Blast crisis is characterized by all of the morbid manifestations of acute leukemia. Patients suffer from severe bacterial or fungal infections and hemorrhages caused by neutropenia and thrombocytopenia, respectively. Blast crisis may be of myeloblastic (80%) and lymphoblastic (20%) types.**

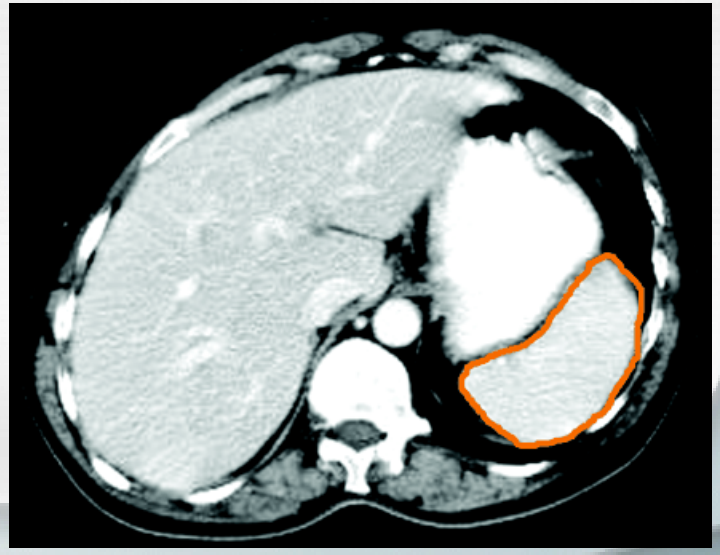
SPLENOMEGALY IN CHRONIC MYELOID LEUKEMIA



Physical examination



Ultrasound scanning

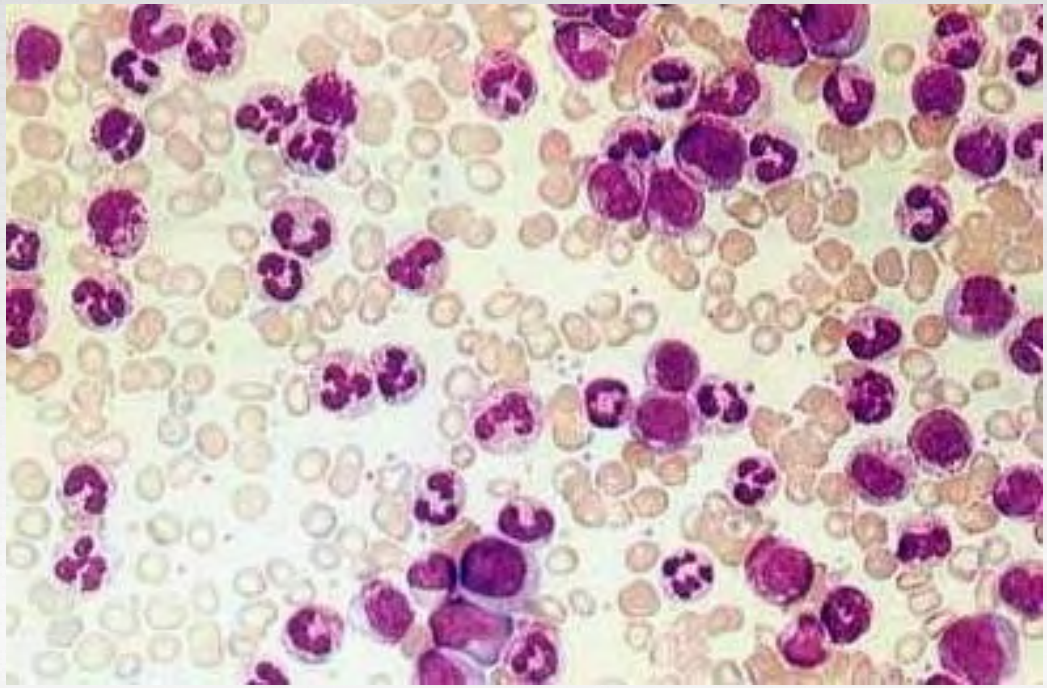


Computerized tomography scanning

BLOOD COUNT IN CHRONIC MYELOID LEUKEMIA

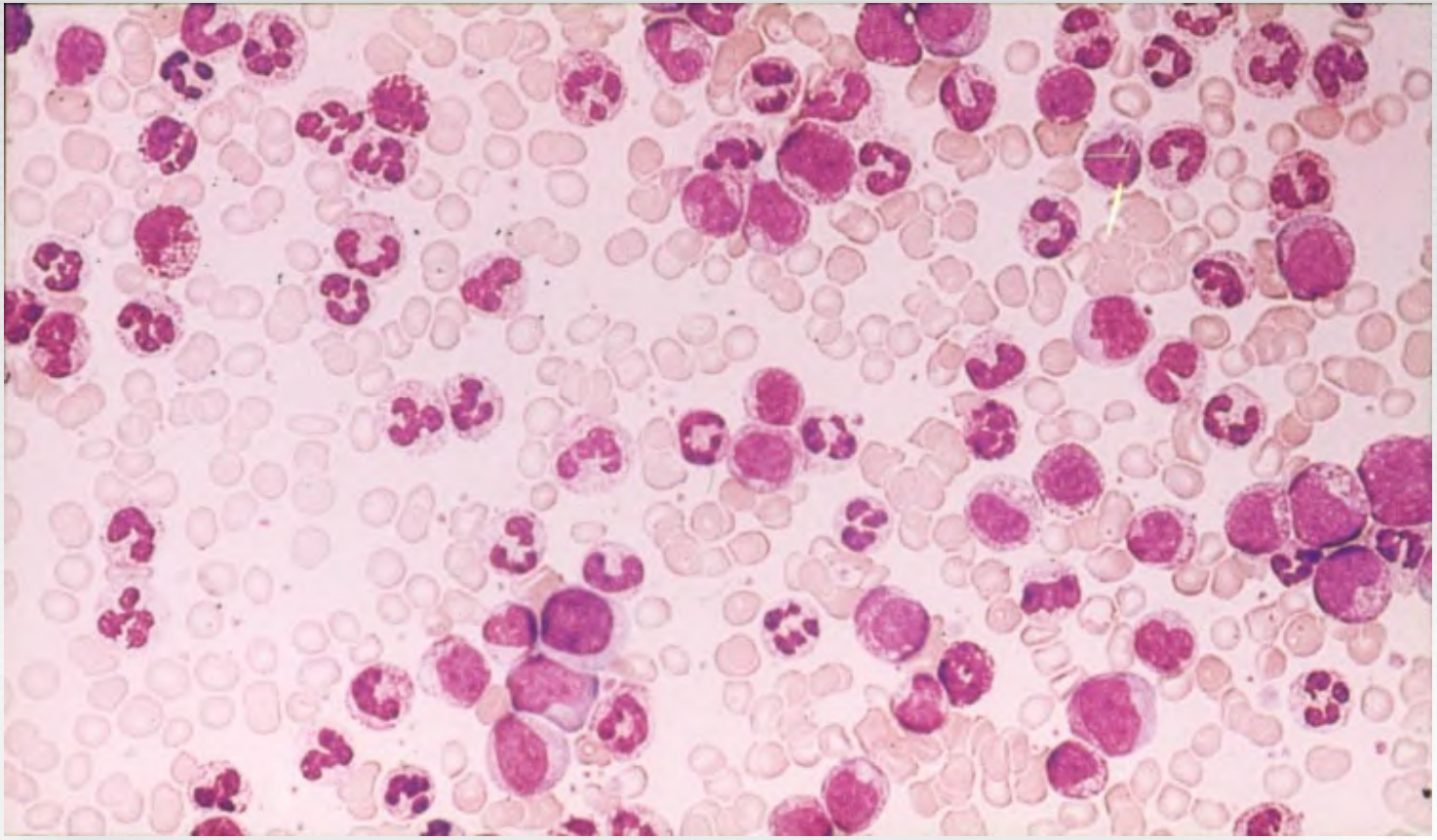
Hemoglobina (g/l)	**145,0**	**130**	**140**
Eritrocite (10^{12}/l)	**5,3**	**4,0**	**4,2**
Leucocite (10^{9}/l)	**12,0**	**52,0**	**220,0**
Celule blastice (%)	**—**	**5**	**2**
Promielocite (%)	**—**	**—**	**3**
Mielocite (%)	**6**	**10**	**24**
Metamielocite (%)	**1**	**2**	**6**
Nesegmentate (%)	**—**	**8**	**15**
Segmentate (%)	**45**	**58**	**45**
Eozinofile (%)	**2**	**—**	**1**
Bazofile (%)	**3**	**1**	**—**
Limfocite (%)	**26**	**15**	**1**
Monocite (%)	**17**	**1**	**—**
Trombocite (10^{9}/l)	**340,0**	**320,0**	**252,0**
VSH (mm/oră)	**5**	**30**	**3**

BLOOD SMEAR IN CHRONIC PHASE OF CHRONIC MYELOID LEUKEMIA



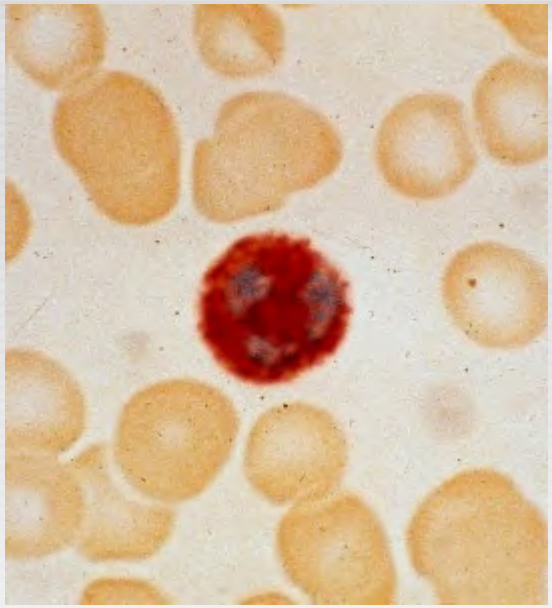
May-Giemsa staining, x 200

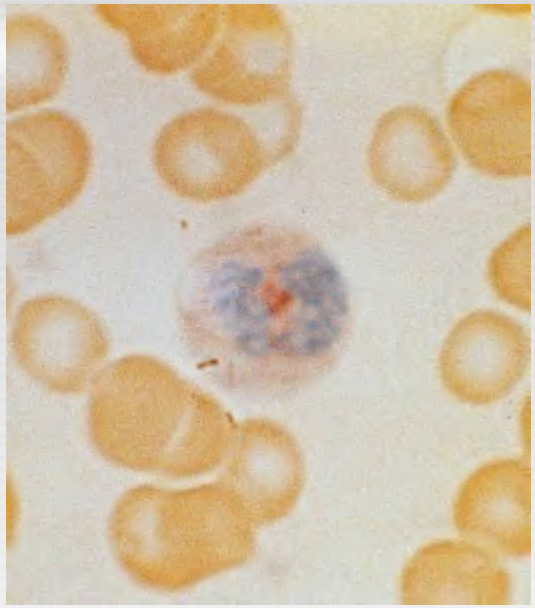
BLOOD SMEAR IN CHRONIC PHASE OF CHRONIC MYELOID LEUKEMIA

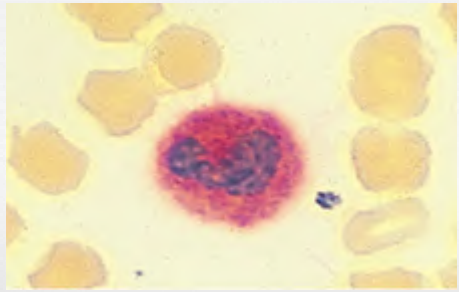


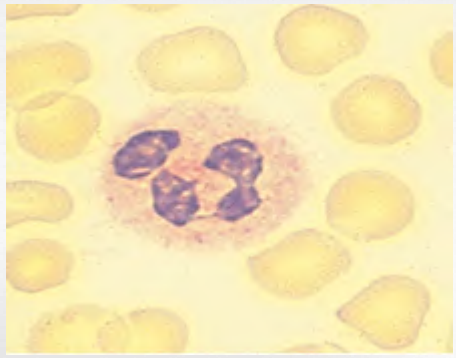
May-Giemsa staining, x 300

BLOOD SMEAR: LEUKOCYTE ALKALINE PHOSPHATASE REACTION





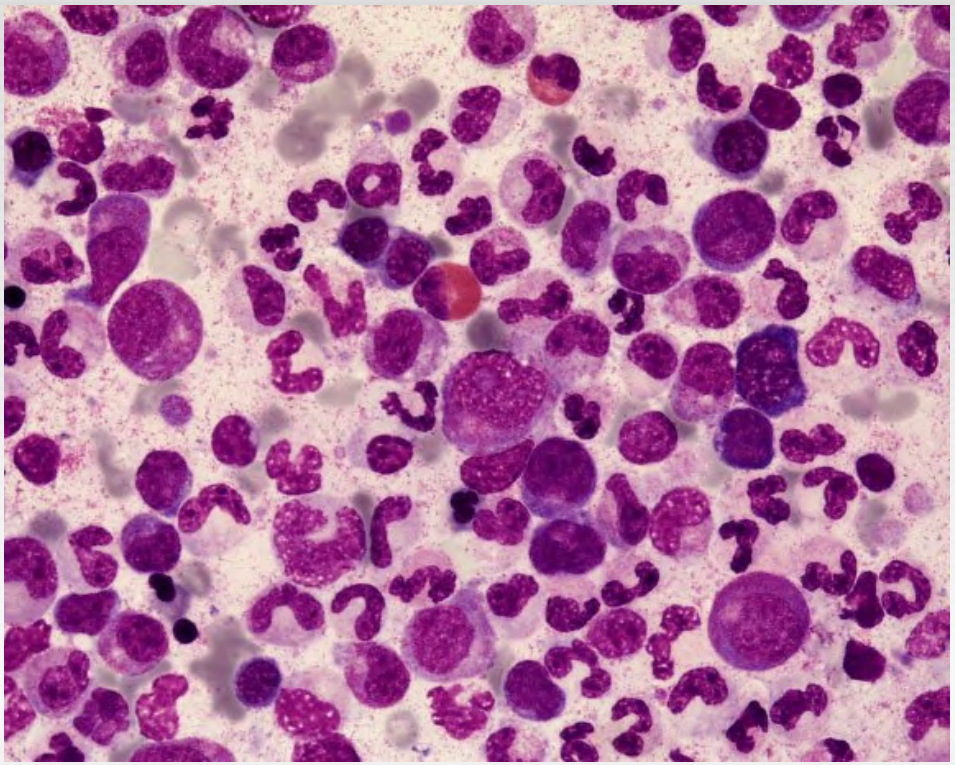




Leukemoid reaction

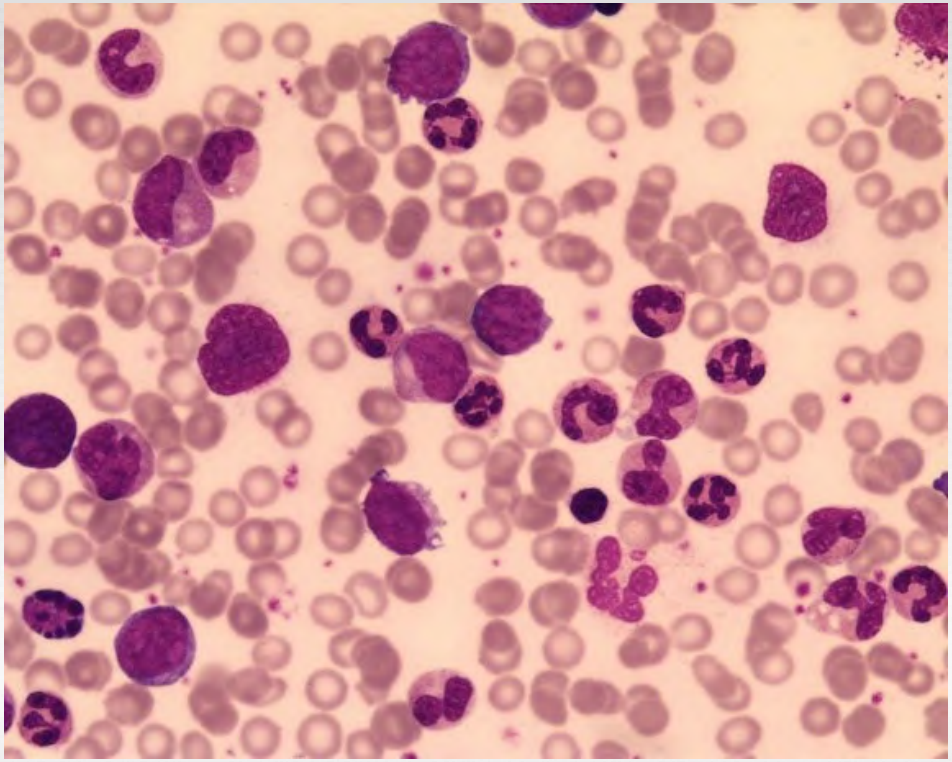
Chronic myeloid leukemia

BONE MARROW SMEAR IN CHRONIC PHASE OF CHRONIC MYELOID LEUKEMIA



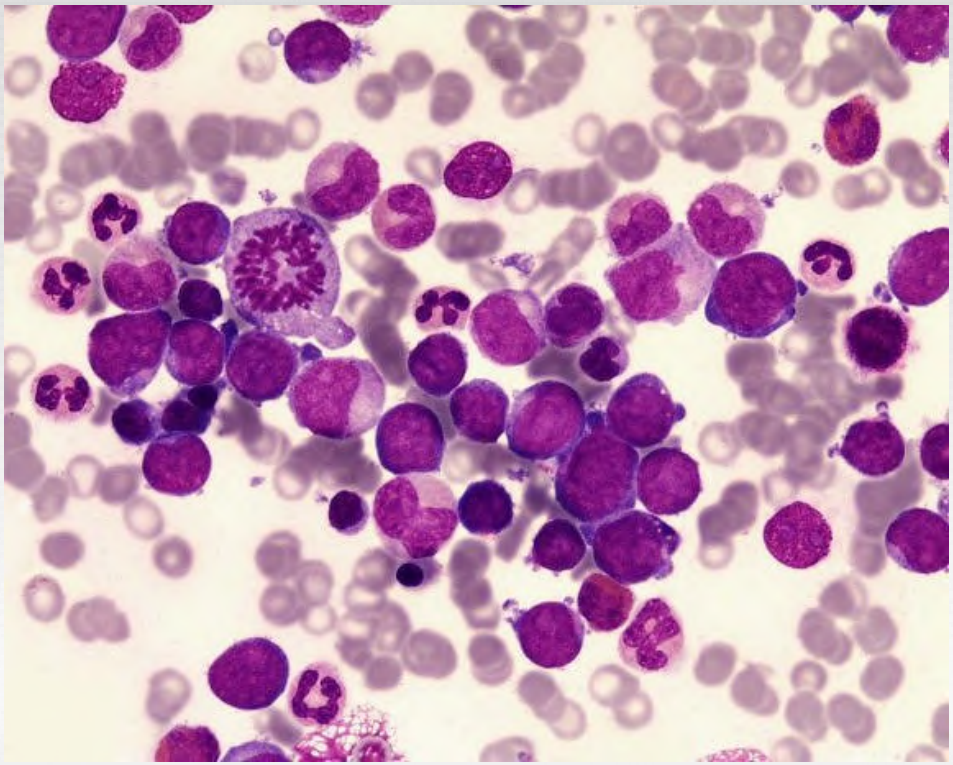
May-Giemsa staining, x 300

BLOOD SMEAR IN ACUTE PHASE OF CHRONIC MYELOID LEUKEMIA



May-Giemsa staining, x 300

BONE MARROW SMEAR IN ACUTE PHASE OF CHRONIC MYELOID LEUKEMIA



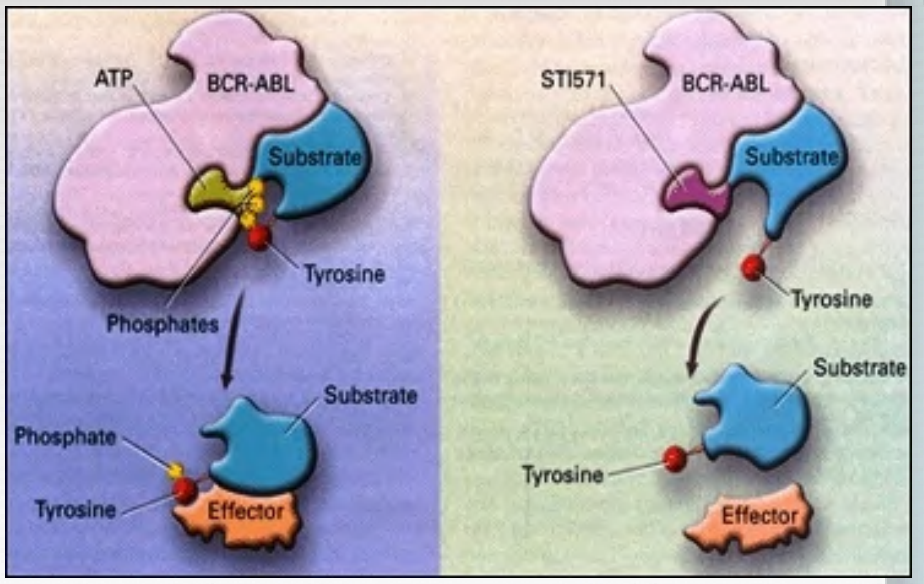
May-Giemsa staining, x 300

DIFFERENTIAL DIAGNOSIS BETWEEN THE INITIAL PHASE OF CML AND THE MYELOID TYPE OF LEUKEMOID REACTIONS

Criteria	CML	LEUKEMOID REACTION
Performance status	satisfactory	corresponds to the severity grade of underlying disease
Basophil-eosinophil association	present	absent
Leukocyte alkaline phosphatase	decreased	increased
Ph (+) cells	are usually found in direct marrow preparations	absent

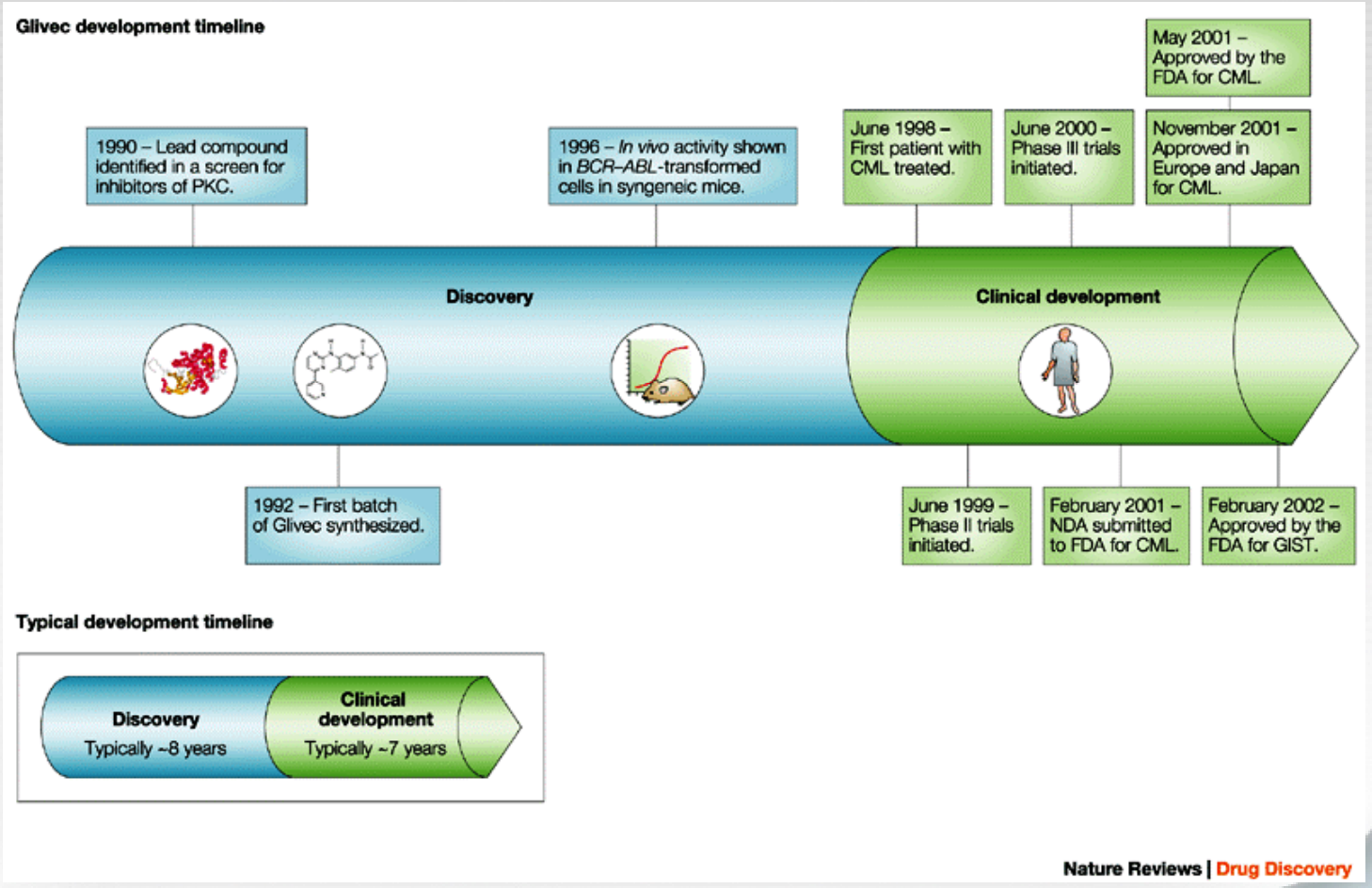
GLIVEC® - imatinib mesylate

Pharmaceutical form



Mechanism of action

DEVELOPMENT OF IMATINIB MESYLATE



DEFINITIONS OF RESPONSE IN CHRONIC MYELOID LEUKEMIA

Response	Category	Criteria
Hematologic remission	Complete	Normalization of WBC counts to $< 9 \times 10^9$/L with normal differential; normalization of platelet counts to $< 450 \times 10^9$/L; disappearance of all signs and symptoms of disease
Cytogenetic response[b]	Complete[a]	No evidence of Ph chromosome-positive cells
	Partial[a]	5%-34% of metaphases Ph chromosome-positive cells
	Minor	35%-95% of metaphases Ph chromosome-positive cells
	None	Persistence of Ph chromosome in all analyzable cells

[a] Major cytogenetic response includes complete and partial cytogenetic responses.

[b] Response assessed on routine cytogenetic analysis with at least 20 metaphases counted.

CRITERIA FOR PRIMARY MYELOFIBROSIS

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

Diagnosis requires meeting all 3 major criteria and 2 minor criteria

Major criteria:

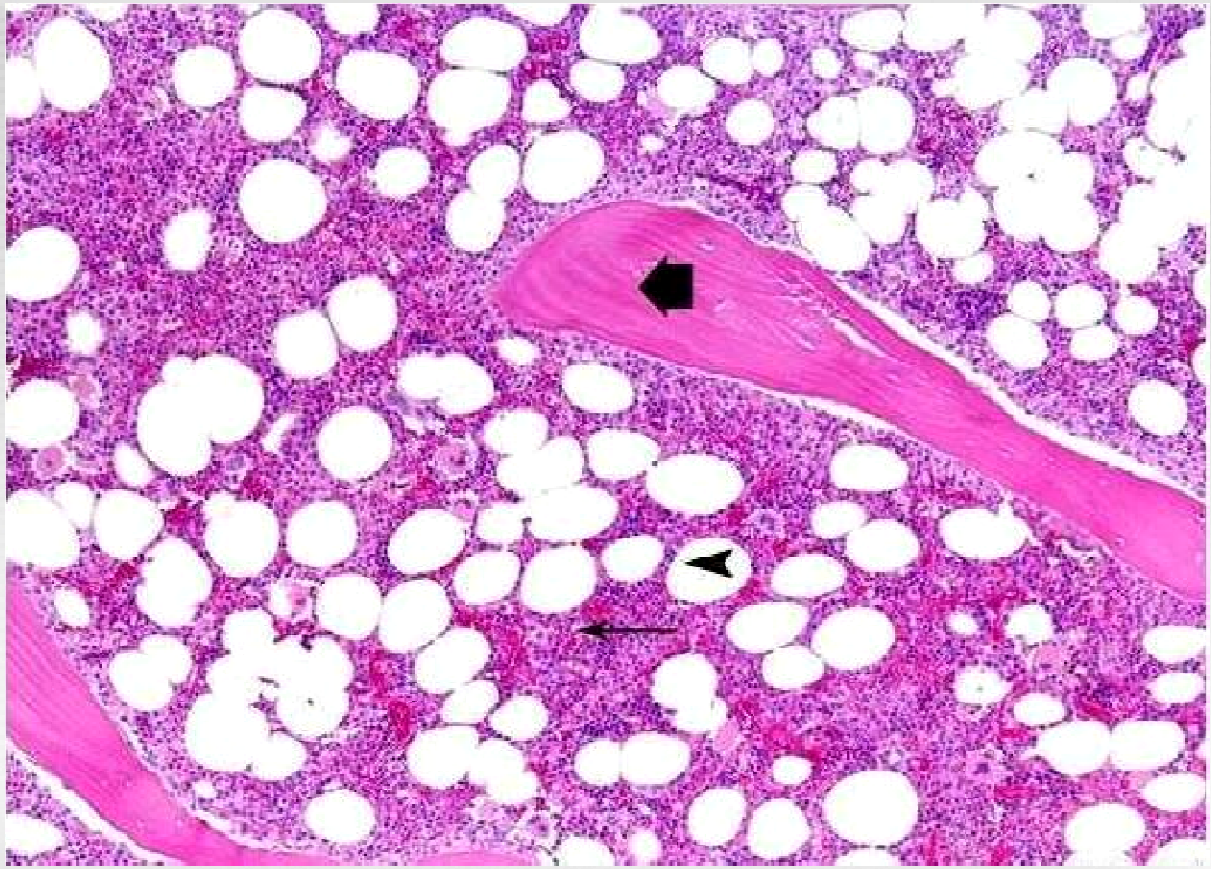
1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin or collagen fibrosis,
or,
in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for polycythemia vera,† *BCR-ABL1–positive chronic* myelogenous leukemia,‡ myelodysplastic syndrome,§ or other myeloid disorders
3. Demonstration of *JAK2 V617F or other clonal marker (eg, MPLW515K/L),*
or,
in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies

Minor criteria:

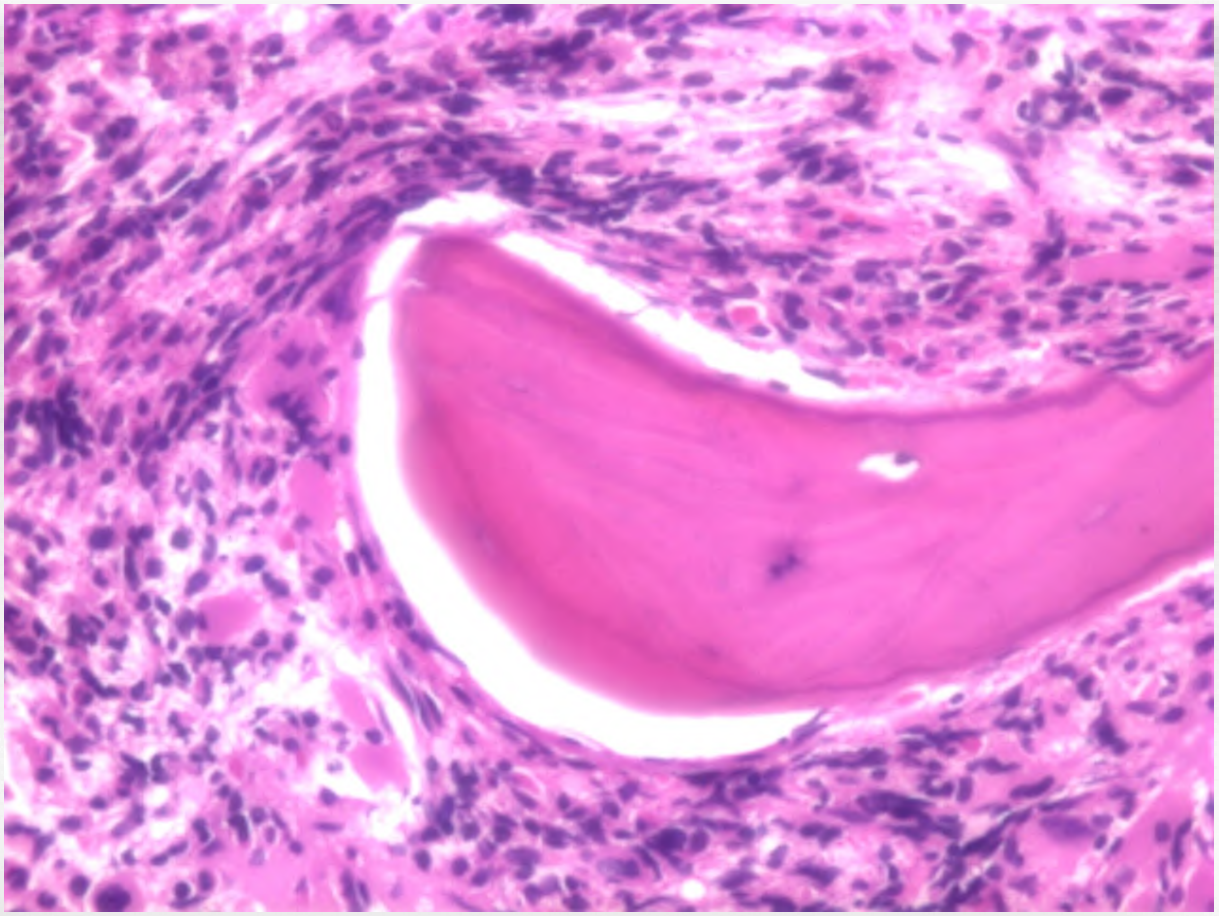
1. Leukoerythroblastosis ¶
2. Increase in serum lactate dehydrogenase level ¶
3. Anemia ¶
4. Palpable splenomegaly ¶

*Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering. †Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required. ‡Requires the absence of *BCR-ABL1.* §Requires the absence of dyserythropoiesis and dysgranulopoiesis. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis, and the diagnosis should be considered in such cases if other criteria are met. ¶Degree of abnormality could be borderline or marked.

BIOPSY: NORMAL BONE MARROW

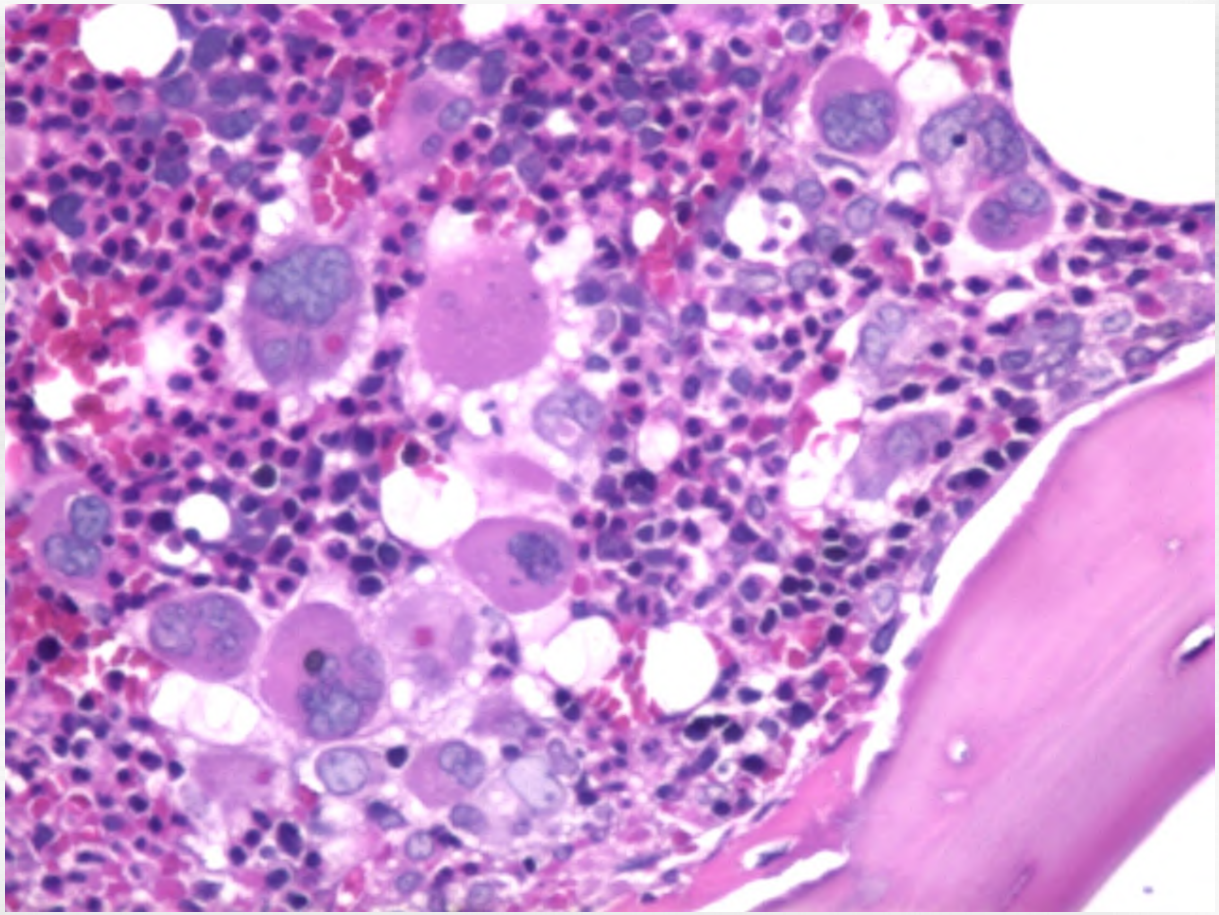


BONE MARROW BIOPSY IN IDIOPATHIC MYELOFIBROSIS



A higher power view highlights the paratrabecular deposition of collagen fibrosis

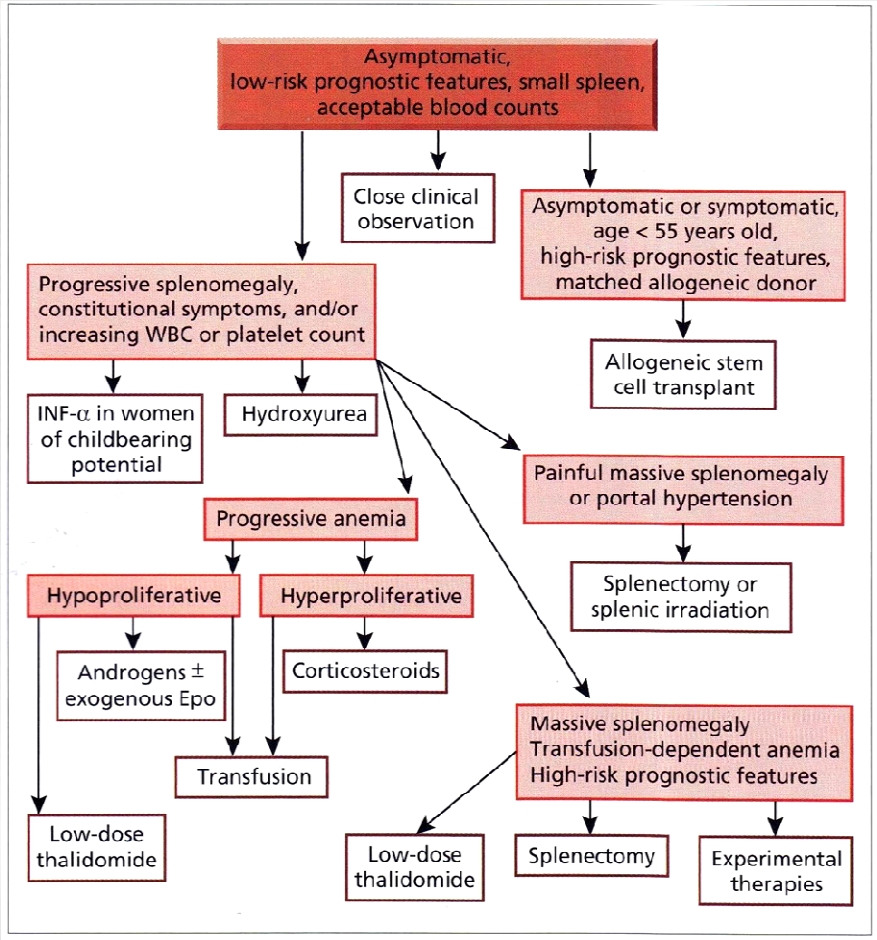
BONE MARROW BIOPSY IN IDIOPATHIC MYELOFIBROSIS



Clusters of atypical megakaryocytes may be found adajacent to trabeculae

STEP-WISE TREATMENT APPROACH TO IDIOPATHIC MYELOFIBROSIS

(Williams M.E., Kahn M.J., American Society of Hematology Self-Assessment Program. Blackwell Publishing: 2005)

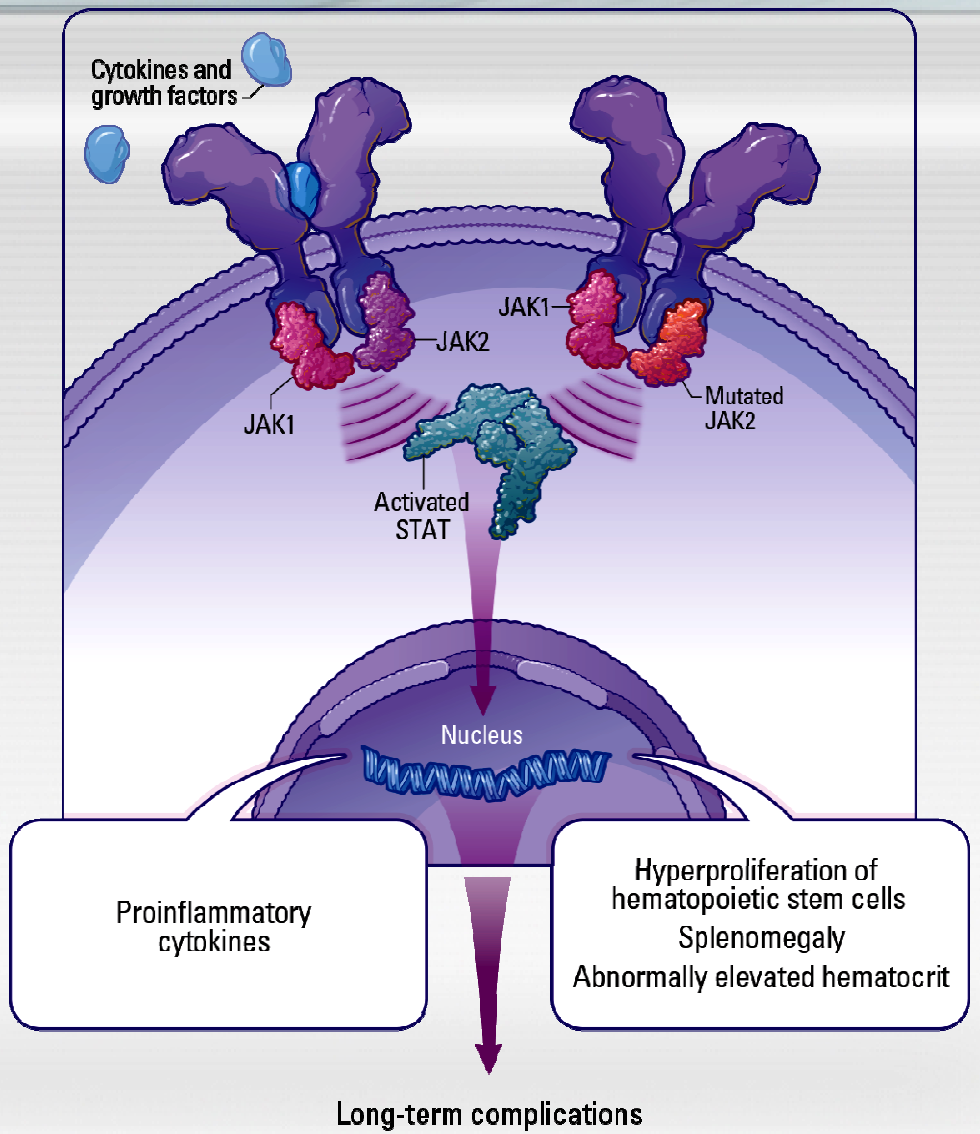


POLYCYTHEMIA VERA **(PV) is a chronic, clonal, myeloproliferative disorder characterized by an absolute increase in the number of red blood cells and in the total blood volume.**

PV **tends to be a disease of older individuals, with a peak incidence observed at 60 years of age. PV appears to be somewhat more common in men. The incidence rate ranges from 0.6 to 1.6 per 100 000 population, being 0.2 per 100 000 persons in Moldova.**

PATHOGENESIS. **Erythremia is a clonal expansion from the early phase of myeloid differentiation – myeloid cell precursors. The bone marrow is hypercellular and exhibits hyperplasia of myeloid, erythroid, and megakaryocyte lineages. Erithrocyte formation is predominantly increased. The symptoms and signs of PV can be attributed in large part to the expanded total blood volume and to the showing of the blood flow as a result of increased blood viscosity. Latent thrombogenic status is present. Arterial hypertension commonly develops.**

PATHOGENESIS OF POLYCYTHEMIA VERA



JAK - Janus-associated kinase; STAT - signal transducer and activator of transcription

STAGING SYSTEM IN POLYCYTHEMIA VERA:

I. The initial stage, or a moderate plethora.

II. The stage of unfolded clinical and hematological manifestations. This stage is divided in:

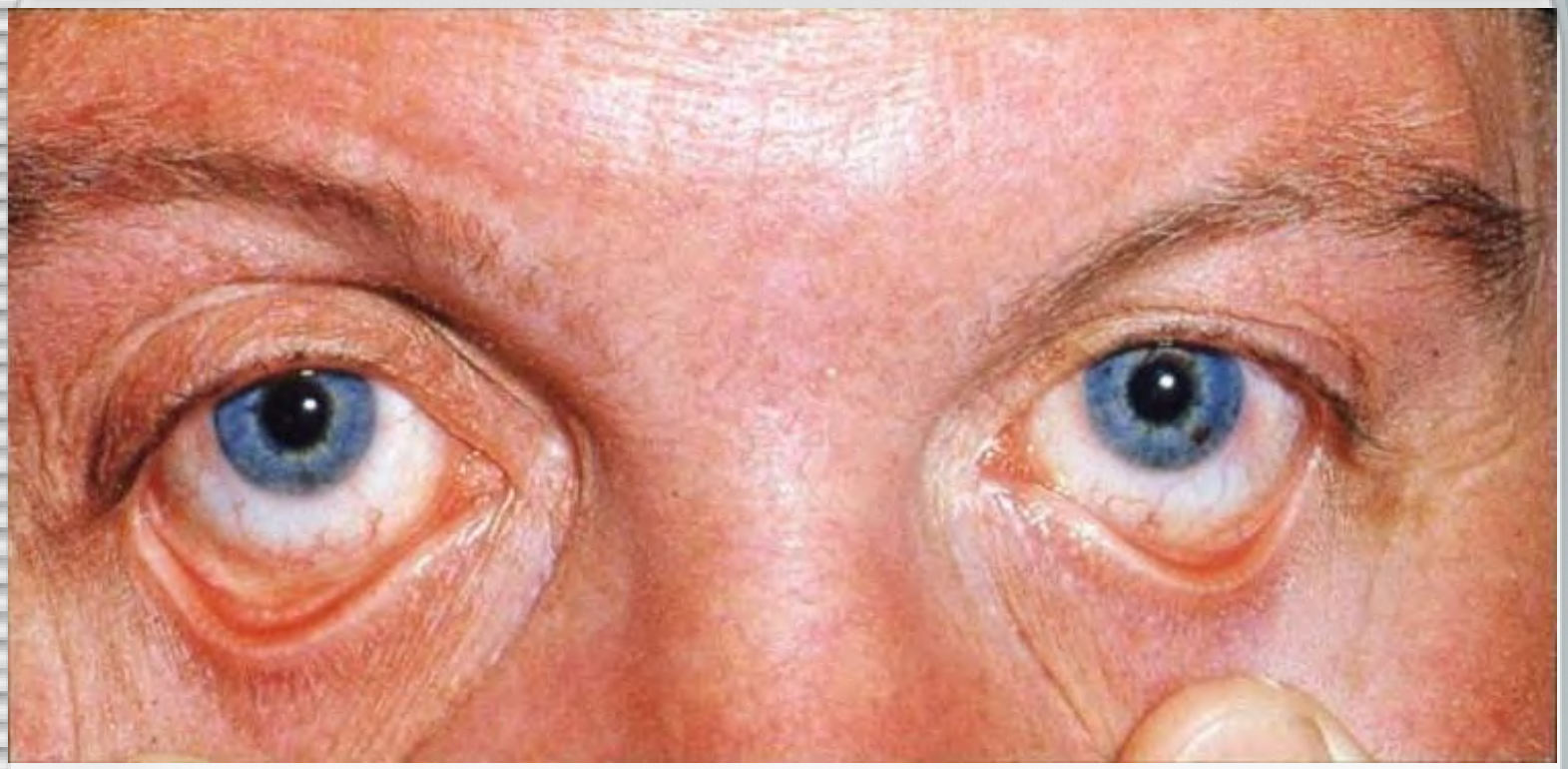
stage II A – without myeloid metaplasia of the spleen,

and

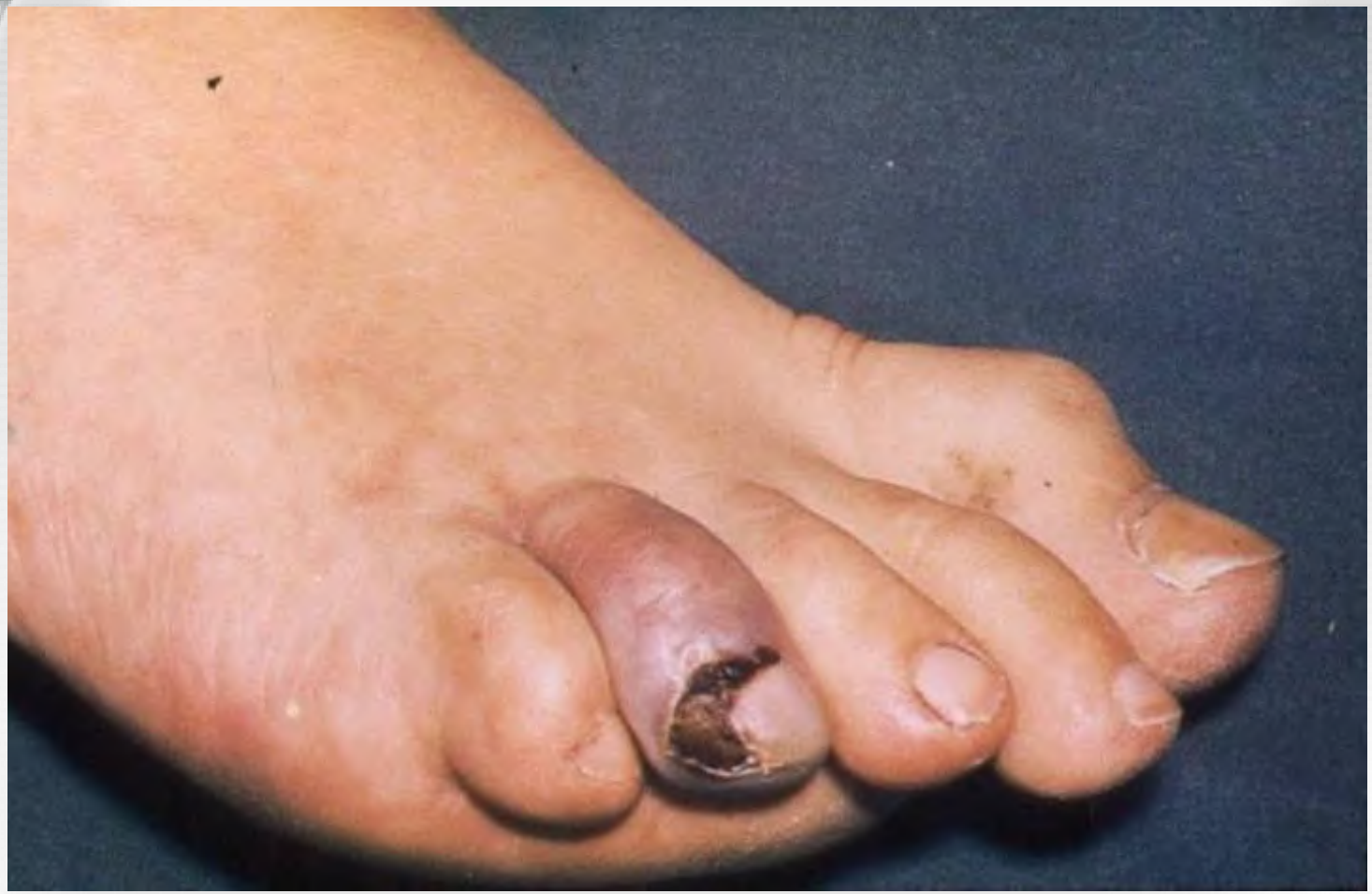
stage II B – with myeloid metaplasia of the spleen;

III. The anemic stage, or the stage of hematological transformations of erythremia.

MARKED PLETHORA WITH "RUDDY" FACE AND CONJUNCTIVAL INJECTION IN POLYCYTHEMIA VERA



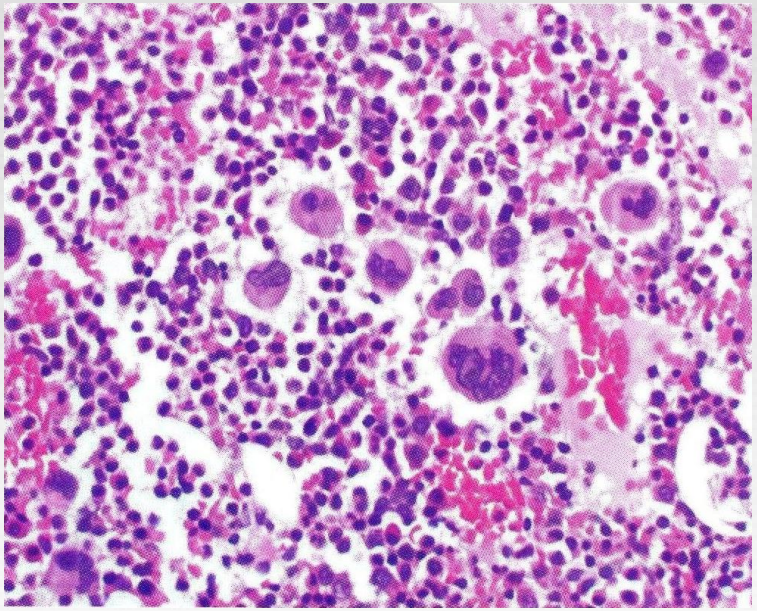
THROMBOTHIC AND VASCULAR COMPLICATIONS IN POLYCYTHEMIA VERA



BLOOD COUNT IN POLYCYTHEMIA VERA

Hemoglobina (g/l)	**200,6**
Eritrocite (10^{12}/l)	**6,3**
Leucocite (10^{9}/l)	**17,4**
Nesegmentate (%)	**—**
Segmentate (%)	**63**
Eozinofile (%)	**6**
Bazofile (%)	**1**
Limfocite (%)	**27**
Monocite (%)	**3**
Trombocite (10^{9}/l)	**492**
VSH (mm/oră)	**1**

BONE MARROW BIOPSY IN POLYCYTHEMIA VERA



The marrow is hypercellular. The hyperplasia involves all of the marrow elements and displaces marrow fat. An increase in megakaryocyte number and size is well documented in association with polycythevia vera.

2016 WORLD HEALTH ORGANIZATION DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

Major criteria:

1. Hemoglobin > 16.5 g/dL(men), Hemoglobin > 16.0 g/dL (women)
or
Hematocrit > 49% (men), Hematocrit > 48% (women)
or
ncreased red cell mass (RCM)

2. BM biopsy showing hypercellularity for age with trilineage growth
(panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of JAK2 or JAK2 exon 12 mutation

Minor criteria:
Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion

POLYCYTHEMIA VERA

download.mp4

CLASSIFICATION OF SYMPTOMATIC ERYTHROCYTOSES:

I. Relative erythrocytoses:

1. Stress- erythrocytoses

2. Geisböck's disease in arterial hypertension, obesity

3. Dehydration erythrocytoses

II . Absolute erythrocytoses:

1. Primary hereditary erythrocytoses

2. Secondary erythrocytoses:

A. Due to hypoxia and hypoxemia

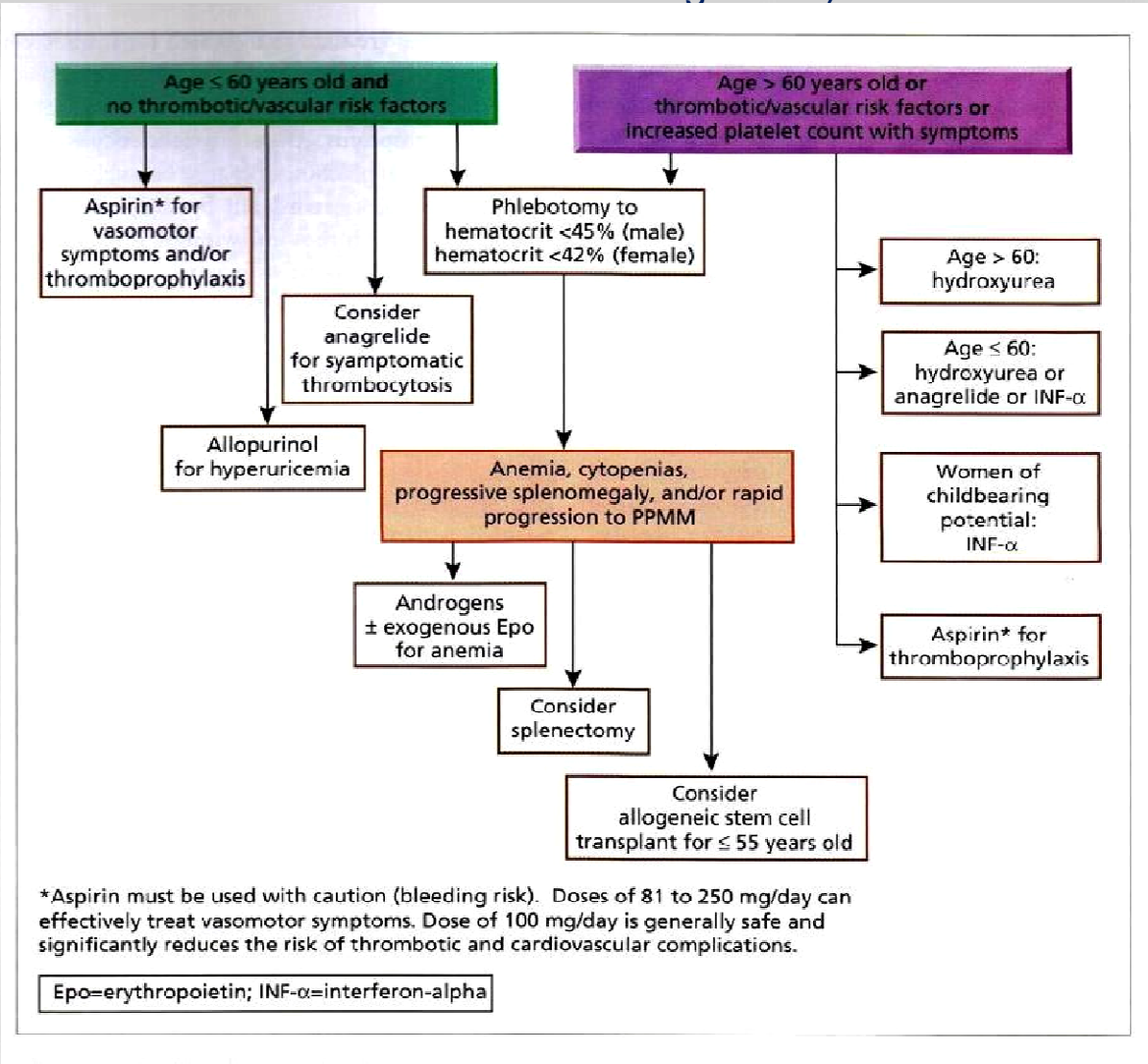
- **Elevated carboxyhemoglobinemia (Smoker's erythrocytosis)**
- **Alveolar hypoventilation (Pickwickian syndrome – sleeping apnea, obesity);**
- **Congenital cardiac defects**

B. Increased erythropoietin production

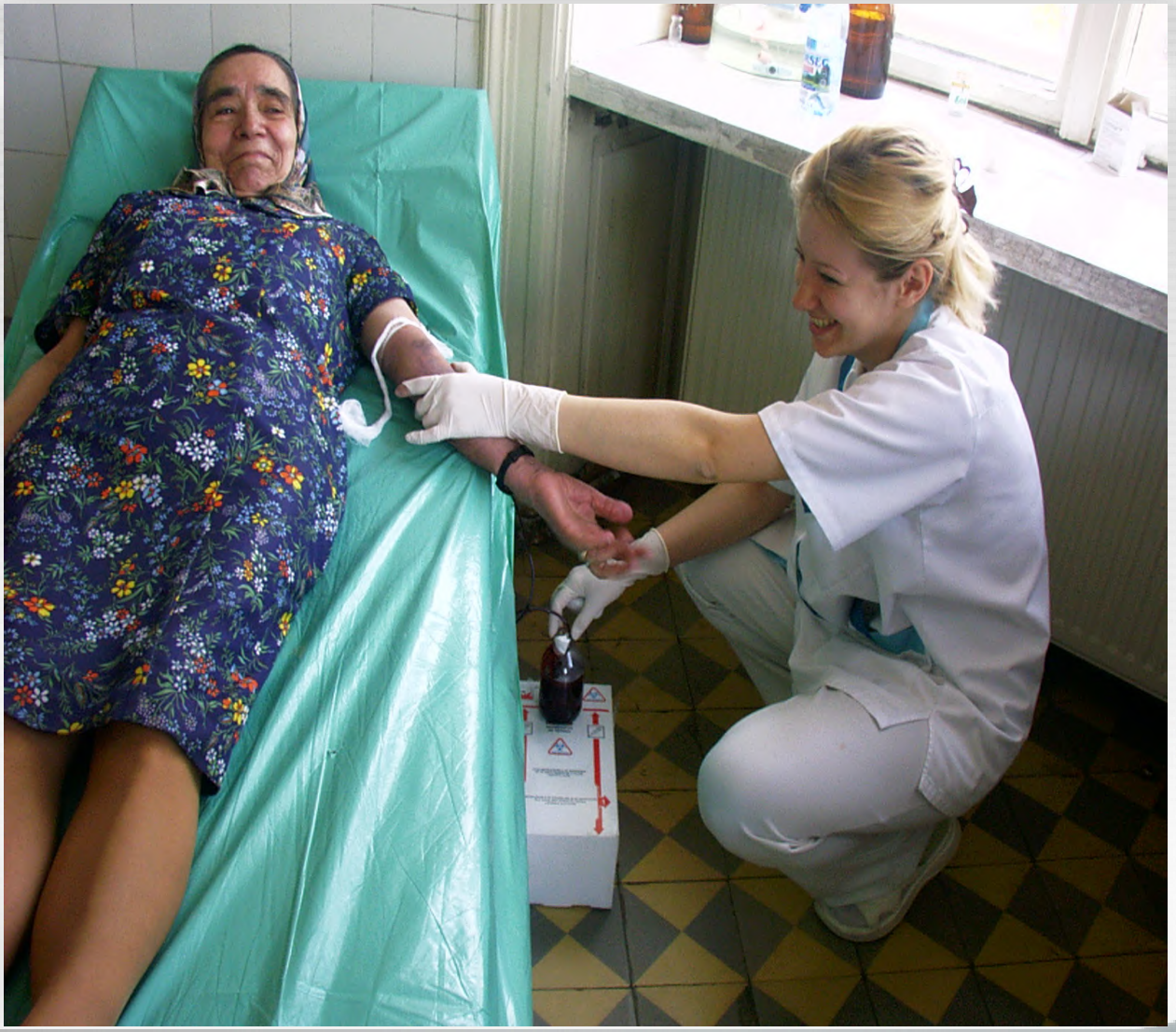
- **Renal diseases (hypernephromatosis, cyst, hydronephrosis)**
- **Extrarenal tumours (hypophysial adenoma, pheochromocytoma, massive uterine leiomyoma, cerebellar hemangioblastoma, etc.)**

TREATMENT ALGORITHMS FOR POLYCYTHEMIA VERA

(Williams M.E., Kahn M.J., American Society of Hematology Self-Assessment Program. Blackwell Publishing: 2005)



BLOOD EXFUSION (PHLEBOTOMIA) IN POLYCYTHEMIA VERA



REFERENCES FOR CHRONIC MYELOID LEUKEMIA:

Butoianu E., Niculescu-Mizil E., *Leucemia mieloidă cronică.* In: Coliţă D., "Medicină Internă. Hematologie. Partea a II-a". Bucureşti: Editura medicală, 1999: 48 – 68.

Corcimaru I., *Leucemia granulocitară cronică.* In: Corcimaru I., "Hematologie". Chişinău: Centrul Editorial – Poligrafic *Medicina*, 2007: 178 – 189.

Cortes E.J., List A., Kantarjian H., *Chronic myelogenous leukemia.* In: Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media, 2004: 773 – 786.

ESMO Gudelines Working Group, *Chronic myelogenous leukemia: ESMO Clinical Recommendations for diagnosis, treatment and follow-up*. Annals of Oncology, 2007; 18 (2): ii51 – ii52.

O'Brien S., Berman E., Devetten M.P. et al., *Chronic myelogenous leukemia. NCCN Clinical Practice Guidelines in Oncology. V 2.2009.* National Comprehensive Cancer Network, Inc., 2008: 1 – 47.

Richard R.E., Linenberger M., *Chronic myeloid leukemia.* In: American Society of Hematology Self-Assessment Program. Blackwell Publishing, 2005: 178 – 189.

Xenocostas A., *Chronic myelogenous leukemia (CML). Hematology Practice Guideline.* London Health Sciences Centre. London Regional Cancer Program, 2007: 1 – 10.

REFERENCES FOR POLYCYTHEMIA VERA, IDIOPATHIC MYELOFIBROOSIS:

American Society of Hematology Self-Assessment Program. Blackwell Publishing, 2005.

Corcimaru I., "Hematologie". Chişinău: Centrul Editorial – Poligrafic *Medicina*, 2007.

McMullin M., Bareford D., Campbell P. et al., *Guidelines for diagnosis, investigation and management of polycythemia/erythrocytosis.* British Journal of Haematology, 2005, 130: 174 – 195.

Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media, 2004.

Thiele J., Kvasnicka H., *The 2008 WHO Diagnostic Criteria for Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis.* In: Current Hematologic Malignancy Reports. Current Medicine Group LLC, 2009; 4: 33 – 40.

Wintrobe's Clinical Hematology, 1999, 10 th Edition, vol.1 – 2.