University of Baghdad
College of Medicine
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Title: WBC Disorders – Part 1B

Grade: 4

Module: PATHOLOGY (Hematology)

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WBC Disorders (Part 1B)

Myeloproliferative Neoplasms

Learning Objectives:

1. Identify the main genetic characteristics in MPNs.
2. Define and classify polycythemia.
3. Characterize the main diagnostic features of polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).
4. Describe the laboratory findings in PV, ET, PMF and CML.

Classic Myeloproliferative Neoplasms

Classic MPNs covers a group of clonal disorders of the hematopoietic stem cells that lead to ***effective proliferation*** of one or more hematopoietic component in the BM, and in many cases, in the liver and spleen leading to ***elevated blood levels*** of one or more myeloid cell lineages (i.e. erythrocytosis, leukocytosis, and thrombocytosis).

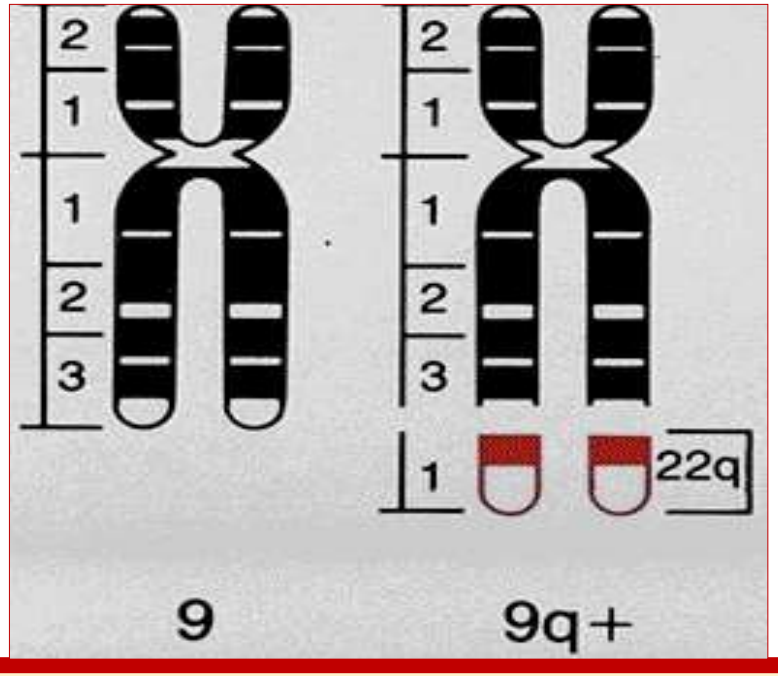
The classic MPNs include:

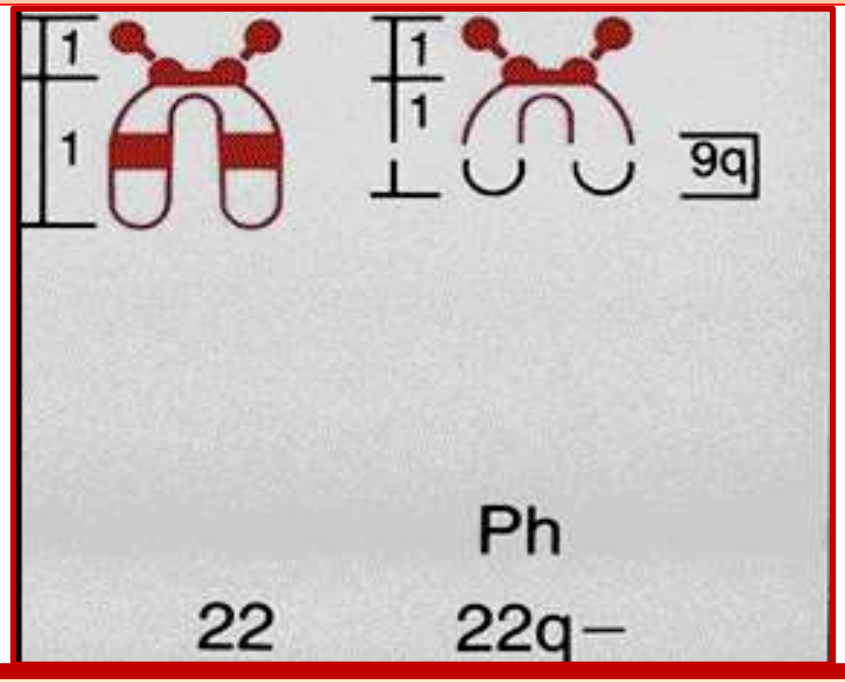
1. **Chronic myeloid leukemia (CML - Ph^{+ve})**
2. **Polycythemia vera (PV)**
3. **Essential thrombocythemia (ET)**
4. **Primary myelofibrosis (PMF)**

These disorders are closely related to each other and transitional forms and evolution from one entity into another occurs during the course of the disease.

Karyotype and Molecular Features

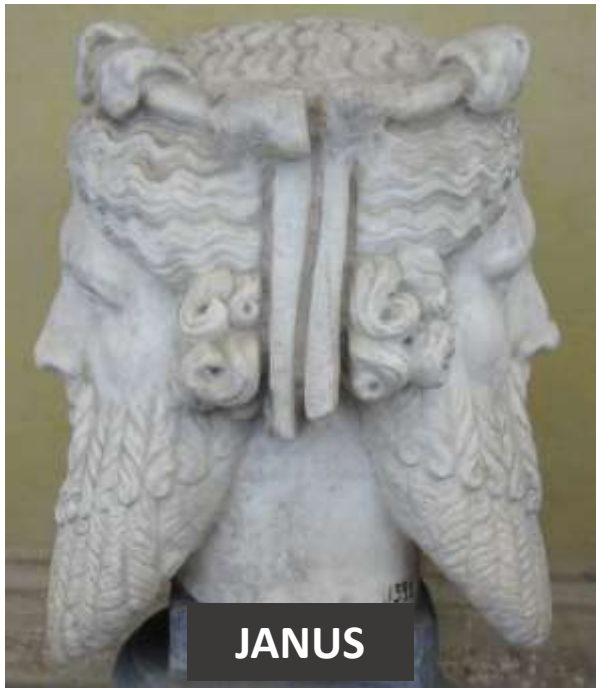
The vast majority of CML show the Philadelphia (Ph^+) chromosome* in (90-95%) and *BCR-ABL* in (99% of patients)





Ph chromosome **is a minute chromosome 22 from which the long arms are deleted (22q-). It is part of reciprocal translocation between chromosome 9 & 22 t(9; 22)(q34; q11) in which part of 22 is clearly visible on 9 but the part of 9 on 22 is too small to be distinguished cytogenetically. It is detected by PCR or FISH techniques**

Janus-Associated Kinase 2 (*JAK2*) Mutation



It occurs in the BM and in the PB granulocytes. It is present in:

- Almost all **PV** patients
- > 50% of **ET** and **PMF** cases

JAK2 gene plays a major role in normal myeloid development.

POLYCYTHEMIA

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What does Polycythemia mean?

Polycythemia is an increase in the hemoglobin (Hb) concentration above the upper limit of normal for the patient's age and gender in a specific population.

What about erythrocytosis (increase in RBC count)?

Classification of Polycythemia according to its pathophysiology

Absolute

Primary: low or normal erythropoietin

1. Polycythemia vera.

Secondary: increased erythropoietin

Caused by compensatory erythropoietin increase in:

1. High altitudes.
2. Pulmonary disease and alveolar hypoventilation (sleep apnoea).
3. Cardiovascular disease, especially congenital with cyanosis.
4. Heavy cigarette smoking.

Caused by inappropriate erythropoietin increase in:

1. Renal diseases (hydronephrosis, vascular impairment, cysts, carcinoma)
2. Tumors (such as uterine leimyoma, renal cell carcinoma, hepatocellular carcinoma).

Relative

Stress or pseudopolycythemia:

1. Cigarette smoking.
2. Dehydration: water deprivation, vomiting.
3. Plasma loss: burns, enteropathy.

POLYCYTHEMIA VERA

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PV is characterized by

generalized hyperplasia of all marrow elements, but

dominated by expansion of the red blood cell mass

What are the diagnostic criteria of PV?

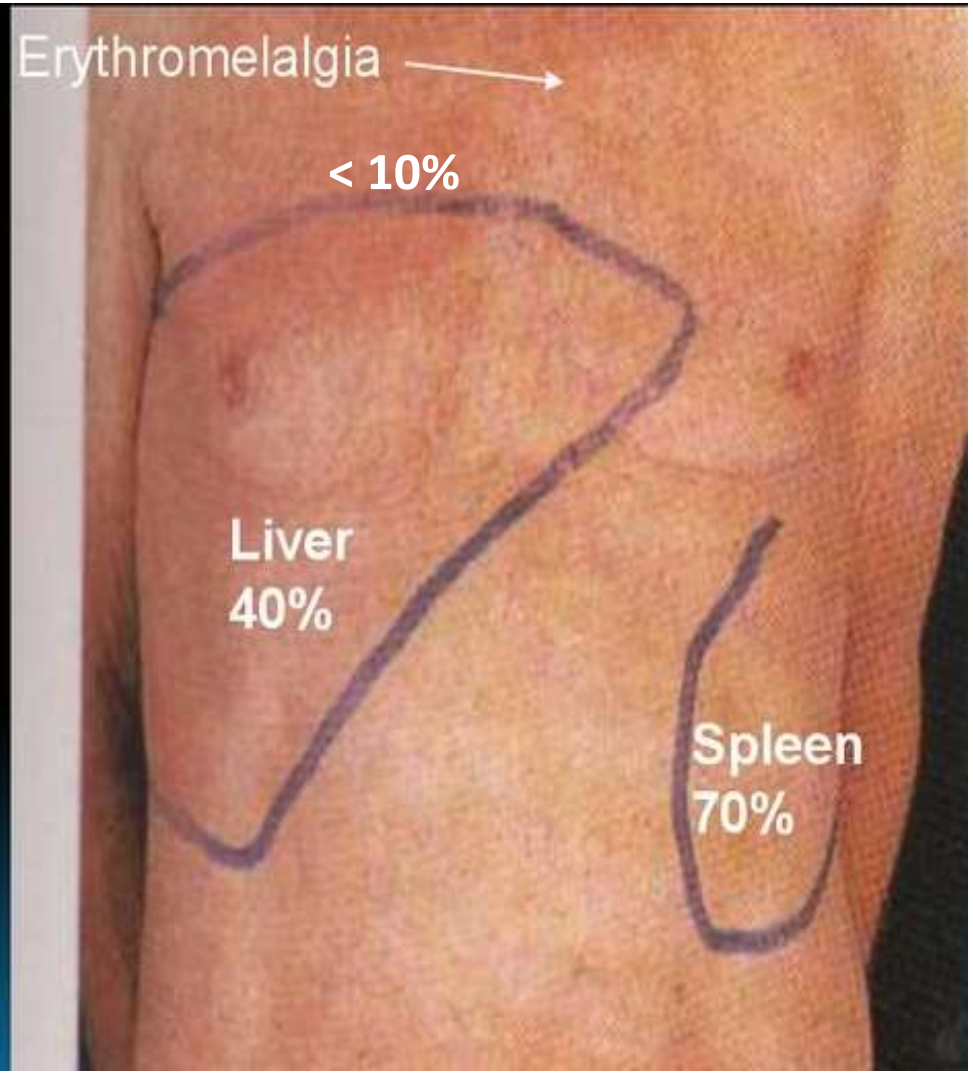
- Sustained **Hb** >18.5 g/dL for men, >16.5 g/dL for women
- Presence of ***JAK2*** mutation
- Subnormal serum **erythropoietin** level

What about neutrophil and platelet counts?

Neutrophilia & thrombocytosis are noted in 50% of cases.

Clinical Features:

- Hepato-splenomegaly
- Erythromelalgia
  - Increased skin temp
  - Burning sensation
  - Redness



What are the major clinical problems?

Thrombosis and hemorrhage.

Hemorrhage results from:

Thrombotic risk increases due to:

Hemorrhage results from:

- Abnormal platelet function.

Thrombotic risk increases due to:

A. The increased PCV leads to:
   - Increased blood viscosity,
   - Rheological abnormalities and
   - Abnormal platelet - endothelial contact.

B. Additionally,
   - Procoagulant changes in platelets (e.g. decreased response to prostaglandin D2),
   - Thrombocytosis and
   - Pre-existing vascular disease

Prognosis:

Is the prognosis good or bad?

Typically, the prognosis is good.

The median survival of 10-16 years.

Are there any evolutions or transitional forms?

Transition from PV to PMF, and AL may occur.

ESSENTIAL THROMBOCYTHEMIA

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ET is characterized by a sustained increase in platelet count, because of *megakaryocytic proliferation and overproduction of platelets*.

What are the diagnostic criteria of ET?

- **Persisting platelet count > 450 × 10^9/L**
- *But other (reactive) causes of raised platelet count need to be fully excluded before the diagnosis can be made*
- Demonstration of *JAK2* **or** other clonal markers

Clinical Features

1. Many cases are ***symptomless***
2. ***Thrombosis*** (venous or arterial).
3. ***Hemorrhage*** .
4. ***Erythromelalgia*** is frequent

Laboratory Findings and Prognosis

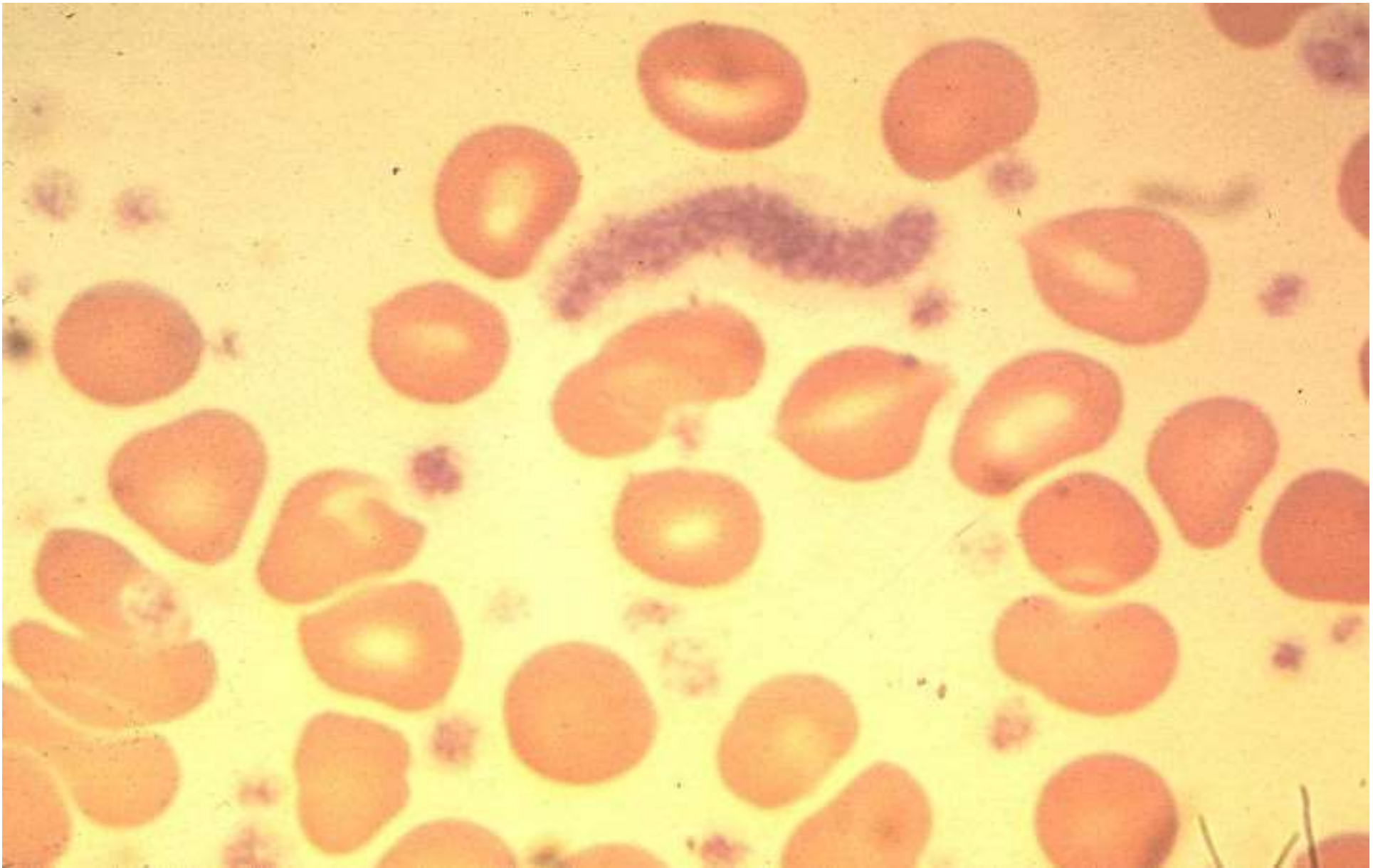
What are the findings in the peripheral blood & BM?

- On blood film abnormal large platelets and megakaryocyte fragments may be seen.
- BM typically shows an excess proliferation of abnormal large and mature megakaryocyte, and no or little granulocyte or erythroid proliferation.

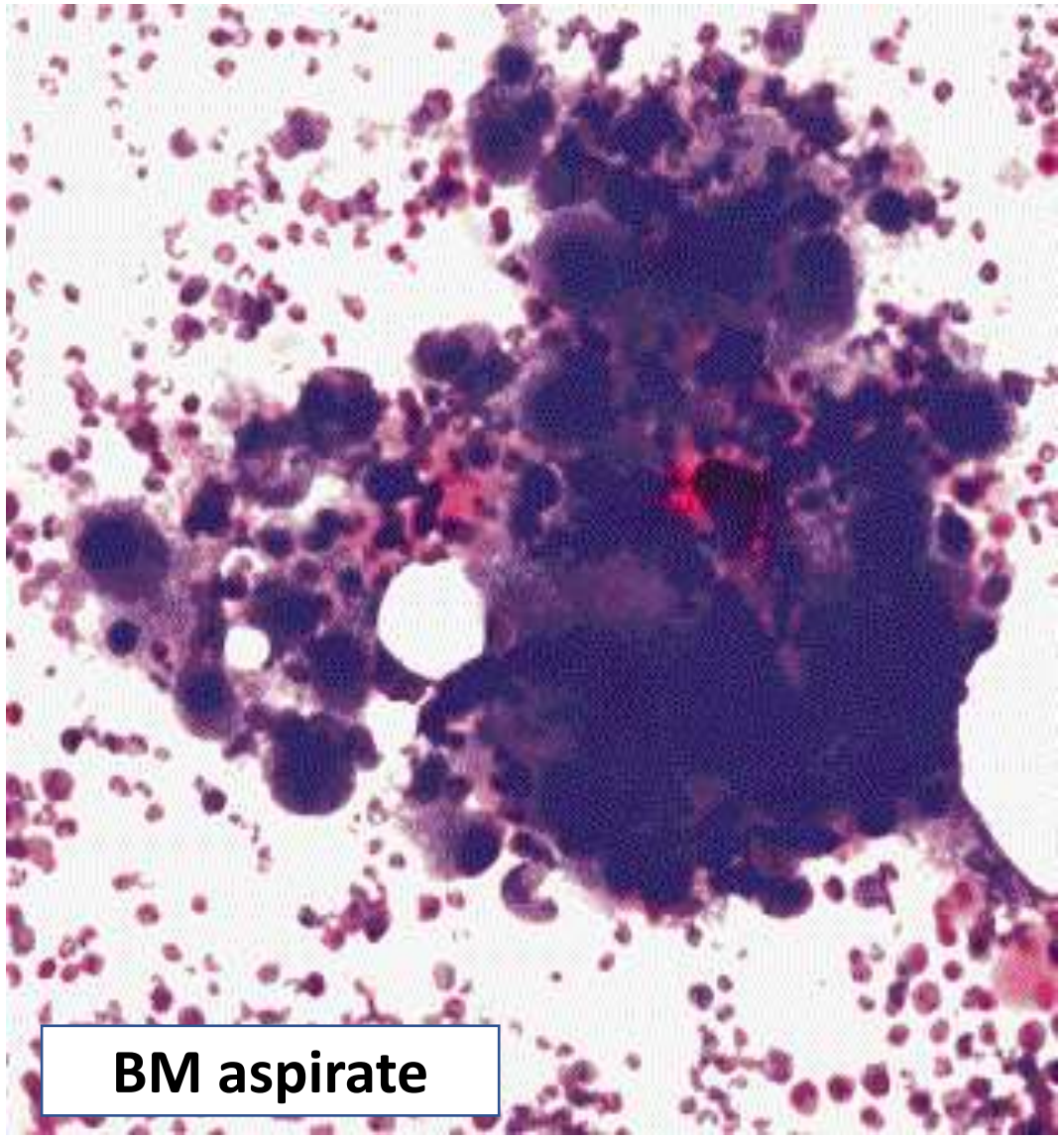
Often the disease is stationary for 10-20 years or more.

ET has a low risk to transform to PMF, AL and PV.

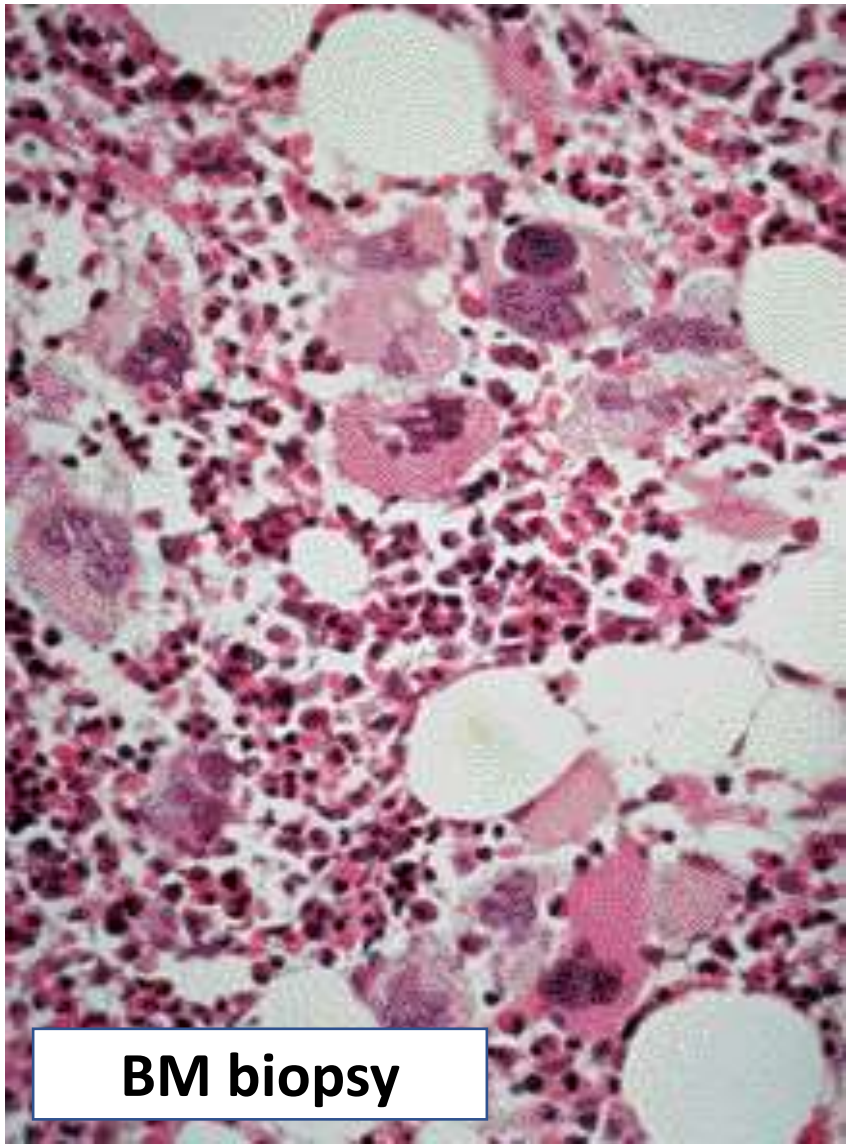
Blood film, ET, showing increased number of platelets with different sizes and morphology.



Bone marrow, ET, typically showing an excess proliferation of abnormal large and mature megakaryocyte, with little granulocyte and erythroid proliferation



BM aspirate



BM biopsy

Primary Myelofibrosis

Synonym: Idiopathic Myelofibrosis (IMF)

PMF is characterized by:

- Proliferation of multiple cell lineages
- *Progressive BM fibrosis*,
- Extramedullary *hematopoiesis in the spleen and liver*.

The onset is insidious with symptoms of anemia.

About ≥ ⅓ of the patients have previous history of PV.

Massive **splenomegaly** is the main physical sign.

Laboratory Findings:

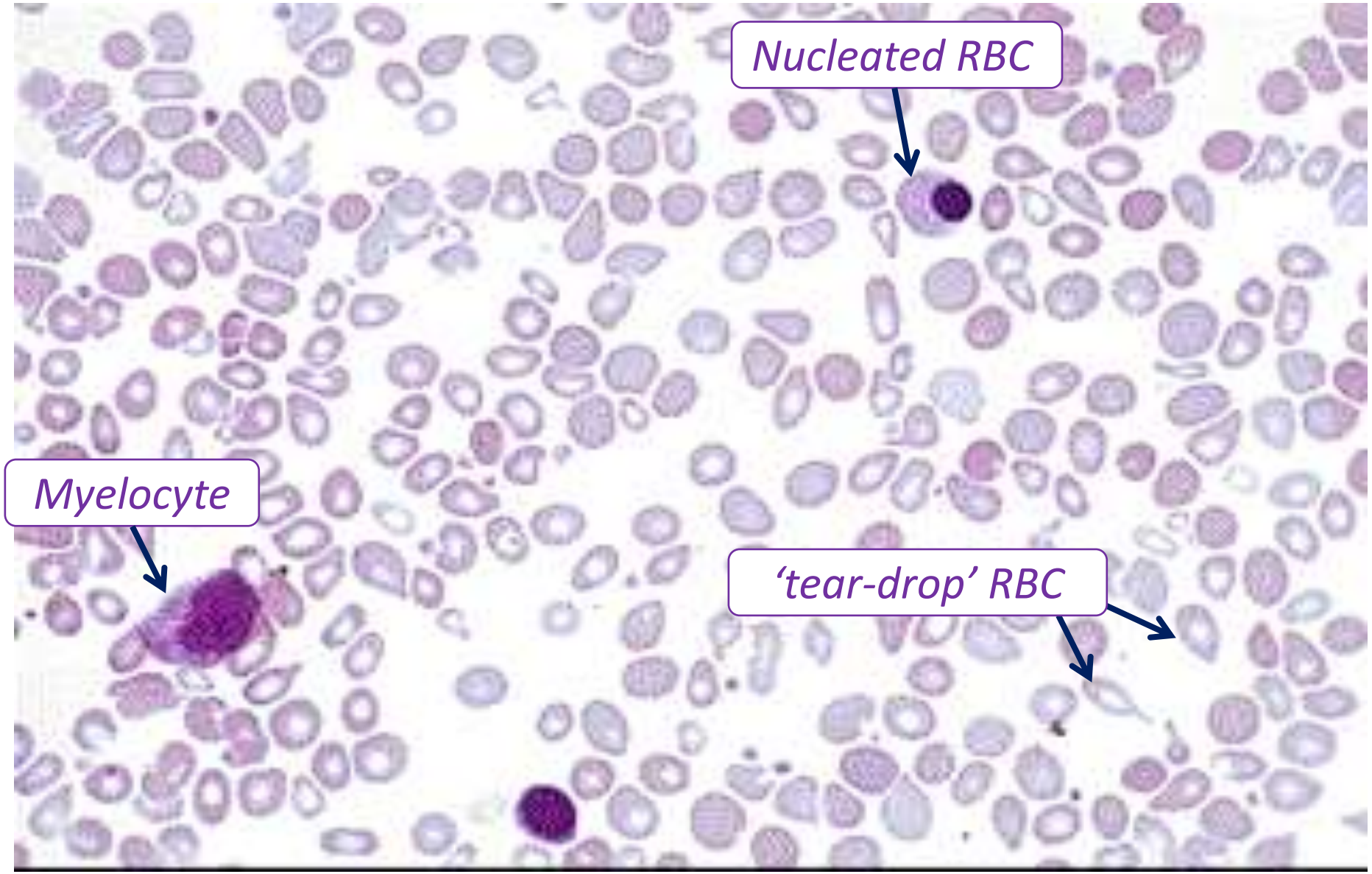
1. **Anemia** is usual.

2. The WBC & platelet counts are frequently **high** at presentation but with advanced disease leukopenia and thrombocytopenia are common.

3. A **leukoerythroblastic blood** film "the co-existence of immature granulocyte - e.g. myelocyte, promyelocyte or blast - and nucleated red cell in the peripheral blood."

4. The red cells show characteristic *'tear-drop'* poikilocytes.

Blood film, PMF, showing excessive tear drop cells with leukoerythroblastic blood picture.



Laboratory Findings:

5. BM is usually unobtainable by *aspiration* (dry tap).

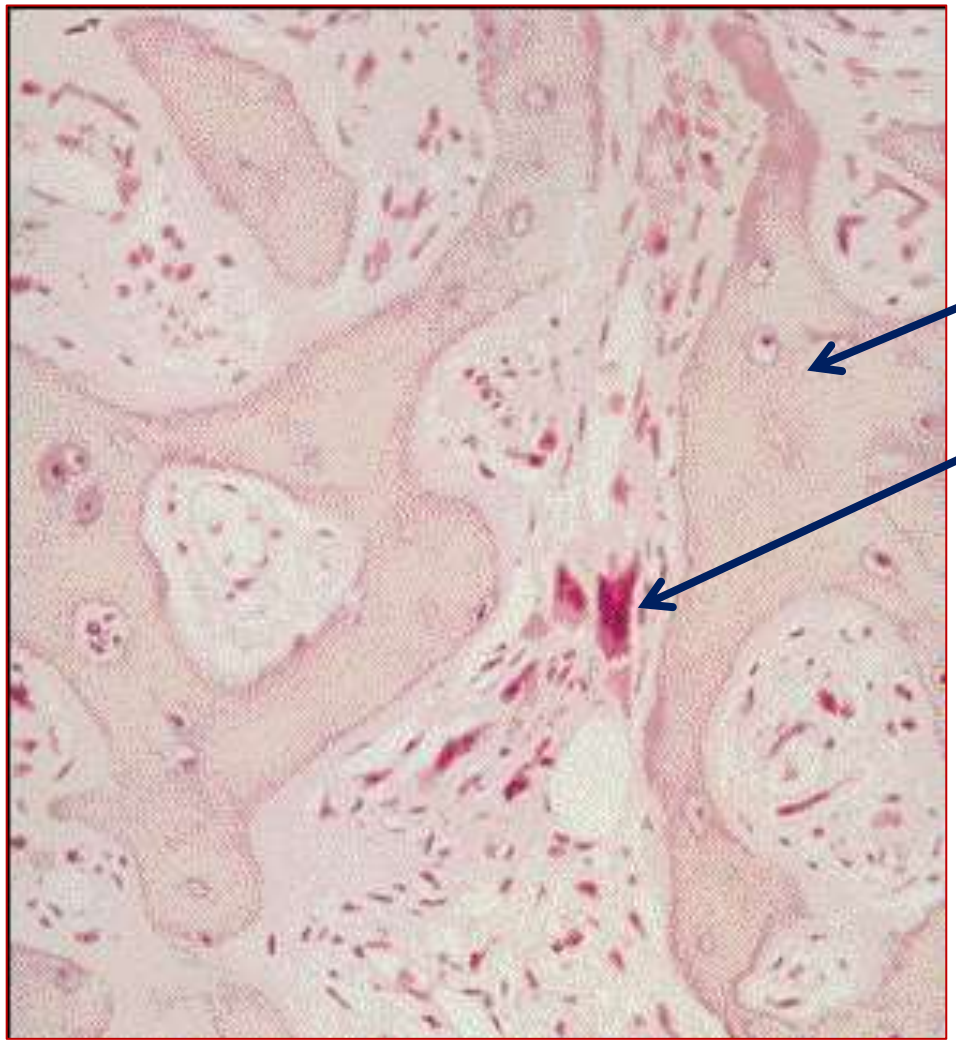
   In trephine BM *biopsy* two phases may be seen:

   - ***Pre-fibrotic phase*** shows *hypercellular marrow*; frequently there is granulocytic proliferation and increased numbers of atypical megakaryocytes with often decreased erythropoiesis.
   - In ***fibrotic phase*** there is *extensive marrow fibrosis*.

6. Demonstration of *JAK2* **or** other clonal markers.

7. Increased serum **LDH**

BM biopsy, PMF in advanced disease, showing replacement of BM by fibrous connective tissue with thick bone trabeculae. There are few megakaryocytes with residual erythroid and granulocytic cells.



Thick bone trabeculae

Megakaryocytes

Prognosis:

Is the prognosis of PMF Good or Bad?

1. It has the poorest prognosis of the MPNs.
2. The median survival is 3-5 years, but the range is very wide (1-15 years).
3. Transformation to AML occurs in 10-20% of cases.

Chronic Myeloid Leukemia

Synonym: *Chronic Granulocytic Leukemia*

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CML is characterized by the proliferation of a population of differentiated cells that gradually replaces normal hematopoiesis and leads to a

greatly expanded total myeloid mass.

CML represents about 15 % of leukemias.

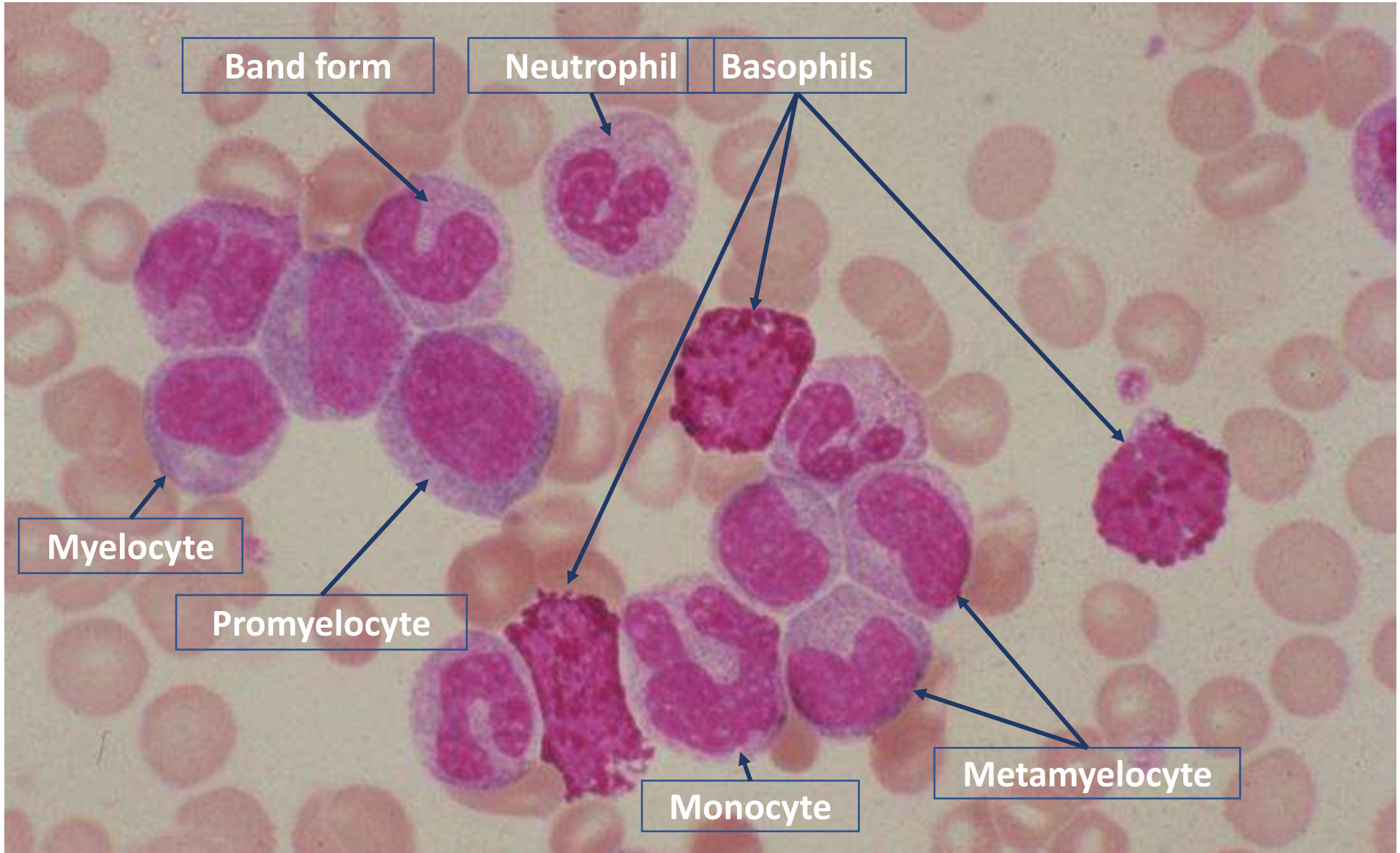
Three phases may be seen during the CML course:

Chronic Phase (CP),
Accelerated Phase (AP), and
Blastic Phase (BP).

Laboratory findings in chronic phase of CML:

1. Anemia; usually normochromic normocytic.
2. Leukocytosis: occasionally patients may present with WBC count >200 $\times 10^9$/L.
3. Blood film shows a full spectrum of granulocytic cells, ranging from blasts (usually <10%) to mature neutrophils, with myelocytes and neutrophils predominating.
4. Eosinophils & basophils are usually increased.
5. Platelet count is usually increased.

Blood Film in CML - CP showing granulocytic cells in various stages of maturation (Promyelocytes, Myelocytes, Metamyelocytes, Band forms, Neutrophils, Basophils and a Monocyte)



6. Bone marrow examination shows:

BM Aspirate:

A. Markedly hypercellular marrow.

B. Blast cells < 10% of ANC.

C. Megakaryocytes are small, hypolobed and increased in numbers.

Clinical findings in the CML-BP

The clinical features are quite variable:

1. Asymptomatic and the diagnosis is based entirely on blood and marrow findings.
2. Occasionally, patients present with generalized lymphadenopathy; **?**

   LN biopsy shows nodal infiltration with blast cells that may be myeloid or lymphoid.
3. Localized skin infiltrates may be seen. Discrete masses of immature leukemia cells may develop at almost any site.

Laboratory findings in CML-BP:

In Blastic Phase:

1. **Blast ≥ 20%** in BF and/or BM, **or**
2. **Extramedullary blast proliferation** (LN, skin, elsewhere)

Philadelphia chromosome is seen in which One of the following Myeloproliferative neoplasms?

A. Polycythemia vera.
B. Essential thrombocythemia.
C. Primary myelofibrosis.
D. Chronic myeloid leukemia.
E. Acute myeloblastic leukemia.

A 60-year-old man presented with pallor, and petechial bleeding for two-month duration. Physical examination revealed a huge splenomegaly with no lymphadenopathy. The blood film showed pancytopenia with tear-drop red cells and leukoerythroblastic blood film. The most likely diagnosis is:

A. Chronic myeloid leukemia.

B. Essential thrombocythemia.

C. Primary myelofibrosis.

D. Polycythemia vera.

E. Acute myeloblastic leukemia.

The laboratory investigations of a 72-year-old woman revealed: Hb 16.7 g/dL, normal platelet and WBC counts, Positive JAK2 mutation with low serum erythropoietin. Physical examination revealed mild splenomegaly with no lymphadenopathy. The most likely diagnosis is:

A. Polycythemia vera.

B. Chronic myeloid leukemia.

C. Essential thrombocythemia.

D. Primary myelofibrosis.

E. Acute myeloblastic leukemia.

Case Scenario

A 53-year-old male:

- Unusually tired for the last 6 months
- Occasional episodes of sweating, especially at night
- Discomfort in his left upper abdomen
- No evidence of weight loss
- Enlarged spleen (4 cm below the left costal margin)
- No lymphadenopathy
- His chest was clinically clear

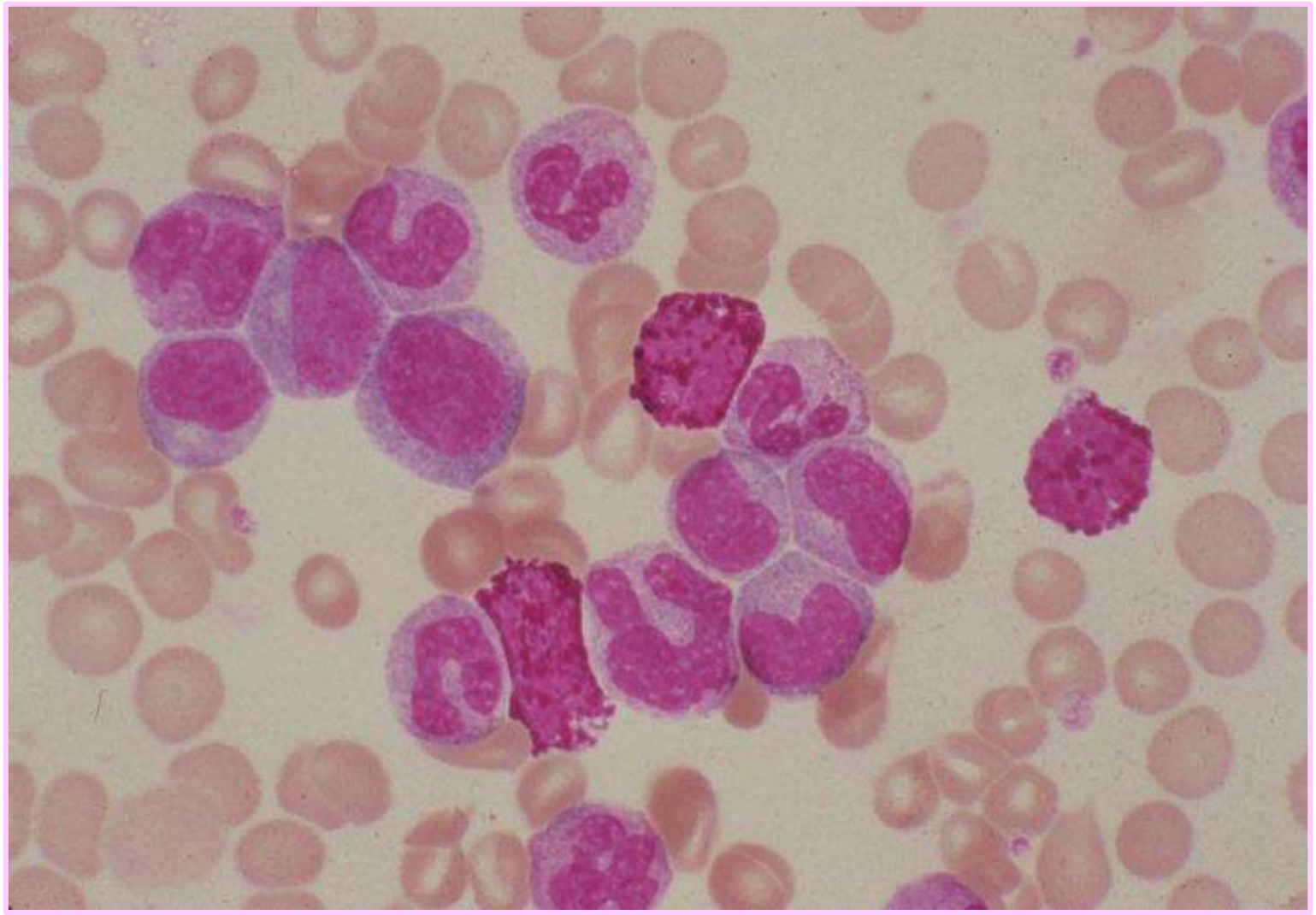
What Laboratory investigations might help to find the cause of the enlarged spleen?

- Full Blood Count.
- Blood Film.

Full Blood Count:

	Patient's Results	Normal Range
Hb	14.5 g/dL	13 – 17 g/dL
WBC	55 × 10^9/L	4 – 11 × 10^9/L
Platelets	600 × 10^9/L	150–410 × 10^9/L

Blood film showing white cell precursors: ●Metamyelocytes. ●Myelocytes. ●Promyelocytes.



What is the possible diagnosis?

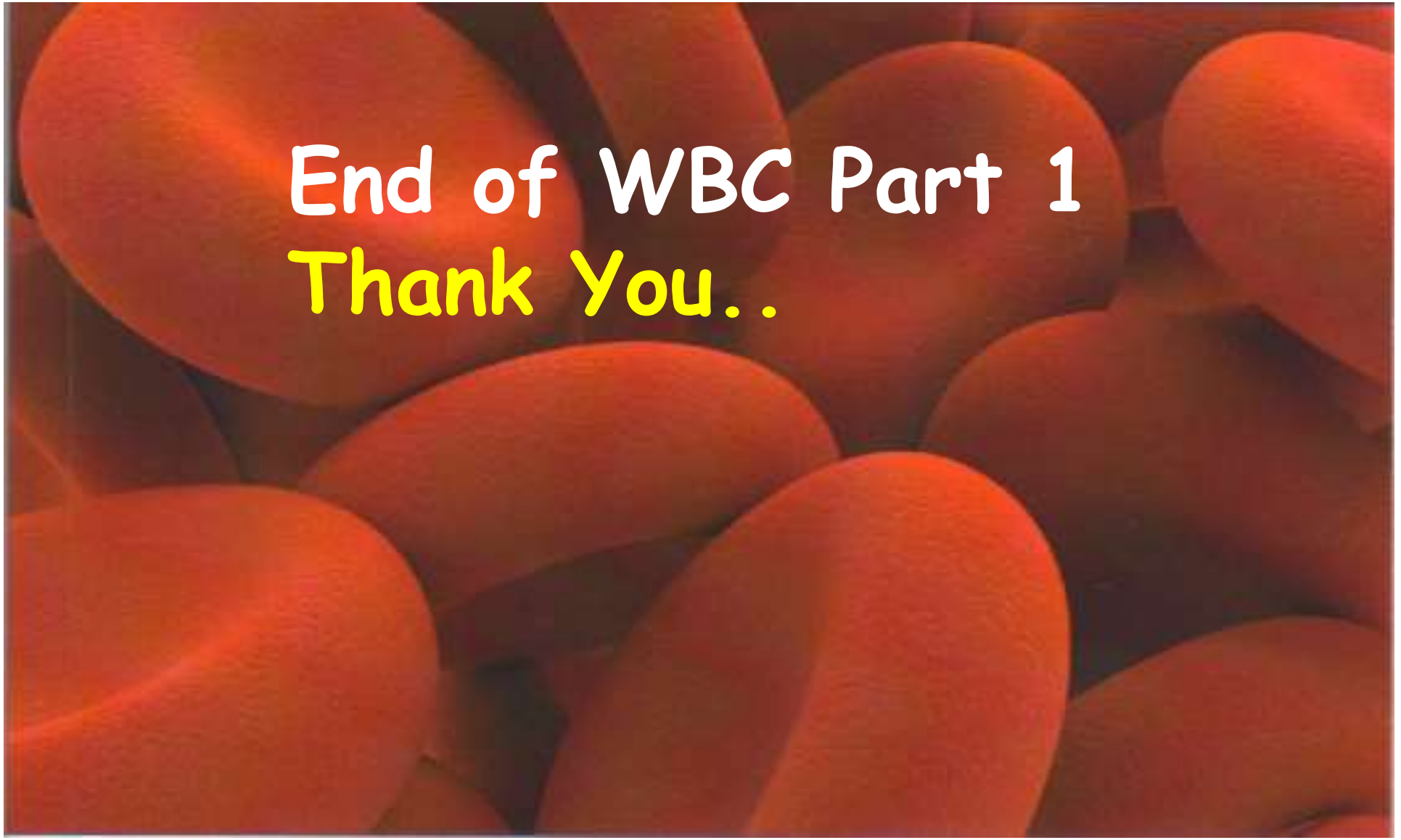
What other confirmatory investigations would the hematologist request?

A BM aspirate sample should be sent to the Genetics Department for:

- **Karyotypic (Cytogenetic) analysis t(9; 22)**
- **Fluorescence In Situ Hybridization (FISH) for *BCR/ABL1* fusion gene.**
- **Polymerase chain reaction (PCR).**

Thank you for listening

Any questions?


End of WBC Part 1
Thank You..