MYELOPROLIFERATIVE DISEASES

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Learning objectives

- Define MPD.
- Know types of MPD.
- Understand common presentation.
- Evaluation of these MPD.
- Management of MPD.

myeloproliferative diseases

- **Introduction:**
- Myeloproliferative disorders is the name for a group of conditions that cause blood cells -- platelets, white blood cells, and red blood cells -- to grow abnormally in the bone marrow.
- Though myeloproliferative disorders are serious, and may pose certain health risks, people with these conditions often live for many years after diagnosis.
- The prognosis largely depends on the type of disorder.
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myeloproliferative diseases

- The **myeloproliferative diseases** (**MPDs**, myeloproliferative neoplasms, MPNs)

➢ are a group of diseases of the bone marrow in which excess cells are produced.

➢ They are related to, and may evolve into, myelodysplastic syndrome and acute myeloid leukemia

myeloproliferative diseases

- **CLASSIFICATION:**
- **Although not a malignant neoplasm like other cancers, MPDs are classified within the hematological neoplasms.**
- **There are four main myeloproliferative diseases, which can be further categorized by the presence of the Philadelphia chromosome**

MPDs- CLASSIFICATION:

1. **Philadelphia Chromosome "positive"**
- Chronic myelogenous leukemia (CML)

2. Philadelphia Chromosome "negative"
- Polycythemia vera (PV)
- Essential thrombocytosis (ET)
- Myelofibrosis (MF)
- In 2001, the World Health Organization classified "chronic eosinophilic leukemia / hypereosinophilic syndrome" and
- chronic neutrophilic leukemia under "Chronic myeloproliferative diseases

MPDs

- All MPDs arise from precursors of the myeloid lineage in the bone marrow.
- The lymphoid lineage may produce similar diseases, the lymphoproliferative disorders (acute lymphoblastic leukemia, lymphomas,
- chronic lymphocytic leukemia and
- multiple myeloma).

Pathophysiology

- Data from G-6-PD studies, cytogenetic analyses, and molecular methods have established the clonal origin of myeloproliferative diseases;
- this clonality potentially occurs at different stem cell levels.
- An attribute common to these disorders appears to be **an acquired activating mutation in the gene coding for various tyrosine kinases**

Pathophysiology—cont--

- In chronic myelogenous leukemia, the tyrosine kinase activity of the *bcr-abl* hybrid gene is increased.
- In **polycythemia vera**, **essential thrombocythemia**, and **myelofibrosis** , the prevalent genetic lesion appears to be a **valine to phenylalanine substitution** at amino acid position 617 (V617F) within the Janus kinase 2 (*JAK2*) gene.

➢ This produces hypersensitivity to erythropoietin.

- At least in myelofibrosis patients the leukemic transformation is probably not related to JAK-2 (V617F) mutation status

MPDs- Diagnosis

- Depending on the nature of the myeloproliferative disorder, diagnostic tests may include;

- red cell mass determination (for polycythemia),
- bone marrow aspirate and trephine biopsy,
- arterial oxygen saturation and
- neutrophil alkaline phosphatase level,
- vitamin B12 (or B12 binding capacity) and
- serum urate

MPDs- Diagnosis

- According to the WHO Classification of Hematopoietic and Lymphoid Neoplasms 2008 myeloproliferative disorders are divided into the following by diagnostic characteristics

1. Chronic myelogenous leukemia (CML)

- Chronic myelogenous leukemia (CML) -- cancer of the bone marrow that **produces abnormal granulocytes**, a type of white blood cell, in the bone marrow.
- with defining translocation t(9;22) BCR-ABL translocation which has three breakpoints:
- a. u-BCR-ABL (p230): leads to CML with usual neutrophilia and basophilia
- b. minor-BCR-ABL (p190): leads to CML which has a tendency to become acute lymphoblastic leukemia (ALL) usually precursor B ALL and rarely precursor T ALL
- c. major-BCR-ABL (p210): normal usual breakpoint

2. Polycythemia vera

- Occurs when the bone marrow **produces too many blood cells, especially red blood cells.**
- More than 95% of people with polycythemia vera carry the blood associated most often with JAK2 mutation in up to 80% of cases:

➢ a. **Cellular phase** - increased megakaryocytes which cluster, reticulin fibrosis, later trichrome fibrosis, and increased myeloid and erythroid precursors
b. **Fibrotic phase** - collagenous fibrosis with lack of marrow elements

3. Primary myelofibrosis

- Primary or idiopathic myelofibrosis, also known as myelosclerosis –
- occurs when the bone marrow **produces too much collagen or fibrous tissue** in the bone marrow.
- This reduces bone marrow's ability to produce blood cells.
- associated with JAK2 mutation in up to 50% of cases and MPL (thrombopoietin receptor) mutation in up to 5% of cases:

➢ a. **Cellular phase** - increased megakaryocytes which cluster, reticulin fibrosis, later trichrome (collagenous) fibrosis, and increased myeloid precursors

➢ b. **Fibrotic phase** - collagenous fibrosis with lack of marrow elements

4. Essential thrombocythemia

- Occurs when the body **produces too many platelet cells,** which help blood to clot.
- Clots can block blood vessels leading to heart attack or stroke.
- associated with JAK2 mutation in up to 20% of cases and MPL (thrombopoietin receptor) mutation in up to 15% of cases:
- a. **Cellular phase** - increased large megakaryocytes with fibrosis and little increase in other bone marrow elements

- b. **Fibrotic phase** - collagenous fibrosis with lack of marrow elements

MPDs-CAUSES

- All myeloproliferative disorders are caused by **overproduction of one or more types of cells**.
- No one knows what triggers the overproduction of cells, but theories include:
- **Genetics** -- Some people with CML have an abnormally shortened chromosome known as the **Philadelphia chromosome.**
- **Environment** -- Some studies suggest that myeloproliferative disorders may result from an **overexposure to radiation, electrical wiring, or chemicals**

MPDs--- Risk Factors:

- **Risk Factors:**
- These factors may increase your risk for developing a myeloproliferative disorder:
- **Polycythemia vera**
- **Gender** -- Men are 2 times more likely than women to develop the condition.
- **Age** -- People older than 60 are most likely to develop the condition, though it may happen at any age.
- **Environment** -- Exposure to intense radiation may increase the risk for the condition.

MPDs--- Risk Factors:

- **Essential thrombocytosis**
- **Gender** -- Women are 1.5 times more likely than men to develop the condition.
- **Age** -- People older than 60 are most likely to develop the condition, though 20% of those with this condition are under 40.
- **Environment** -- Some researchers suggest that exposure to chemicals or to electrical wiring may increase a person's risk for the condition
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MPDs--- Risk Factors:

- **Chronic myelogenous leukemia (CML)**
- **Gender** -- Men are more likely than women to develop the condition.
- **Age** -- People ages 45 - 50 are the most likely to develop the condition.
- **Environment** -- Exposure to intense radiation may increase the risk of developing the condition
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MPDs--- Risk Factors:

- **Primary myelofibrosis**
- **Gender** -- Men are slightly more likely than women to develop the condition.
- **Age** -- People ages 60 - 70 are most likely to develop the condition.
- **Environment** -- Exposure to petrochemicals, such as benzene and toluene, and intense radiation may increase the risk of developing the condition.
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Signs and Symptoms:

- Many people with myeloproliferative disorders have **no symptoms** when their doctors first make the diagnosis.
- One symptom shared by all myeloproliferative disorders, **with the exception of essential thrombocytosis**, is **an enlarged spleen**.
  - An enlarged spleen can cause abdominal pain and a feeling of fullness

Signs and Symptoms:

- Some signs and symptoms of the different types of myeloproliferative disorders include:

Chronic myelogenous leukemia (CML)

- Fatigue, general malaise
- Weight loss or loss of appetite
- Fever and night sweats
- Bone or joint pain
- Heart attack or stroke
- Dyspnoea
- Gastrointestinal bleeding
- Infection
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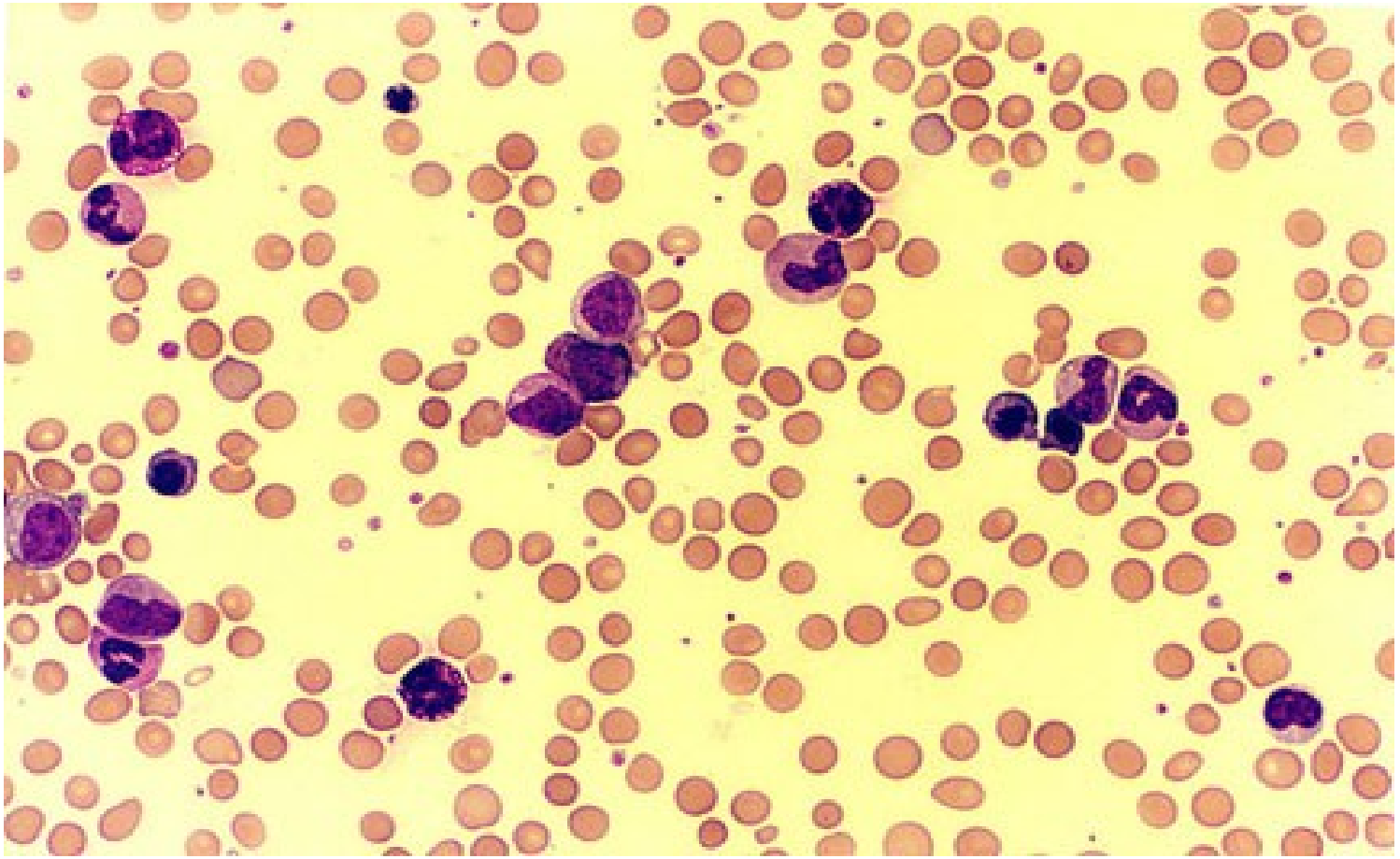
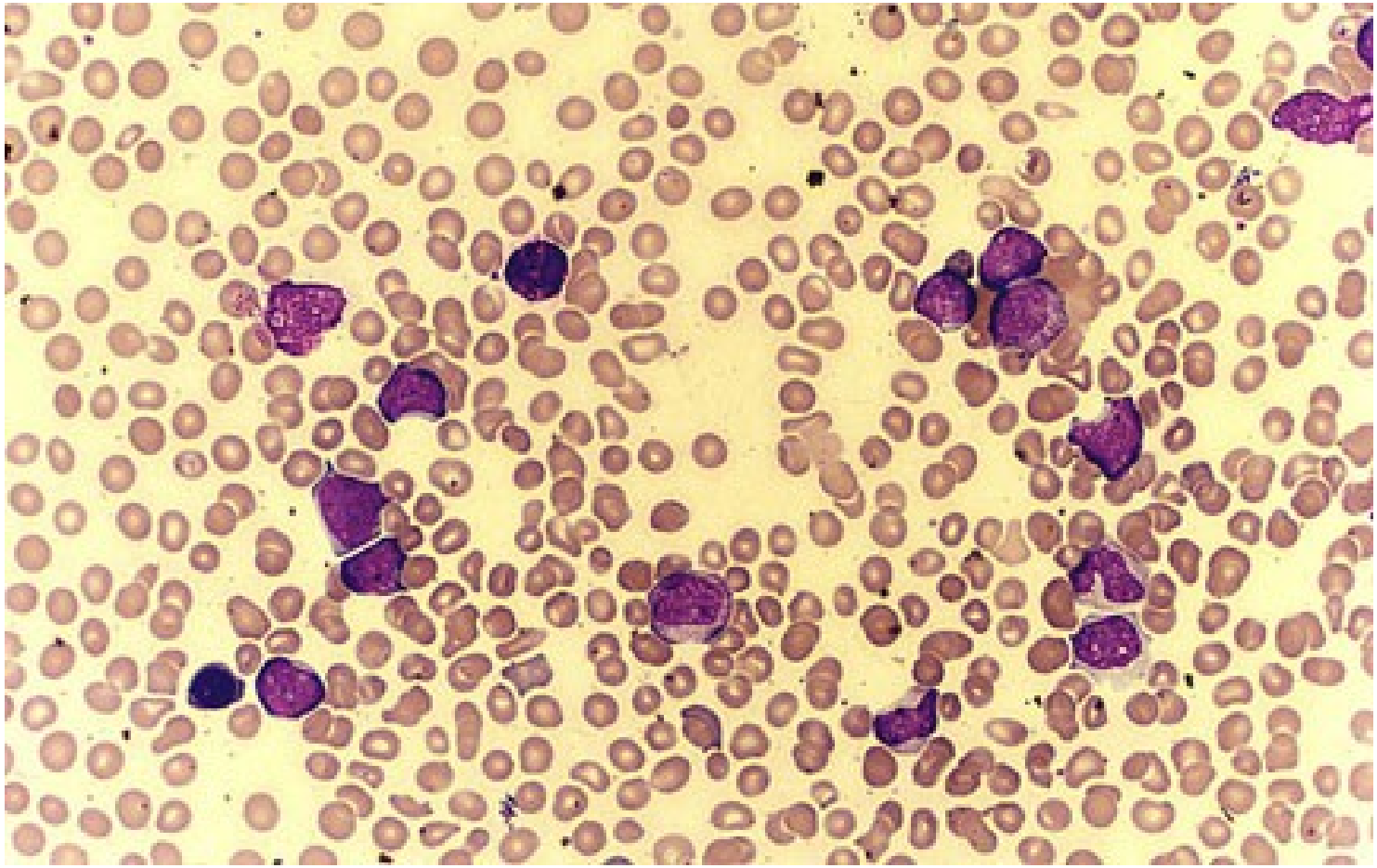
Peripheral smear of a patient with chronic myelogenous leukemia (CML) shows leukocytosis with extreme left shift and basophilia



Peripheral smear of a patient with chronic myelogenous leukemia (CML) in blastic phase shows several blasts.



Signs and Symptoms:

- Some signs and symptoms of the different types of myeloproliferative disorders include:

- **Polycythemia vera**
- Fatigue, general malaise
- Dyspnoea
- **Intense itching after bathing in warm water**
- Abdominal pain
- Purple spots or patches on the skin
- Nosebleeds, gum or stomach bleeding, or blood in the urine
- Throbbing and burning pain in the skin, often with darkened, blotchy areas
- Headache and problems with vision
- **High blood pressure**
- **Blockage of blood vessels.** (Infarctions)

- This may cause heart disease, stroke, or gangrene of the arms and legs.

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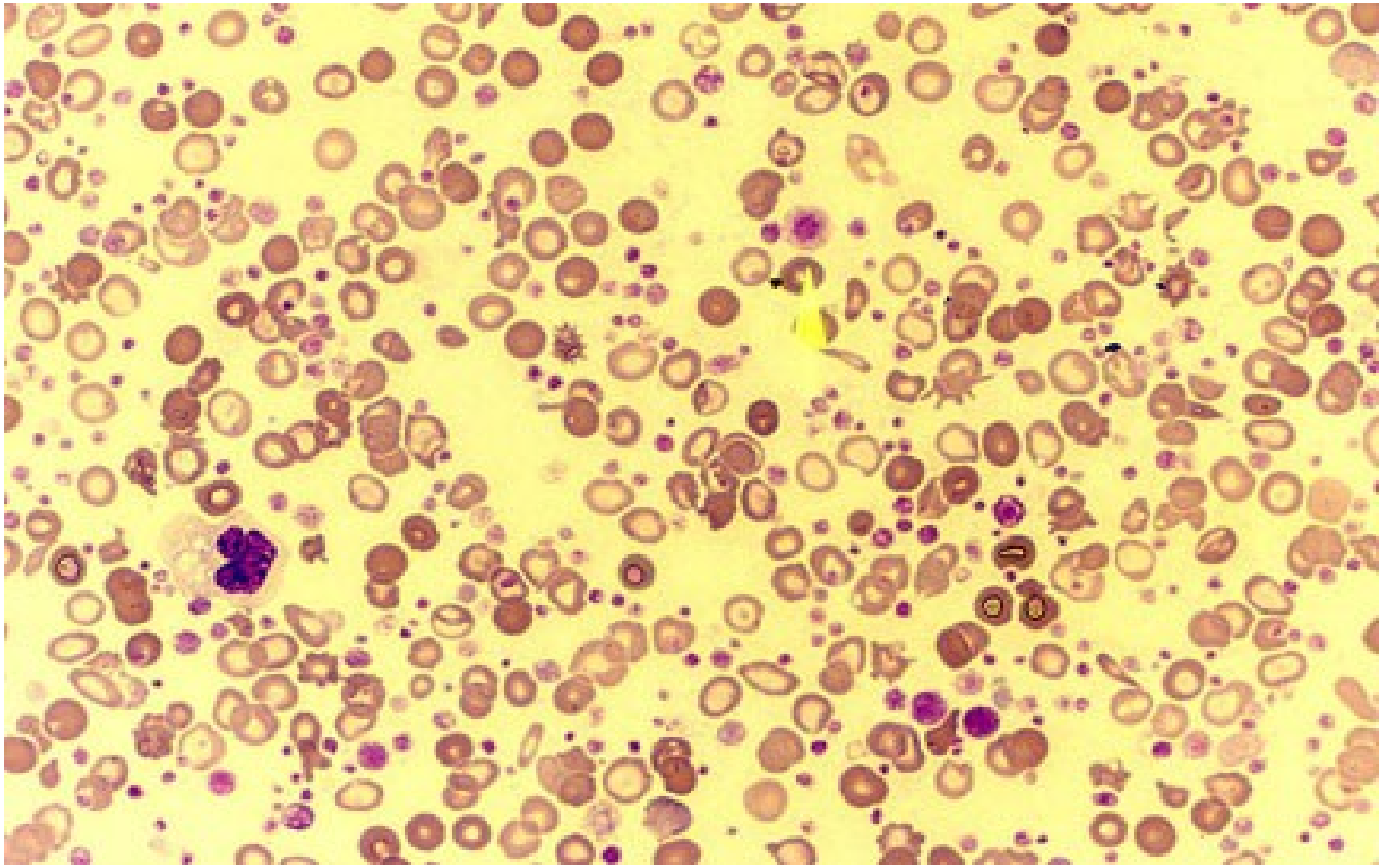
Signs and Symptoms:

- **Essential thrombocytosis**
- Heart attack (myocardial infarction) or stroke
- Headache
- Burning or throbbing pain, redness, and swelling of the hands and feet
- Bruising
- Gastrointestinal bleeding or
- blood in the urine

Peripheral smear of a patient with essential thrombocythemia (ET) shows markedly increased number of platelets. Some of the platelets are giant

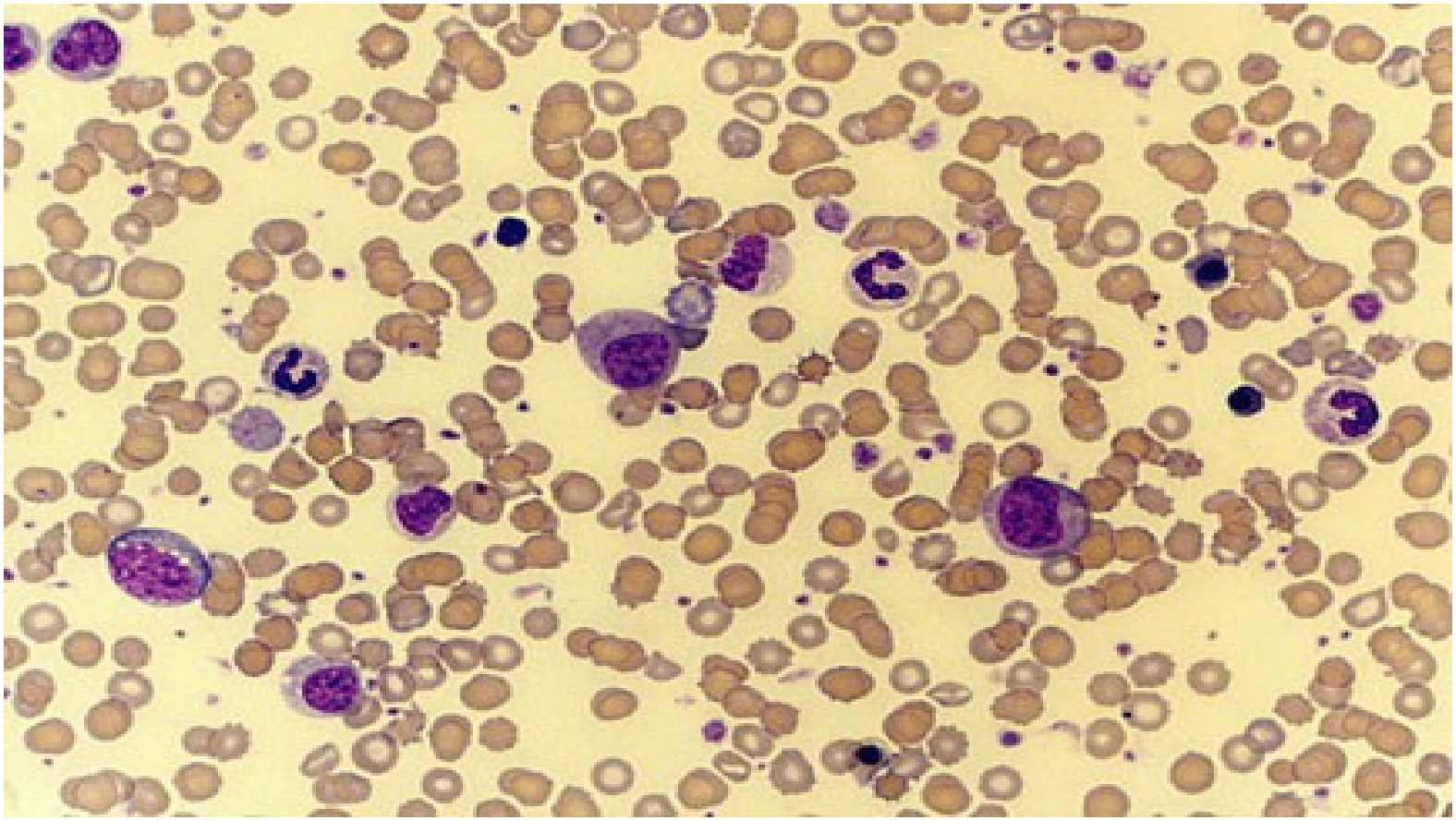


Signs and Symptoms:

- **Primary myelofibrosis**
- Fatigue, general malaise
- Dyspnoea
- Anemia
- Weight loss
- Fever and night sweats
- Abnormal bleeding

Peripheral smear of a patient with agnogenic myeloid metaplasia (myelofibrosis) shows leukoerythroblastosis.

This photomicrograph also shows giant platelets.



Diagnosis

- A sign shared by all myeloproliferative disorders, with the exception of essential thrombocytosis, is an enlarged spleen.
- In addition to doing a physical exam, the doctor may also conduct the following tests:
- **Blood tests** -- to find abnormal types or numbers of red or white blood cells. They can also detect anemia and leukemia.
- **Bone marrow biopsy** -- sample of bone marrow may be taken after blood tests. It can show the presence of abnormal types or numbers of red or white blood cells and may detect certain types of anemia and cancer in the marrow.
- **Cytogenetic analysis** -- views blood or bone marrow are viewed under a microscope to look for changes in the chromosomes.

Treatment:

- **There is no cure for most myeloproliferative disorders**.
- There are, however, several treatments that help improve symptoms and prevent complications associated with the conditions.
- The treatment for each type of myeloproliferative disorder is slightly different:
- **Polycythemia vera** –
- lower red blood cell count by removing blood, called **phlebotomy**.
- Treatment with medication, called **myelosuppressive therapy**, is also available.

Treatment: -- cont--

- **Essential thrombocytosis** –
  - treat symptoms, when present, with medications
- **Primary myelofibrosis** –
  - treat symptoms, when present, with medications and blood transfusion
- **CML –** Treatment options for CML have expanded greatly and may include:
  - targeted therapy,
  - chemotherapy, biologic therapy,
  - high-dose chemotherapy with stem cell transplant,
  - donor lymphocyte infusion (DLI),
  - surgery

Photomicrograph of a peripheral smear of a patient with agnogenic myeloid metaplasia (myelofibrosis) shows findings of

leukoerythroblastosis, giant platelets, and few teardrop cells