Haematology

Hematology

Benign & Malignant Leukocyte Disorders

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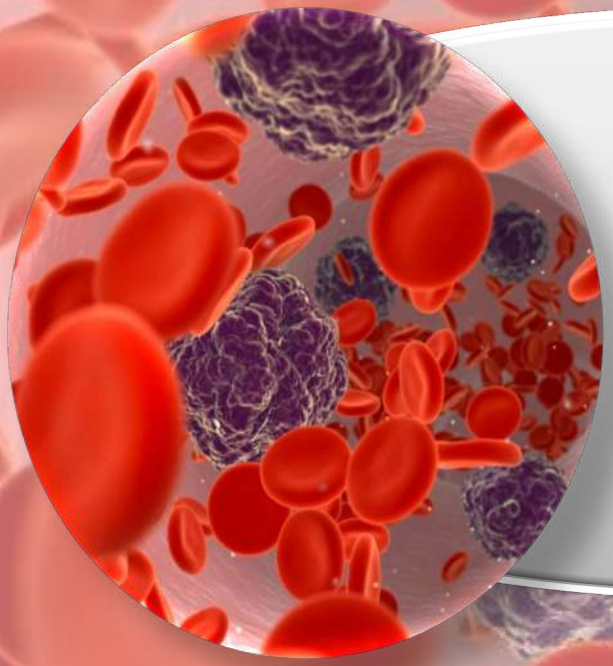


CHRONIC LEUKEMIAS

Objectives

1. Hemopoiesis.
2. Anemia, Types and Related Disorders.
3. Granulopoiesis and White Blood Cell Disorders.
4. **Hematological Malignancies.**
5. Hemostasis.
6. Transfusion Medicine.

Objectives

1. Chronic Lymphoid Leukemia (CLL).

2. Chronic Myeloid Leukemia (CML).

3. Others rare; Chronic Eosinophilic Leukemia (CEL) and Chronic Neutrophilic Leukemia (CNL).

LYMPHOPROLIFERATIVE DISORDERS

Group of disorders characterized by a chronic persistent lymphocytosis. Subtypes are distinguished by:

1. Morphology.

2. Immunophenotype.

3. Cytogenetics

4. DNA analysis.

CHRONIC LYMPHOID LEUKEMIA

Group of;

- Clonal malignant disorders
- Characterized by accumulation of mature lymphocytes, whether B- or T-cells in the blood
- Chronic persistent (>3 months)
- Lymphocytosis (>5 × 10^9/L)

WHO classification of Chronic Lymphoid Leukemia

B-cell	T-cell
1. Chronic lymphocytic leukemia (CLL)	1. Large granular lymphocytic leukemia
2. Prolymphocytic leukemia (PLL)	2. T-cell prolymphocytic leukemia (T-PLL)
3. Hairy cell leukemia (HCL)	3. Adult T-cell leukemia/lymphoma
3. Plasma cell leukemia	4. Sézary syndrome

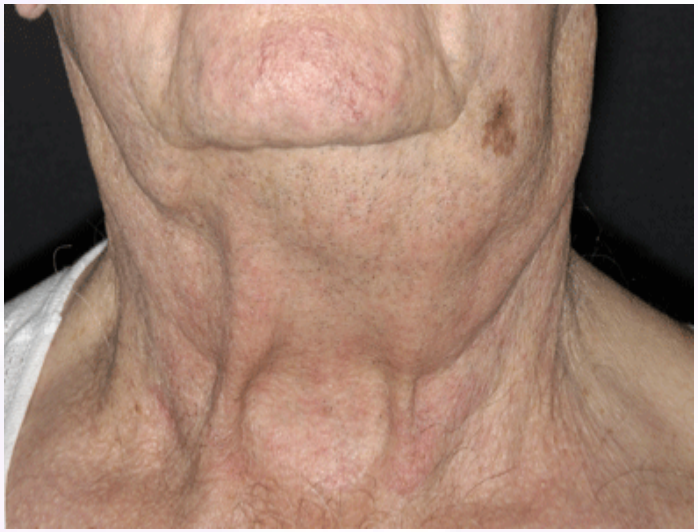
CHRONIC LYMPHOCYTIC LEUKEMIAS

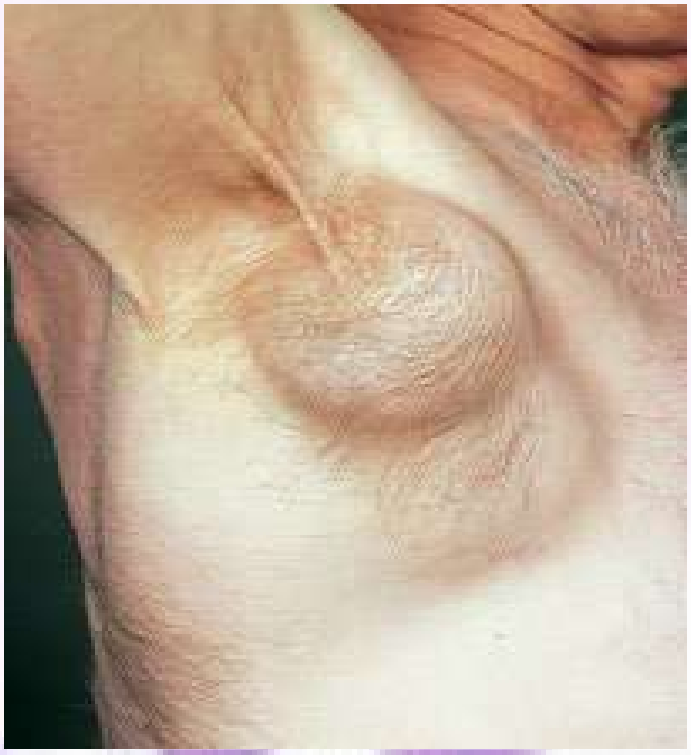
Chronic lymphocytic leukemia (CLL) of B-cell type

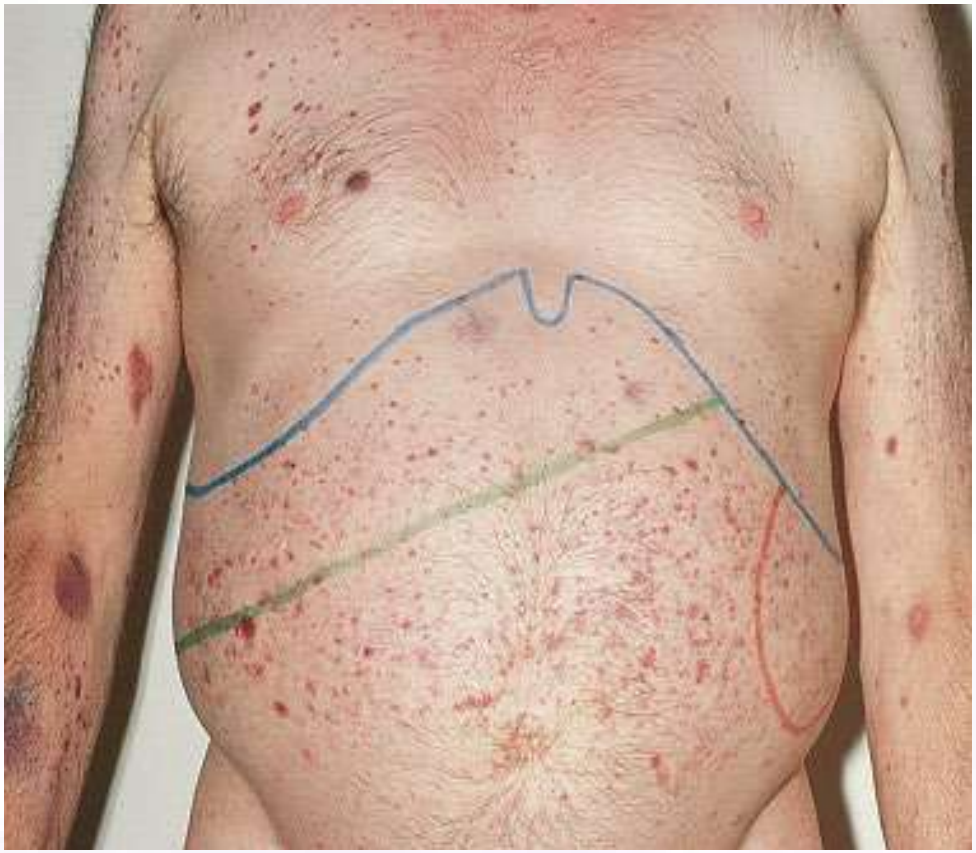
- Most common form of the chronic lymphoid leukemias
- Disease of old age group.
- The cell appears to a relatively mature B cell with weak surface expression of immunoglobulin (IgM or IgD).
- The cells accumulate in the blood, bone marrow, liver, spleen and lymph nodes as a result of increased production and prolonged lifespan with impaired apoptosis
- Must be of a monoclonal B-cell count of $>5 \times 10^9/L$ or tissue involvement outside the bone marrow.

❖Clinical Features:

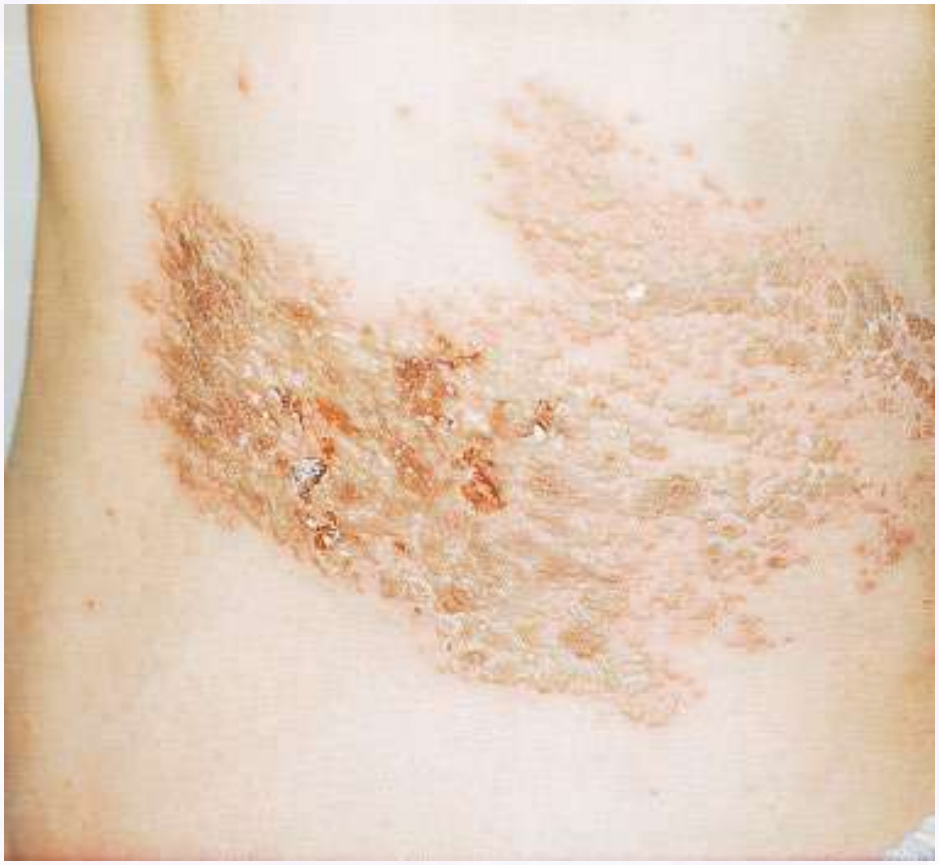
- Mostly above age of 50 years (60-80) and more in males
- Usually asymptomatic and discovered incidentally (routine bd examination).
- Vague illness; weakness, weight loss, chills, fever and night sweats
- Lymphadenopathy; usually discrete and non-tender and tonsillar enlargement may be a feature.
- Features of anemia or thrombocytopenia due to BM suppression or autoimmune.
- Hepatosplenomegaly; features of abdominal discomfort.
- Hypogammaglobulinemia (immunosuppression); bacterial, viral and even fungal infections may be a feature.

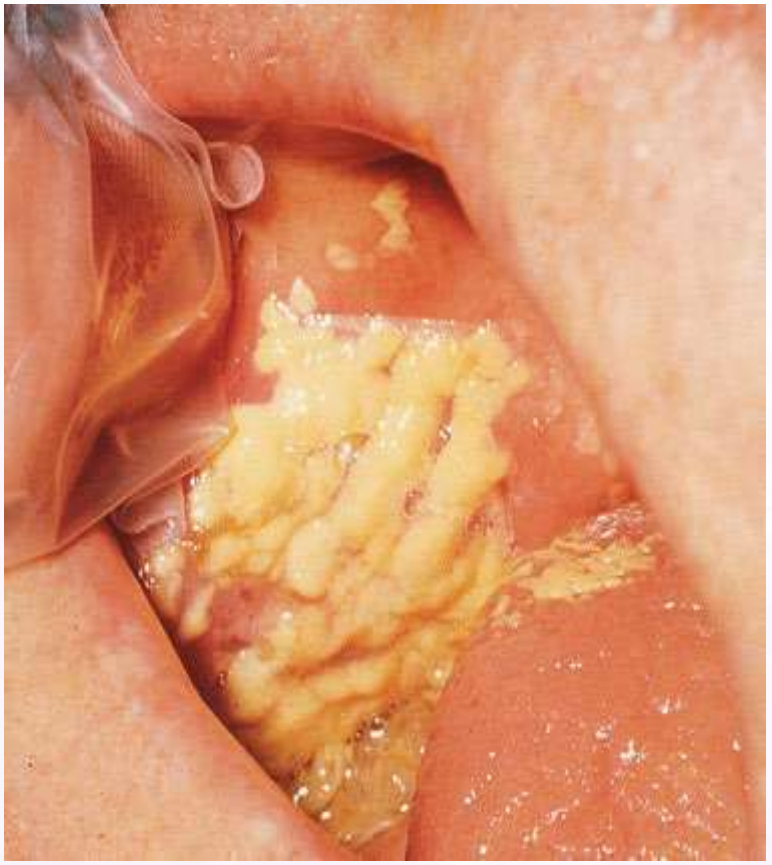






CLL; cervical and bilateral LAP and hepatosplenomegaly

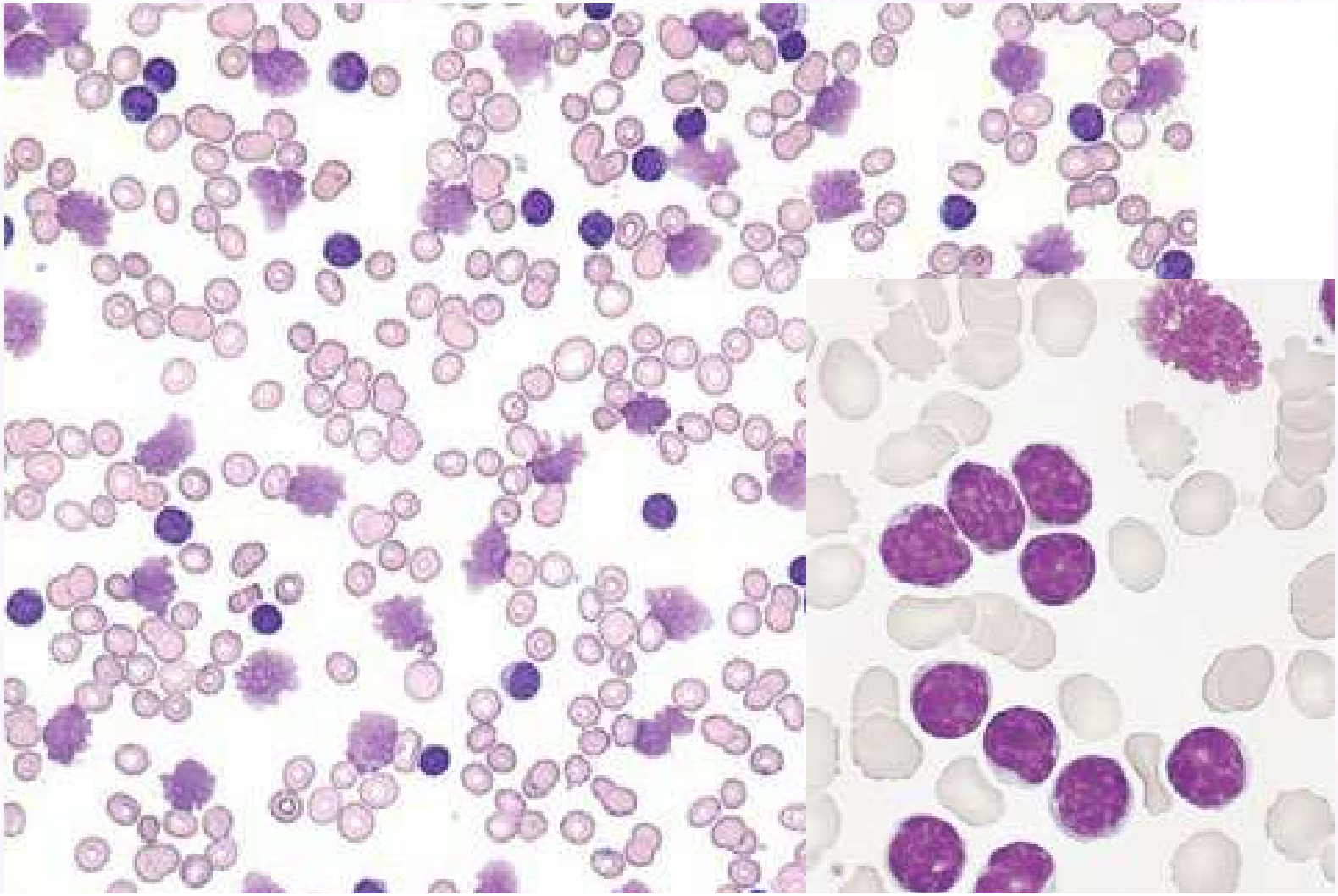




CLL; left; viral infection (herpes zoster) and right; buccal mucosa fungal infection (*candida albicans*)

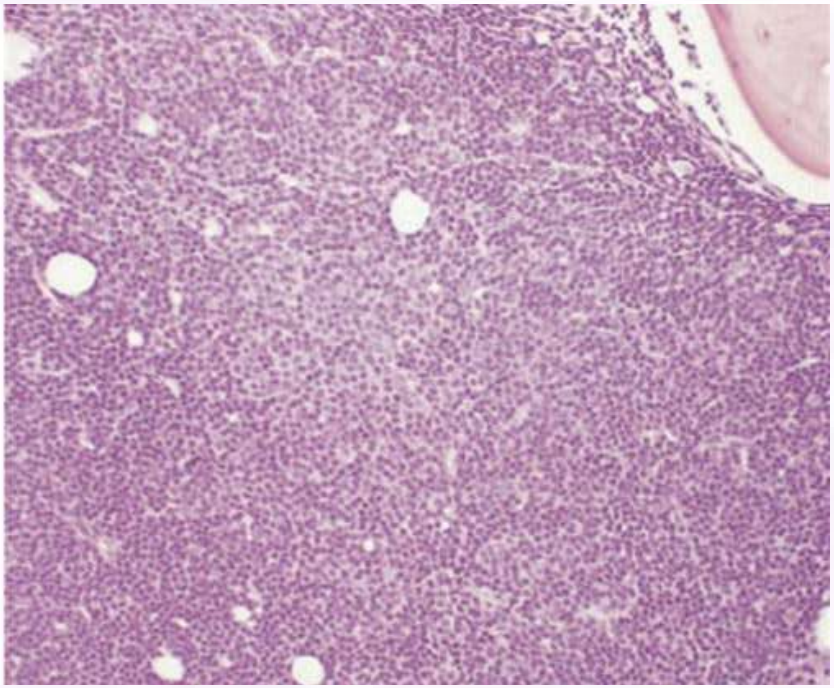
❖Laboratory findings:

- Lymphocyte leukocytosis; >5×10^9/L may be up to >300×10^9/L.
- Anemia; in later stages due to BM failure, or hypersplenism. AIHA and nutritional deficiencies may also occur.
- Thrombocytopenia; seen in later stages due to BM failure, hypersplenism or autoimmune process.
- Blood film; small mature looking lymphocytes with smudge (smear) cells.
- Coombs' test (+ve); Autoimmune hemolytic anemia or immune thrombocytopenia.
- Flow cytometry Immunophenotyping ($CD19^+$) with weak surface IgM or IgD.

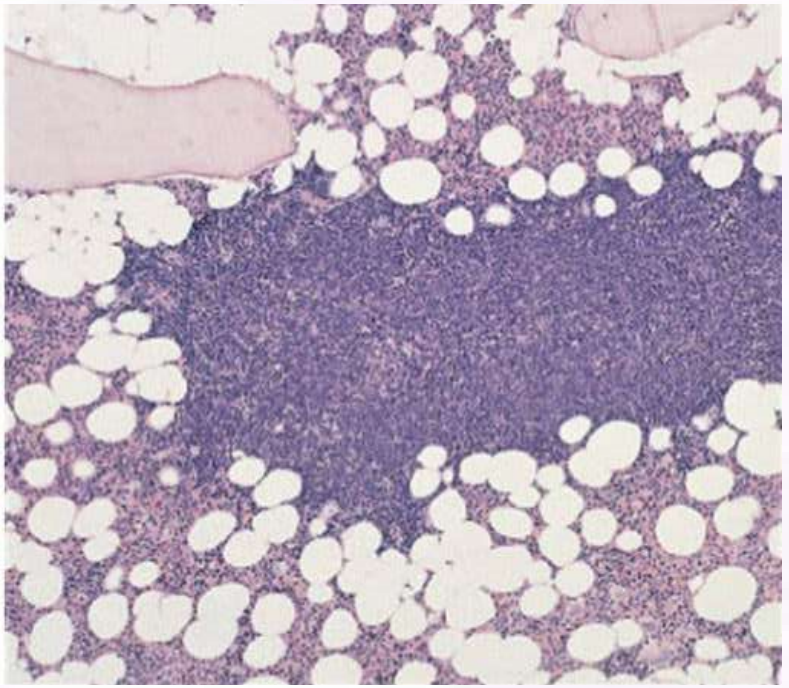


CLL; blood film shows only lymphocytes of mature looking with scanty (thin rims) cytoplasm and presence of smudge (smear) cells (low and high power).

- Bone marrow shows lymphocyte infiltration >30 % of all nucleated marrow cells. BM biopsy; useful for the type of involvement; diffuse, focal or interstitial.
- Chromosomal cytogenetics; for prognostic outcome.



Diffuse Marrow involvement



Focal Marrow involvement

❖Treatment:

- Symptomatic and supportive; in most cases unless there is a considerable anemia and thrombocytopenia.
- Radiotherapy for debulking and splenectomy with or without corticosteroid for immune HA.
- Chemotherapy; in combination with monoclonal Abs.
- Corticosteroids
- The prognosis depends on the stage of the disease.
- It may transfer to lymphoma (Richter's syndrome) or prolymphocytic leukemia (PLL) or to.

❖Staging of CLL

(a) Rai Classification

Stage	
0	Absolute lymphocytosis >15 × 10^9/L
I	As stage 0 + enlarged lymph nodes (adenopathy)
II	As stage 0 + enlarged liver and/or spleen ± adenopathy
III	As stage 0 + anemia (Hb <10.0 g/dL) ± adenopathy ± organomegaly
IV	As stage 0 + thrombocytopenia (platelets <100 × 10^9/L) ± adenopathy ± organomegaly

(b) International Working Party classification (Binet)

Stage	Organ enlargement*	Haemoglobin** (g/dL)	Platelets**(x 10^9/L)
A (50–60%)	0, 1 or 2 areas		
B (30%)	3, 4 or 5 areas	≥10	≥100
C (<20%)	Not considered	<10	and/or <100

**One area = lymph nodes >1 cm in neck, axillae, groins or spleen, or liver enlargement. **Secondary causes of anemia (e.g. iron deficiency) or autoimmune HA or autoimmune thrombocytopenia must be treated before staging.*

Other types of Chronic lymphoid Leukemias;

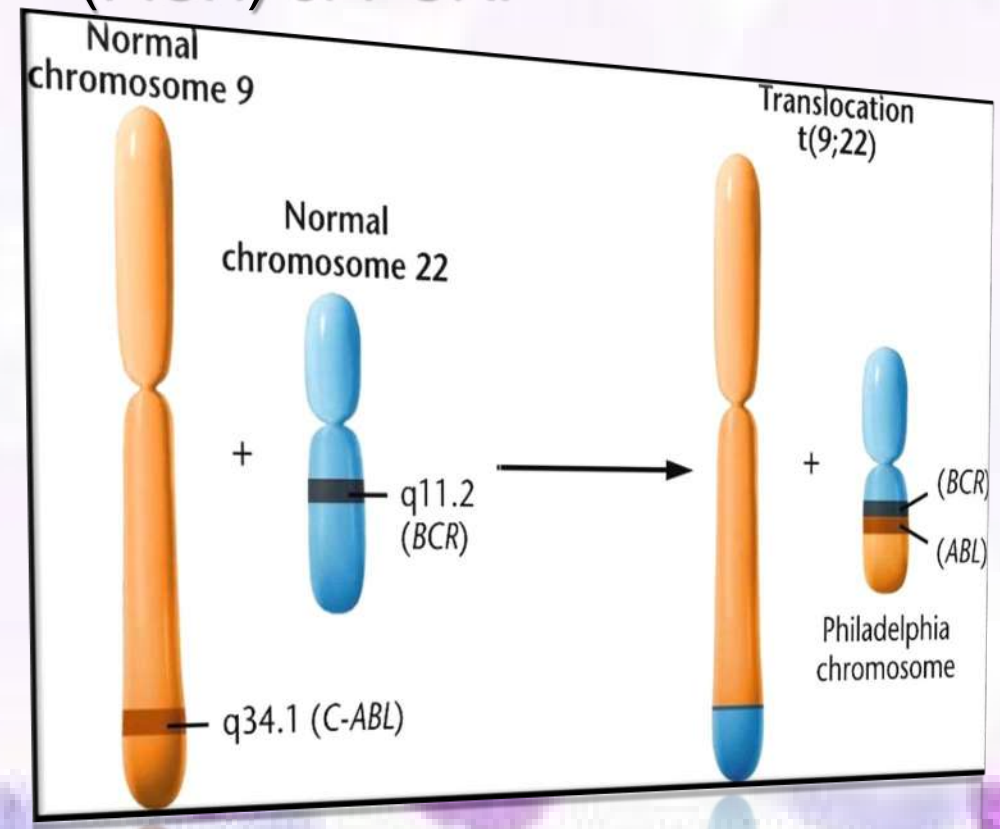
- **B-Prolymphocytic Leukemia (PLL)**
- **Hairy Cell Leukemia (HCL); a cause massive splenomegaly**
- **T-Cell Disease; T-Cell CLL and large Granular LL**

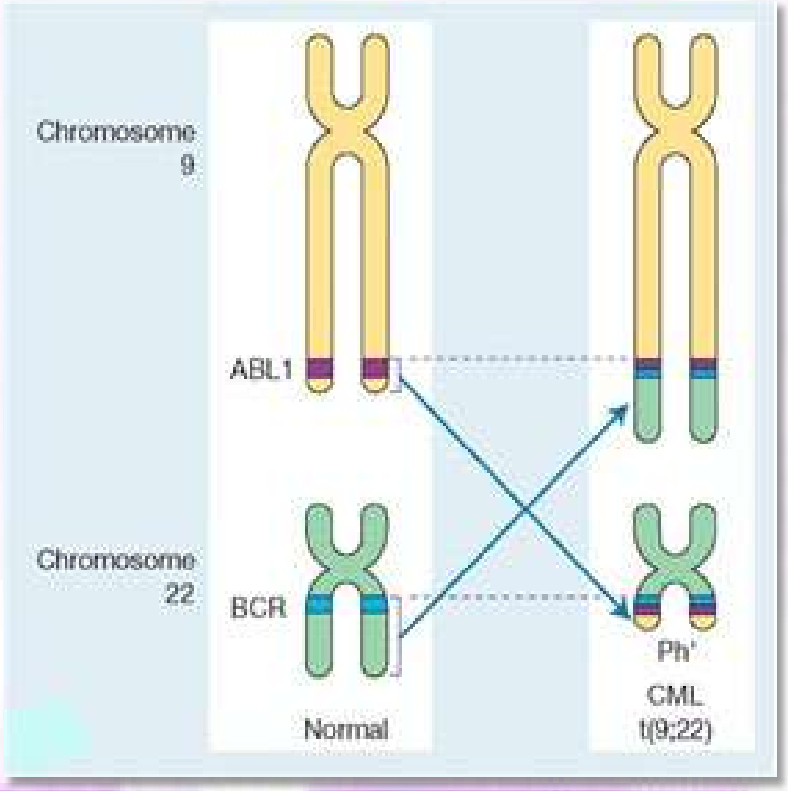
CHRONIC MYELOID LEUKEMIA

- Chronic myeloid leukemia BCR-ABL1+; a clonal disorder of a pluripotent stem cell.
- CML accounting around 15% of leukemias and occur at any age.
- Characterized by presence of Philadelphia chromosome.
- This translocation of Abelson gene (ABL) located on chromosome 9 and breakpoint cluster region (BCR) located on chromosome 22 lead to the creation of chimeric BCR-ABL fusion gene. This BCR-ABL fusion gene activates protooncogene tyrosine kinase, which is responsible for dysregulation of cell differentiation, proliferation and apoptosis.

Translocation of part of the long arm of chromosome 22 to the long arm of chromosome 9 and reciprocal translocation of part of the long arm of chromosome 9 to chromosome 22 form Ph chromosome.

Ph chromosome diagnosed by chromosomal karyotypic examination and by fluorescence *in situ* hybridization (FISH) or PCR.





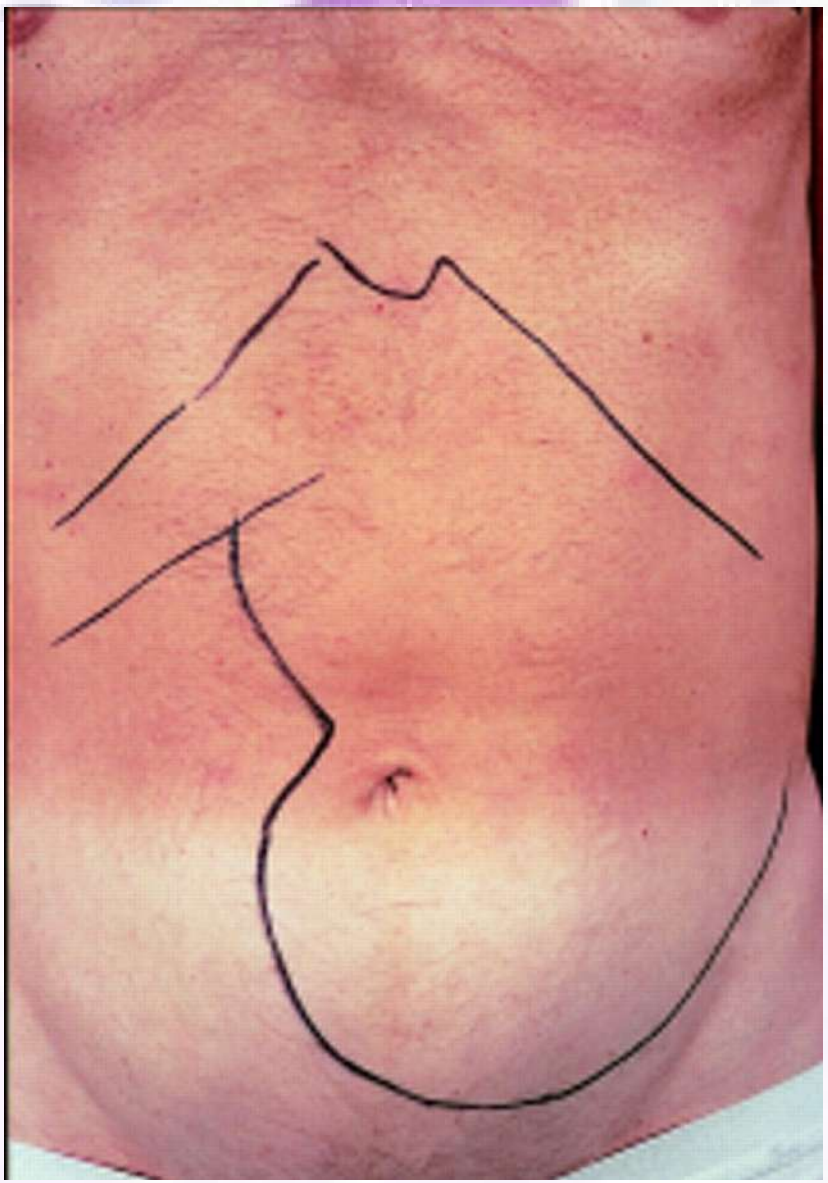
CML usually passes into 3 phases during its course:

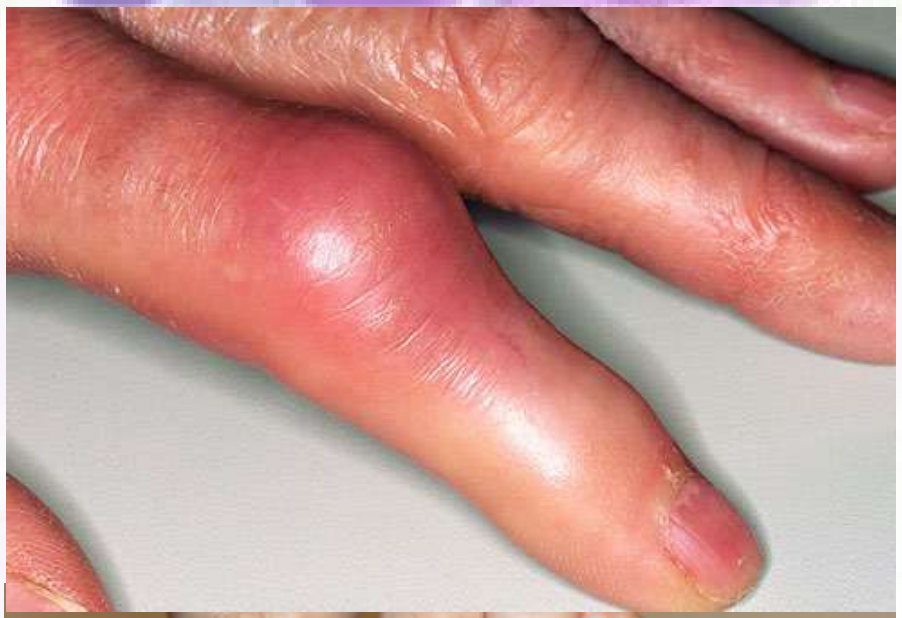
1. **Chronic Phase (CP)**
2. **Accelerated Phase (AP)**
3. **Blastic Phase (BP)**

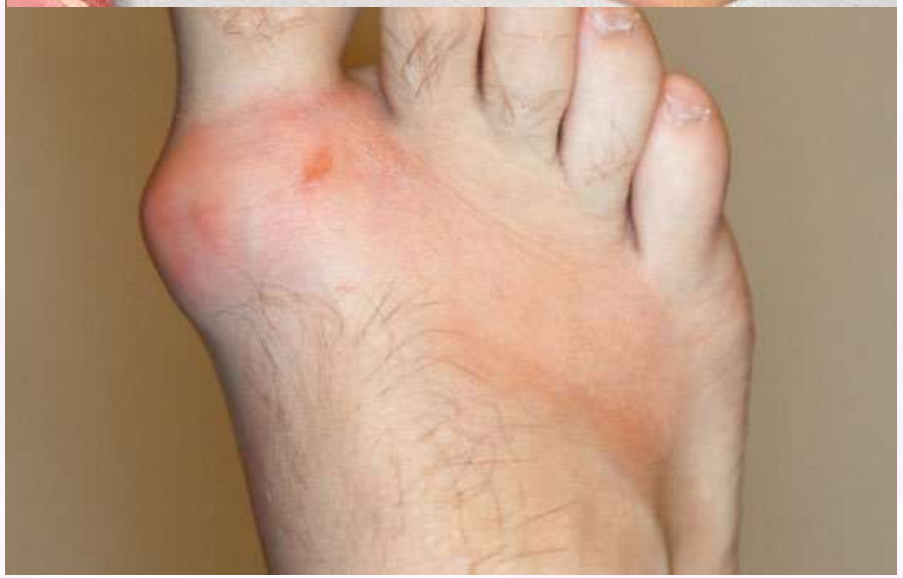
❖Clinical Features (Chronic Phase):

The Chronic phase usually lasts 2-7 years and in 50% of cases it is transformed to blastic phase directly.

- More common in male (1.4:1.0), occur at any age, but mostly between age 40-60 years.
- Asymptomatic in about 50%, and diagnosis is made incidentally from a routine blood count.
- Hypermetabolism; wt. loss, anorexia and sweating.
- Abdominal discomfort and pain, due to splenomegaly and frequently massive.
- Features of anemia; pallor, dyspnea, and tachycardia.
- Bleeding (bruising, epistaxis, menorrhagia); due to abnormal platelets function.
- Hyperuricemia with gout.



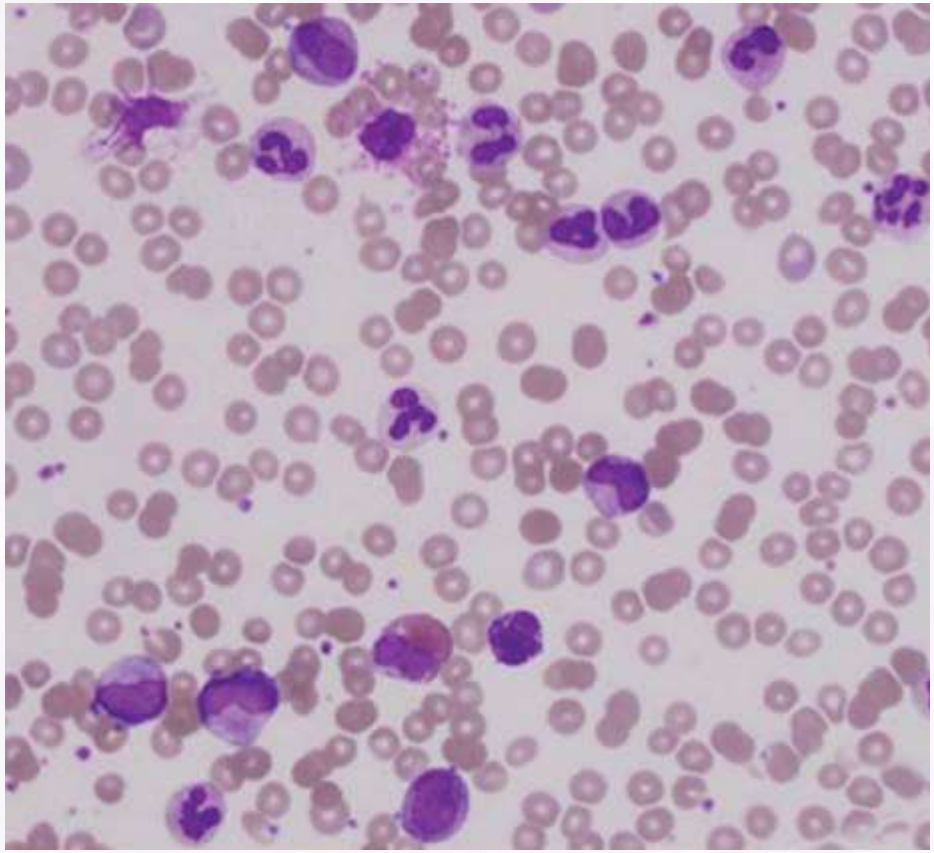


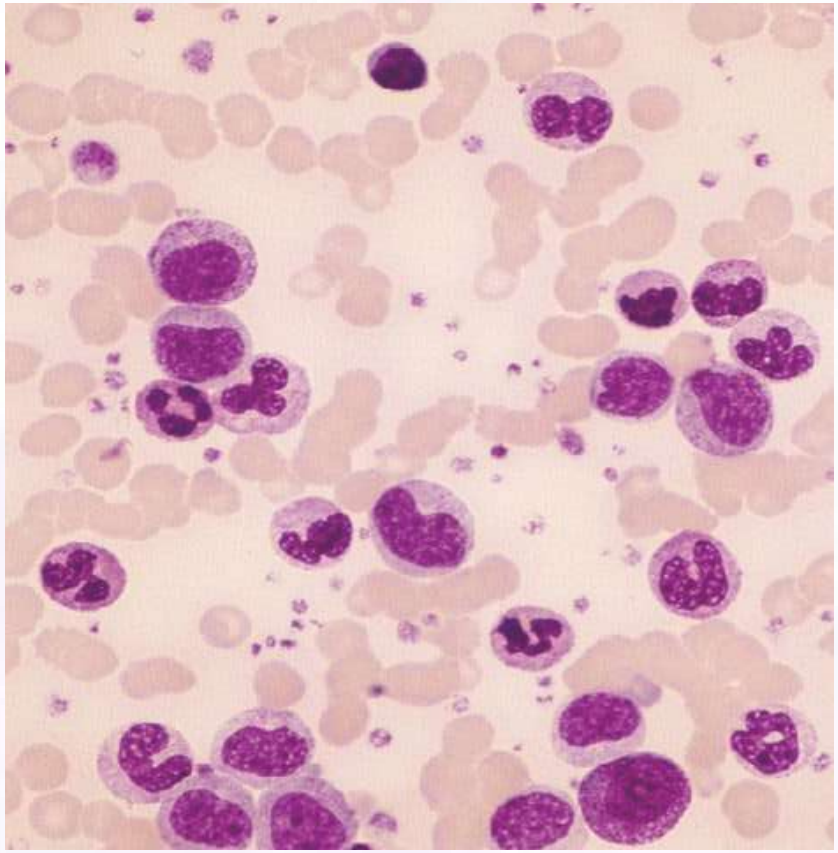


CML; Massive Splenomegaly and gout of hand and foot

❖Laboratory Features:

- Leukocytosis; usually >50×10^9/L and may be >500.
- Anemia; normochromic normocytic.
- Basophilia and eosinophilia.
- Platelets; mostly increased (300-600 × 10^9/L) and may be normal or low.
- Blood film; shows a complete spectrum of myeloid cells (sever left shift) is seen in the peripheral blood.
- The levels of neutrophils and myelocytes exceed those of blast cells and promyelocytes.





CML; blood film showing prominent increase in WBC cells with various stages of granulopoiesis including promyelocytes, myelocytes, metamyelocytes and band and segmented neutrophils. basophil and an eosinophil can be seen

- BM usually loss of fat spaces due to dense hypercellularity with active of all cell lines and increased megakaryocytes and blast cells <12%.
- Karyotyping for Ph chromosome.
- PCR for *BCR-ABL1*.
- Raised uric acid.

❖Treatment:

- Tyrosine kinase inhibitors; Imatinib (Glivec) is the first line treatment act as a specific inhibitor of the BCR-ABL1 fusion protein and blocks tyrosine kinase activity. Monitoring of the response by count response, karyotype analysis and PCR.
- Hydroxyurea; can control the high WBC count.
- α-Interferon; previously used after the reduction of the WBC count.
- Stem cell transplantation (SCT); curative treatment and used in Imatinib failure, because of the SCT risks.

❖ Course and Prognosis

- In general, the outcome is good, but transformation to accelerated phase or leukemia may occur.
- Patients with CML in chronic phase usually show an excellent response with prolonged survival by imatinib.
- Responders to imatinib may never relapse.
- Transformation to acute leukemia (AML).
- Death usually occurs from terminal blastic transformation or intercurrent hemorrhage or infection.

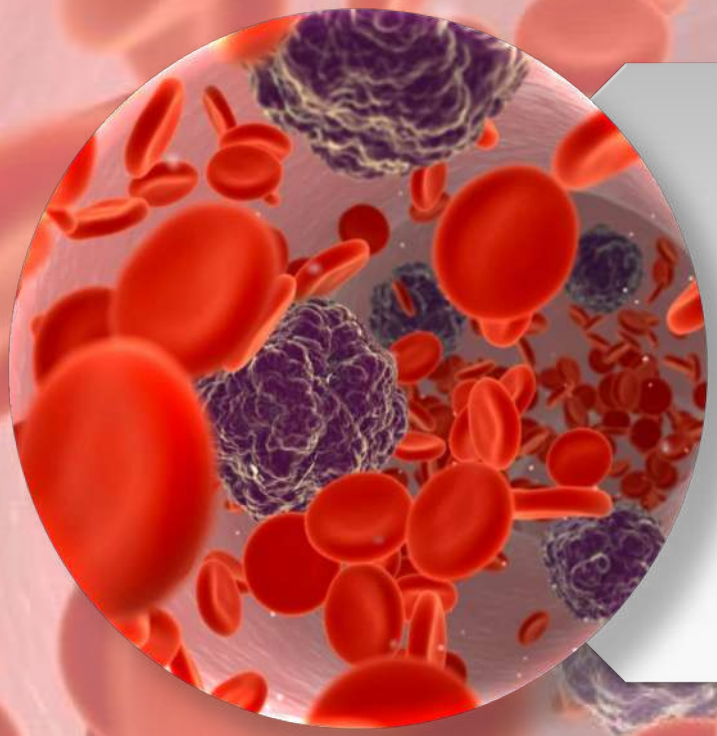
- CML may transformed to one of the 2 forms:

❑ ***Accelerated phase;***

Characterized by; anemia, thrombocytopenia, basophilia and eosinophilia or increased blast cells 10-19% with increase spleen size.

❑ ***Blast transformation;***

Which mains development of AML >20% blast.



Non-LEUKEMIC MYELOPROLIFERATIVE DISORDERS (MPD)

Myeloproliferative Disorders

A group of clonal disorders of the hematopoietic stem cells that lead to effective proliferation of one or more hemopoietic component in the BM, and in many cases, in the liver and spleen leading to an elevated blood levels of one or more cell lines (i.e., erythrocytosis, leukocytosis, and thrombocytosis).

- Hypercellular marrow with maturation.
- Elevated peripheral blood levels of one or more cell line:
  - ✓ Erythroid (polycythemia vera)
  - ✓ Granulocytic (CML; agnogenic myeloid metaplasia)
  - ✓ Platelets (essential thrombocythemia)
- Hepatosplenomegaly.

Myeloproliferative disorders include;

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

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. They have many overlapping features and a shift in the affected series (diagnosis) may occur.

❖ Karyotype, and Molecular Features

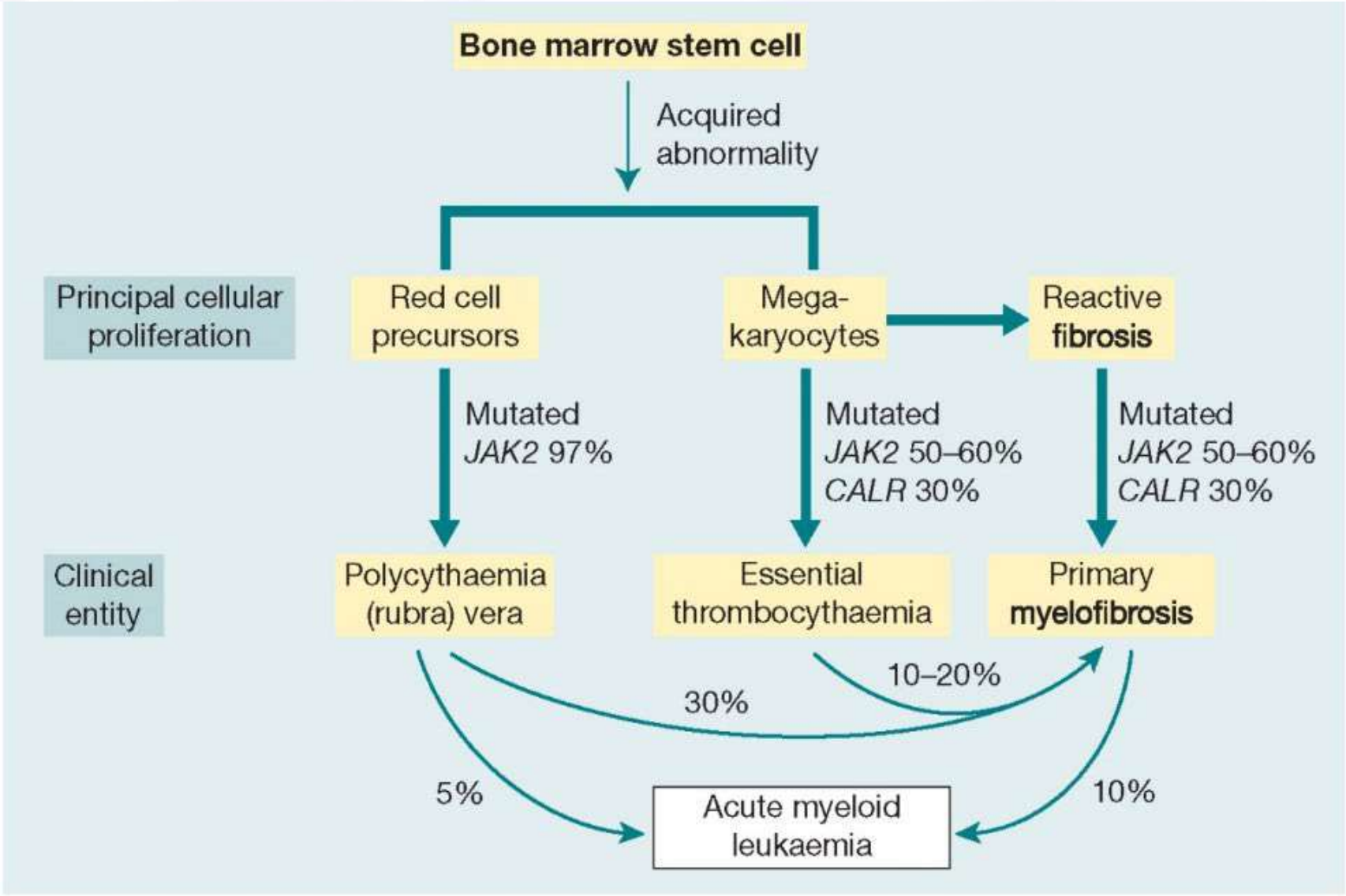
- The vast majority of CML (90-95%) show Philadelphia chromosome t(9;22) and 99% with BCR-ABL.
- Nearly all PV patients, and about 50% of ET and MF cases show a single acquired mutation of cytoplasmic Janus-Associated Kinase 2 (*JAK2*) that occurs in the BM and in the peripheral blood granulocytes. This mutation is not found in secondary polycythemia, or reactive thrombocytosis.
- *JAK2* plays a major role in normal myeloid development. It does not appear to be the initiating mutation.

NON- LEUKEMIC MYELOPROLIFERATIVE NEOPLASMS (MPN)

Myeloproliferative neoplasms (MPN) are a group of disorders with clonal proliferation of hemopoietic component, mostly of the bone marrow, but liver and spleen may be other sites.

1. Polycythemia vera (PV).
2. Essential thrombocythemia (ET).
3. Primary myelofibrosis (MF); Chronic idiopathic MF (CIMF)

- Characterized by *JAK2* mutation (tyrosine kinase Janus-associated kinase 2).
- Tyrosine kinase plays an important role in myeloid development
- These disorders show the ability to transform from one form to another, in addition to AML transformation.


Bone marrow stem cell
Acquired abnormality
Principal cellular proliferation
Red cell precursors
Mega-karyocytes
Reactive fibrosis
Mutated JAK2 97%
Mutated JAK2 50–60% CALR 30%
Mutated JAK2 50–60% CALR 30%
Clinical entity
Polycythaemia (rubra) vera
Essential thrombocythaemia
Primary myelofibrosis
30%
10–20%
5%
10%
Acute myeloid leukaemia

POLYCYTHEMIA (Rubra) VERA (PV)

Is an increase of the Hb level above the upper limit for the age and sex.

- **Absolute;** increased red cell volume.
  - Primary; due to progenitor cells abnormalities.
  - Secondary; causes outside the erythroid compartment.
- **Relative** (pseudopolycythemia); decreased plasma volume with normal red cell mass, such as in sever dehydration or burn.

❖ Cause of Polycythemia

1- Primary erythrocytosis

Acquired; Polycythemia vera (PV)

Congenital; Erythropoietin receptor mutations

2- Secondary erythrocytosis

Acquired:

-Erythropoietin-mediated; Smoking, High altitude, Central hypoxia (chronic lung and cardiac diseases) and CO poisoning.

-Local hypoxia; Wide variety of renal disease.

-Pathologic erythropoietin production; Tumors; cerebellar tumors, parathyroid tumors, hepatocellular carcinoma, renal cell cancer, pheochromocytoma, uterine leiomyoma.

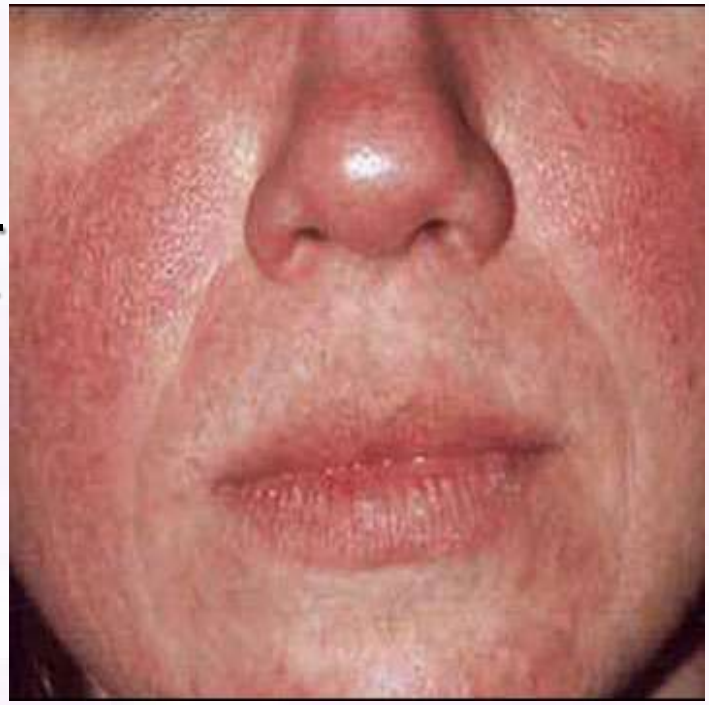
-Drug-associated; EPo and Androgen administration

Congenital; Defects of the oxygen-sensing pathway; many gene mutations in addition to the high oxygen-affinity hemoglobin

❖Clinical features:

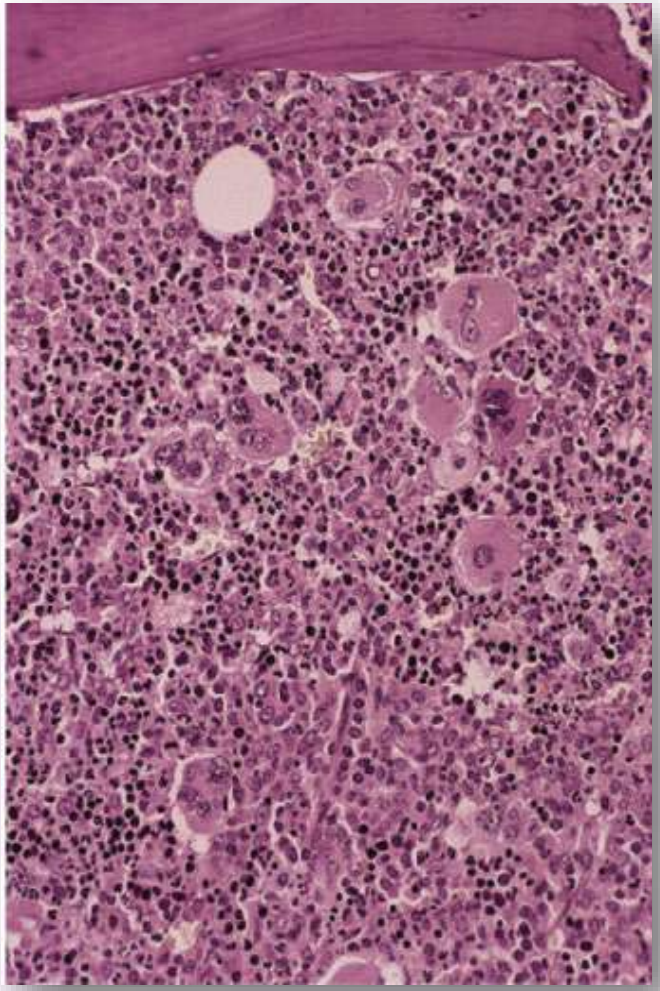
Features of hyperviscosity, hypervolemia and hypermetabolism.

- Headaches, dyspnea, blurred vision and night sweats.
- Pruritus, characteristically after a hot bath.
- Plethoric appearance: conjunctival suffusion and retinal venous engorgement.
- Splenomegaly in 75% of patients.
- Hemorrhage or thrombosis either arterial or venous.
- Gout (hyperuricemia)
- Hypertension
- Usually have good prognosis.



❖Laboratory Feature:

- High haemoglobin (Hb) and hematocrit (PCV) with increased red blood cell count
- Platelet usually high.
- Neutrophilia and sometimes basophilia.
- Bone marrow; hypercellular (panmyelosis) and better by biopsy
- Uric acid; increased.
- *JAK2* mutation (PCR and gene sequencing techniques) and chromosome abnormalities.



❖Treatment:

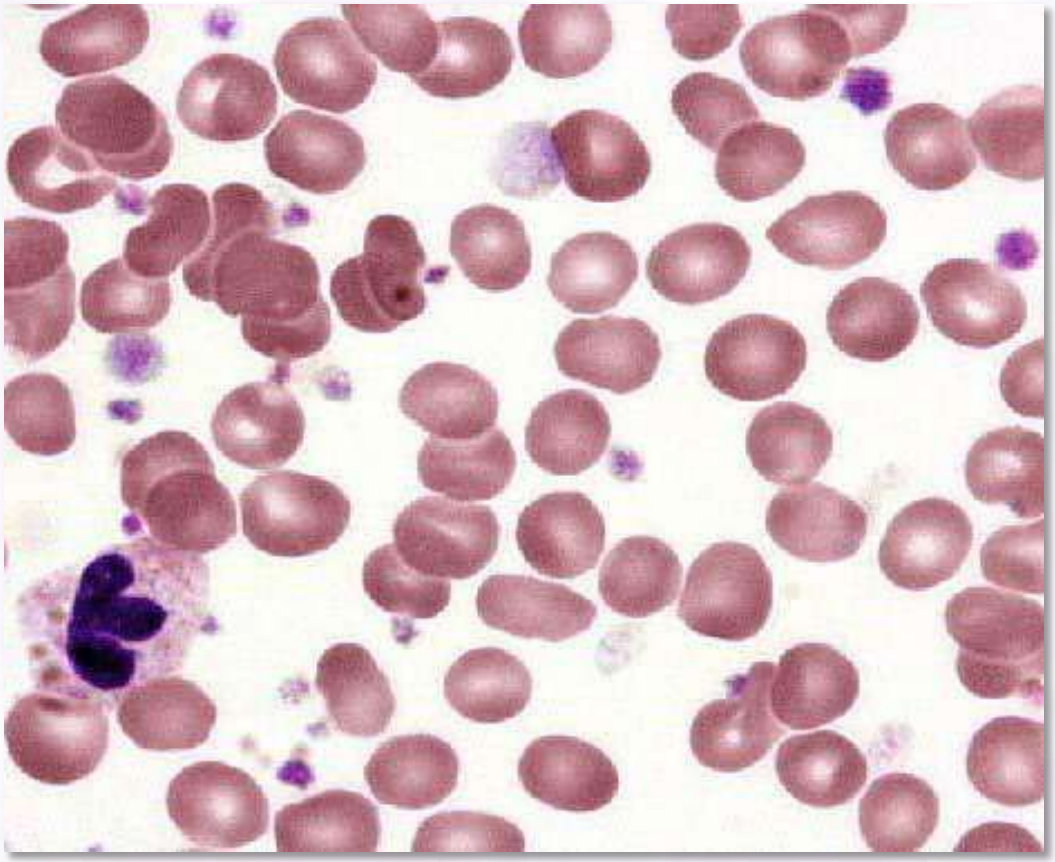
The aim; to control PCV and platelets count.

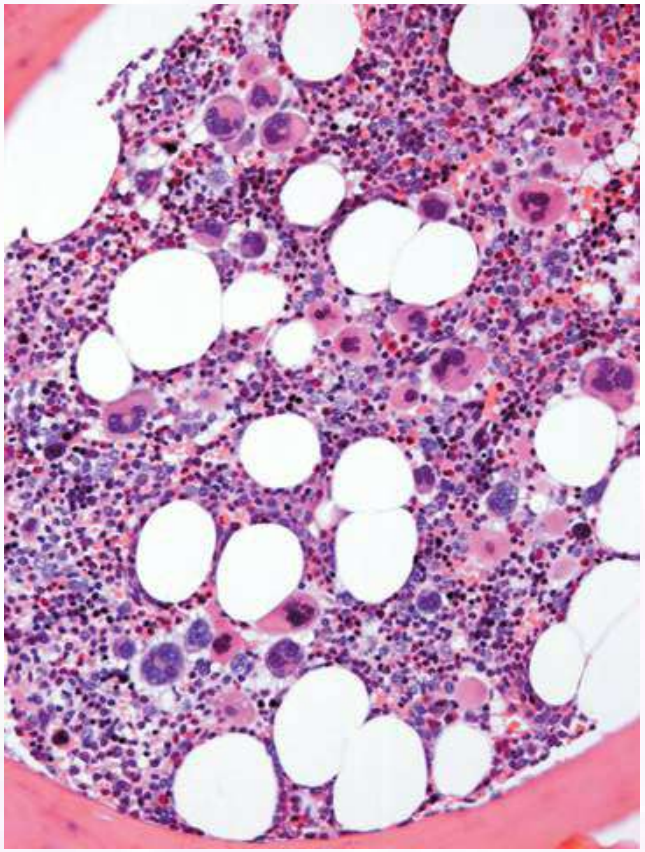
- Venesection; in young and in mild cases.
- Hydroxycarbamide (hydroxyurea); for myelosuppression.
- α-interferon
- *JAK2* inhibitors.
- Aspirin; low dose to reduce thrombosis.

ESSENTIAL THROMBOCYTHEMIA

Sustained increase in platelet count (>450×10^9/L), because of megakaryocyte proliferation with over production of platelets

- Asymptomatic, Usually diagnosed incidentally during routine blood count
- Hemorrhage or thrombosis may be the presenting feature
- Hand or feet burning sensation relieved by aspirin (erythromelalgia).
- Splenomegaly or splenic atrophy (splenic arteries infarctions).





ET; peripheral blood smear (left) showing marked thrombocytosis and platelets show anisocytosis and bizarre forms. BM biopsy (right) shows hypercellularity with marked increase of megakaryocytes.

❖Treatment:

The aim of the treatment is to reduce the possibilities of hemorrhage and thrombosis.

- Concerns of the precipitating factors; obesity, hypertension, smoking and hypercholesterolemia.
- Hydroxyurea and α-interferon are the most popular treatment
- *JAK2* inhibitors are a recently in clinical trials.

❖ *Causes of Thrombocytosis*

➢ ***Reactive***

- Hemorrhage; trauma, postoperative
- Chronic iron deficiency
- Malignancy
- Chronic infections
- Connective tissue diseases (e.g. rheumatoid arthritis)
- Post-splenectomy

➢ ***Endogenous***

- Essential thrombocythemia (ET)
- Cases of; primary myelofibrosis (MF), chronic myeloid leukemia (CML), myelodysplasia (MDS)

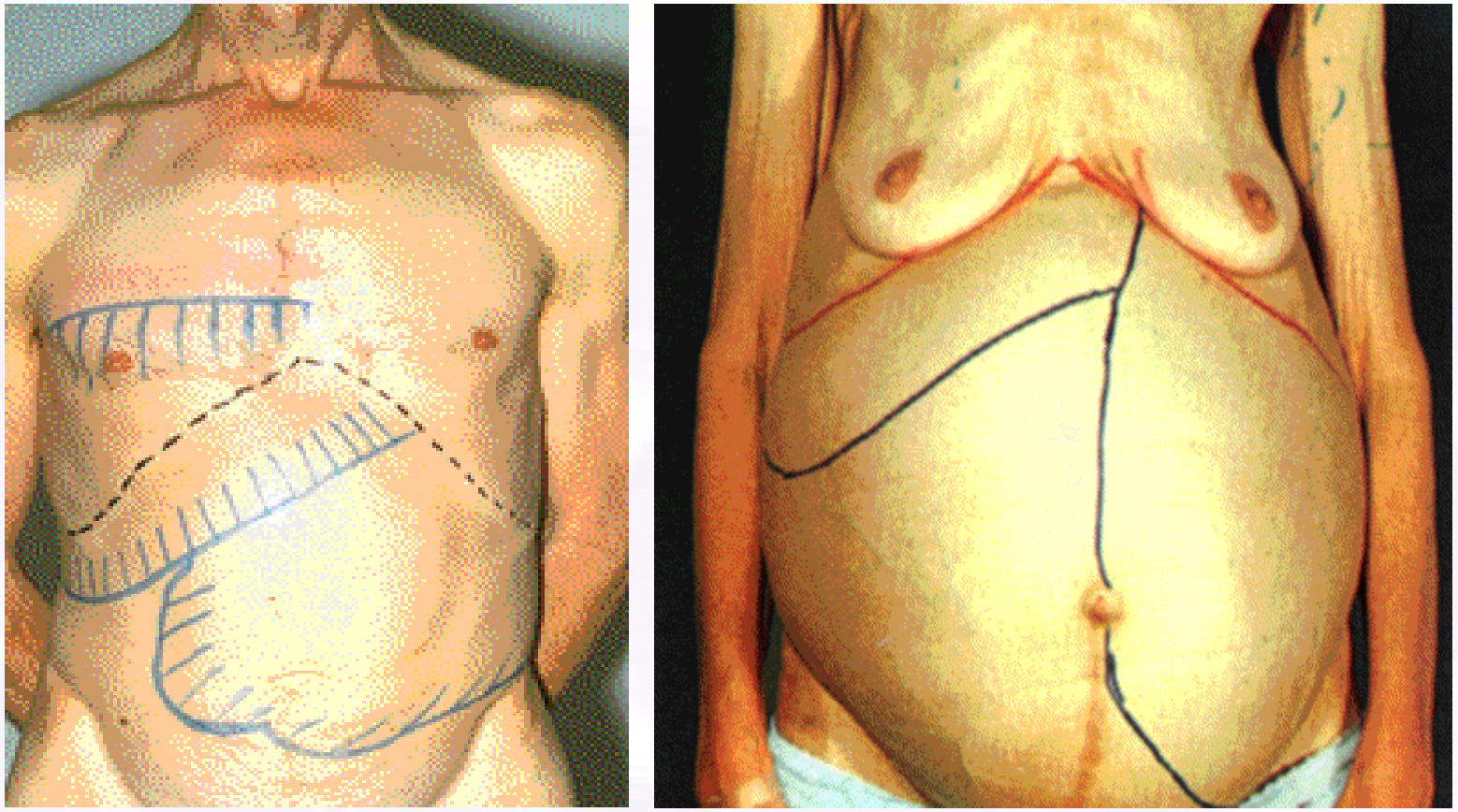
PRIMARY MYELOFIBROSIS (MF)

Chronic idiopathic myelofibrosis (CIMF) another synonym for MF

- Clonal stem cell disease
- Progressive generalized reactive fibrosis of the BM
- Extramedullary hemopoiesis (spleen and liver)
- Anemia
- Massive splenomegaly

❖Clinical features:

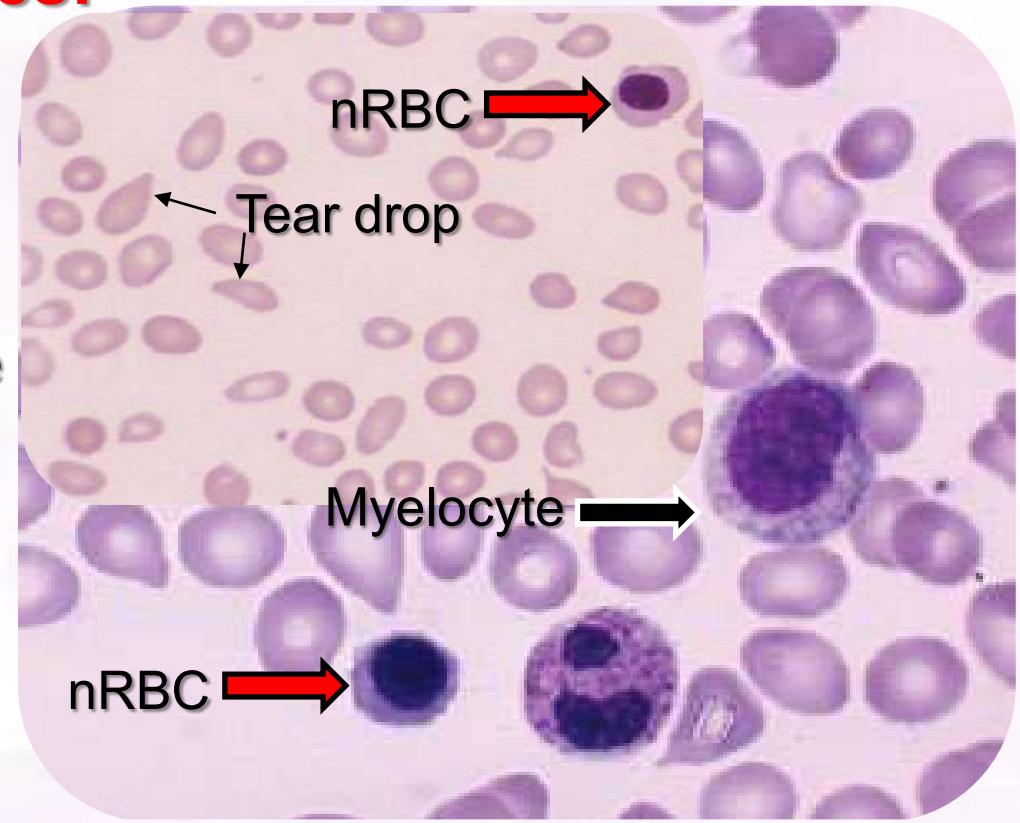
- Asymptomatic in first years of the disease.
- Old age with anemia of insidious onset.
- Massive splenomegaly; abdominal discomfort, pain or indigestion.
- Hypermetabolic status; loss of weight, anorexia, fever and night sweats.
- Bleeding problems, bone pain or gout occur may be a feature.



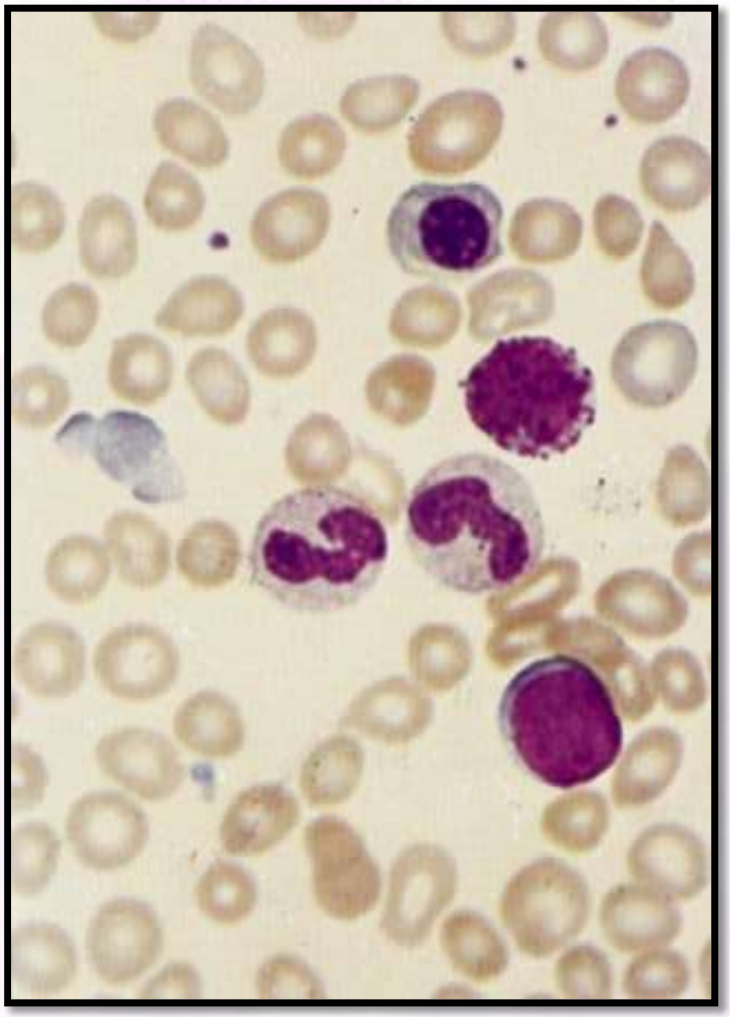
Myelofibrosis: both show massive splenomegaly. Gross wasting and abdominal distension (right)

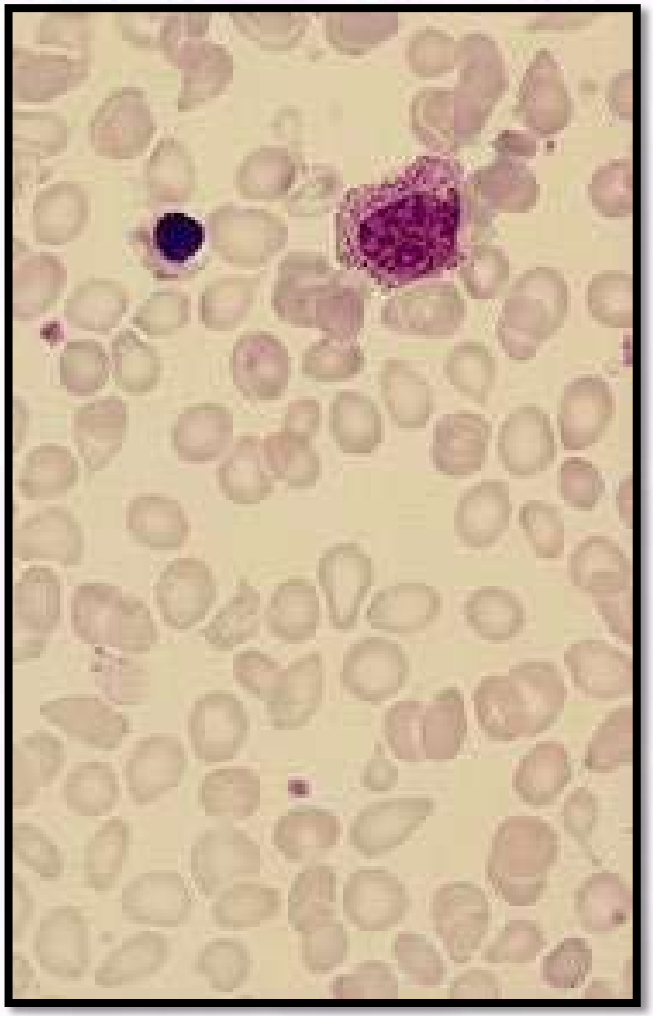
❖ Laboratory Features:

- Hb level; variable.
- WBC and platelets; usually high before the advancing of the disease.
- Blood film; leucoerythroblastic, with 'tear-drop' RBCs.



- High serum urate and LDH levels.
- *JAK2* kinase mutation in approximately 50% using PCR and gene sequencing techniques





Teardrop-shaped red blood cells indicative of membrane damage from its passage through the spleen, a leukoerythroblastic picture indicative of extramedullary hematopoiesis.

Bone marrow examination:

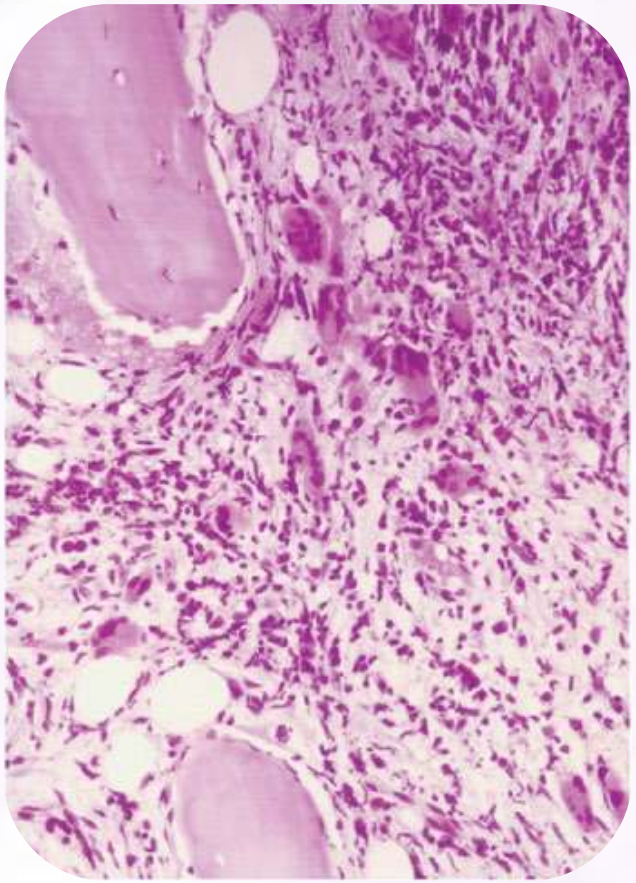
- Aspirate; the aspirate is unobtainable (dry tab)
- BM trephine biopsy (BMB);

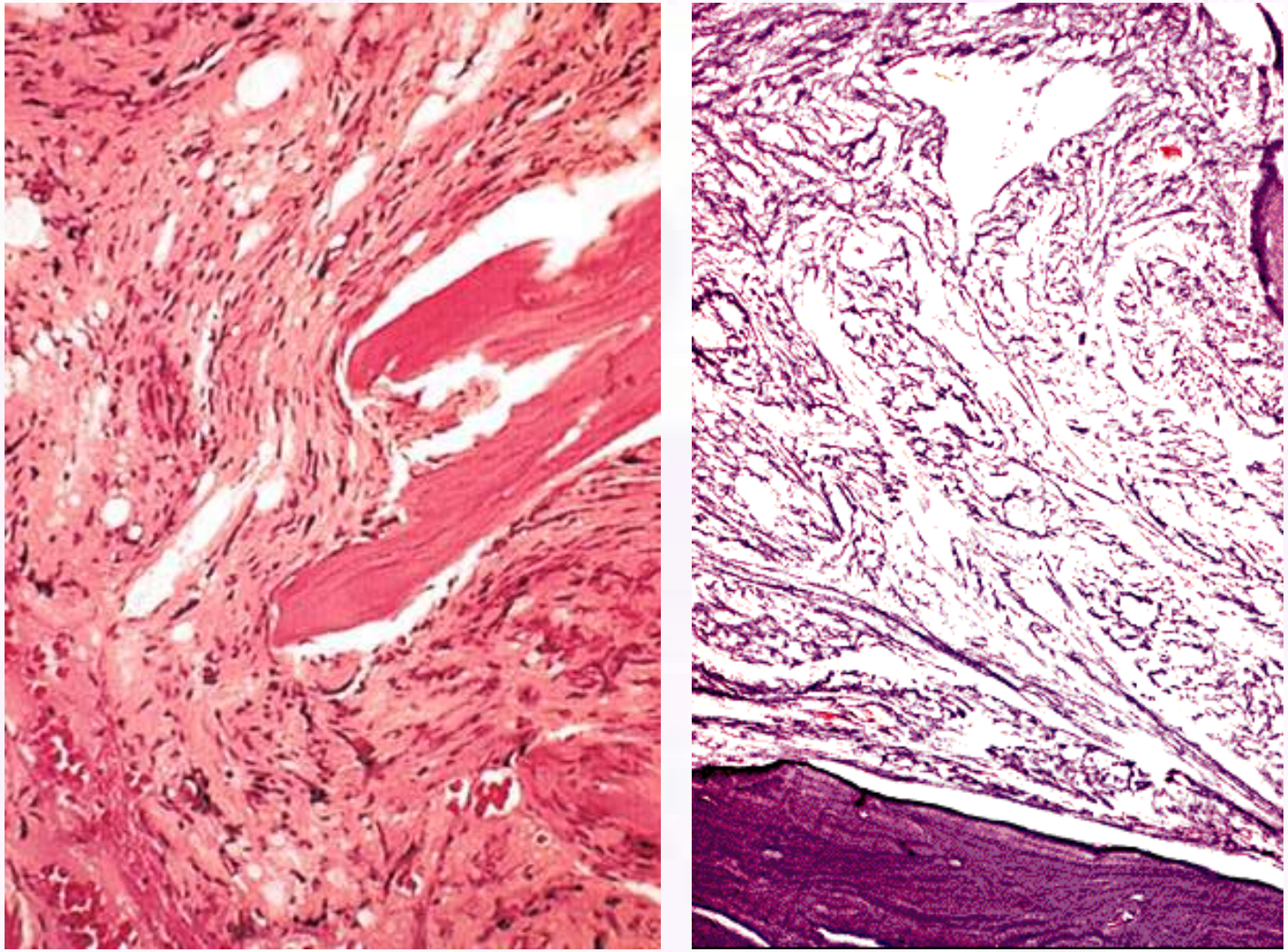
➢ Fibrotic hypercellularity

➢ Loss of normal architecture

➢ Increased megakaryocytes.

➢ Silver stain; increased reticuline fibers density and thickness.





BM biopsy; left; marrow cavity replaced by fibrous tissue composed of reticulin fibers and collagen. Right; silver impregnation stain shows increased reticulin fiber density and thickness.

❖Treatment:

The aim is to reduce the effects of anemia and splenomegaly.

- Blood transfusions and regular folic acid.
- Hydroxyurea may help to reduce splenomegaly and hypermetabolic symptoms.
- Splenectomy in severely symptomatic patients.
- Erythropoietin can also be tried but may cause splenic enlargement.
- SCT a curative protocol for young patients.
- JAK2 inhibitors; in clinical trials.

MYELODYSPLASTIC SYNDROMES (Myelodysplasia)

- Myelodysplastic syndrome is a clonal disorders of hemopoietic SCs.
- Quantitative and qualitative bone marrow failure with abnormalities of blood cell lineages maturation.
- The hallmark of proliferation and apoptosis of the hemopoietic cells leading to *ineffective erythropoiesis*
- Hypercellular marrow and pancytopenia.
- Tendency to progress to AML.
- Primary or secondary.

❖**Classified in to main groups;**

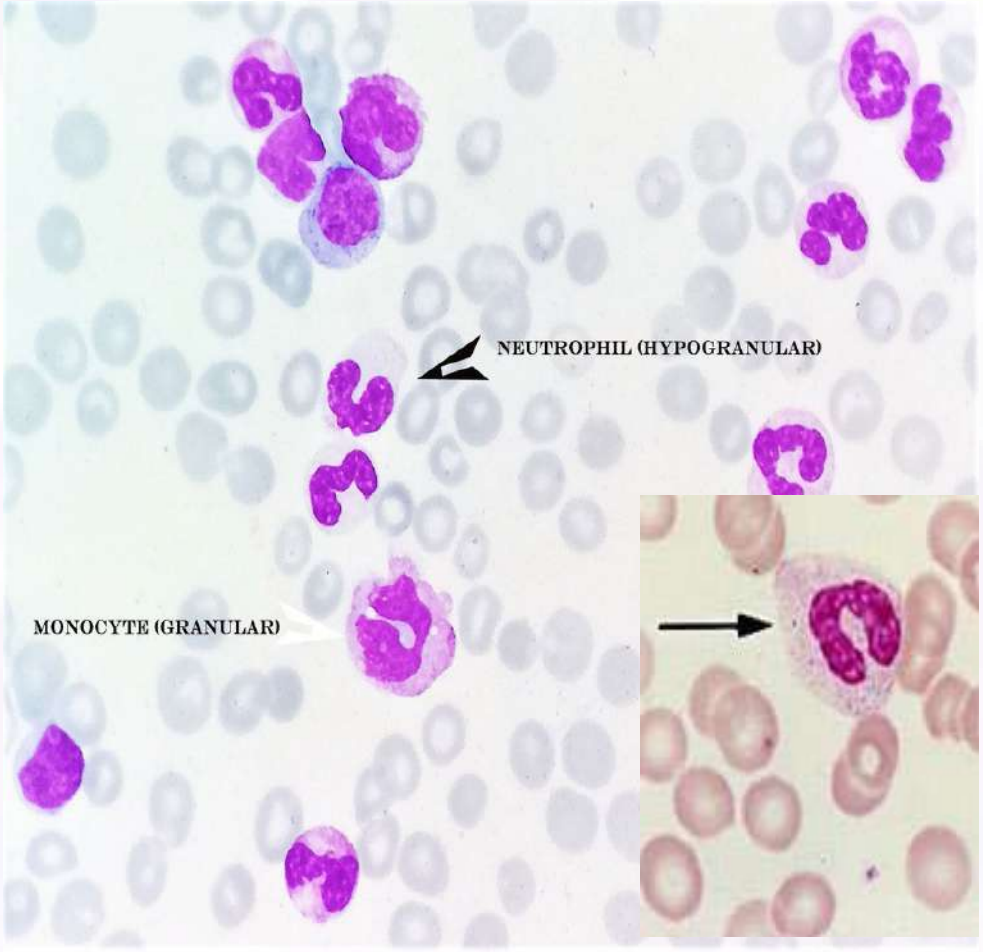
1. Refractory cytopenia with single lineage (unilineage) dysplasia (RCUD)
2. Refractory cytopenia with multilineage dysplasia (RCMD)
3. Erythroid dysplasia (refractory anemia) with ring sideroblasts (RARS).
4. Refractory anemia with excess blasts (RAEB).
5. 5q-syndrome; more in woman with anemia and thrombocytopenia.

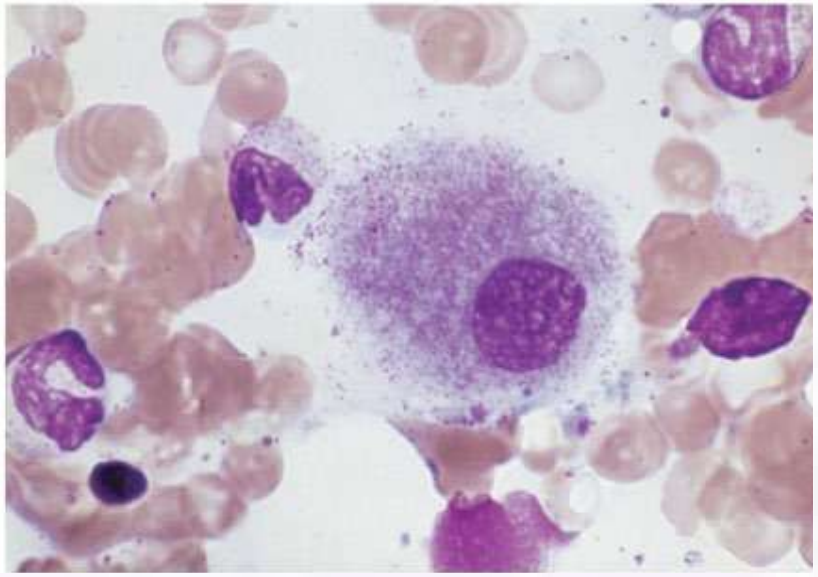
❖Clinical features:

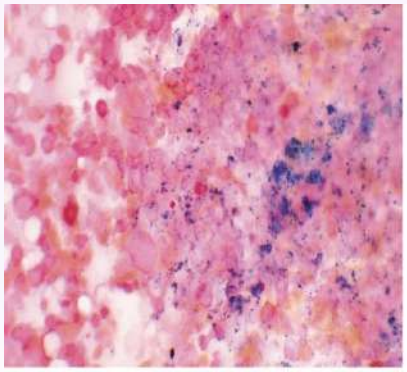
- Its mostly disease of old age (>70 years).
- Asymptomatic, diagnosed by routine blood examination or for unrelated disease.
- Features of marrow failure; anemia (transfusion-dependent), recurrent infections (neutrophils and monocytes are often functionally impaired) and easy bruising or bleeding (platelets are often functionally impaired)
- Splenomegaly in some cases.

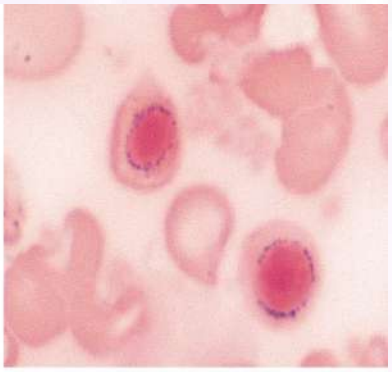
Laboratory findings:

- Pancytopenia.
- Anemia usually macrocytic, but may be dimorphic or normochromic
- Neutropenia with hypogranularity and abnormal lobulation.
- Reticulocyte; low.
- Blast cells; if increased (BM blasts ≥ 5%) indicate poor prognosis.
- BMA; hypercellular with abnormal hemopoietic changes and presence of ring sideroblasts (Perls' stain).
- Cytogenetic abnormalities.







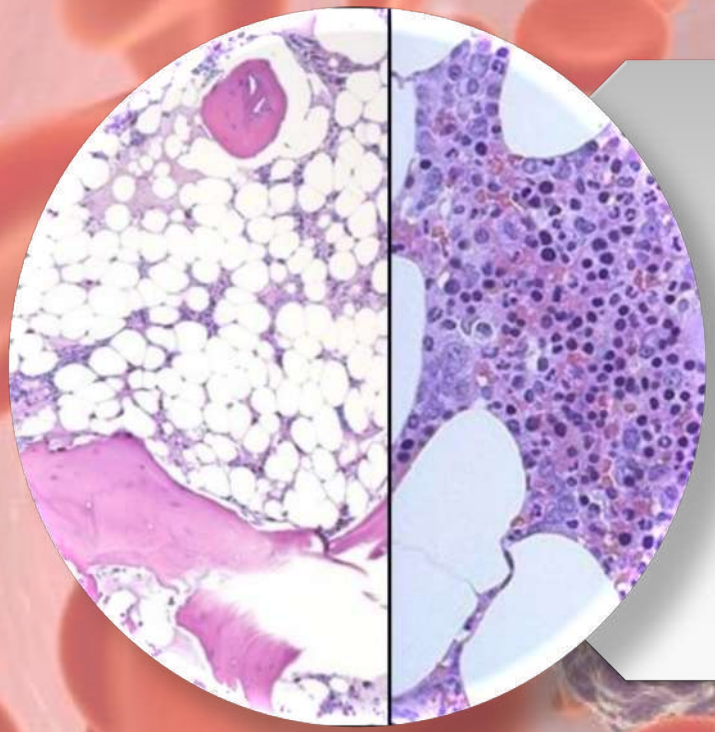


MDS; left; neutrophils show and hypolobulation.

Right; BMA; abnormal small mononuclear megakaryocyte. Perl's Prussian stain; shows presence of ring sideroblasts.

❖Treatment:

- Low risk group (marrow blasts <5% with favorable cytogenetics);
  - ➢ Transfusion for anemia and care for thrombocytopenia and for infections.
  - ➢ EPo or G-CSF
  - ➢ SCT may be a choice in certain cases.
- High risk group needs more aggressive or intensive treatment due to the high possibility of AML transformation.



Aplastic Anemia

APLASTIC ANEMIA

Aplastic (hypoplastic) anemia (AA); a pancytopenia resulting from aplasia of bone marrow.

- Pancytopenia is a reduction in the blood cell count of all the major cell lines (red cells, white cells and platelets).

❖ Primary;

- Congenital (Fanconi anemia)
- Idiopathic.

❖ Secondary; caused by; irradiation, chemicals including benzene, drugs (chemotherapy, chloramphenicol …) and viral infections including hepatitis and EBV.

❖ Causes of Pancytopenia

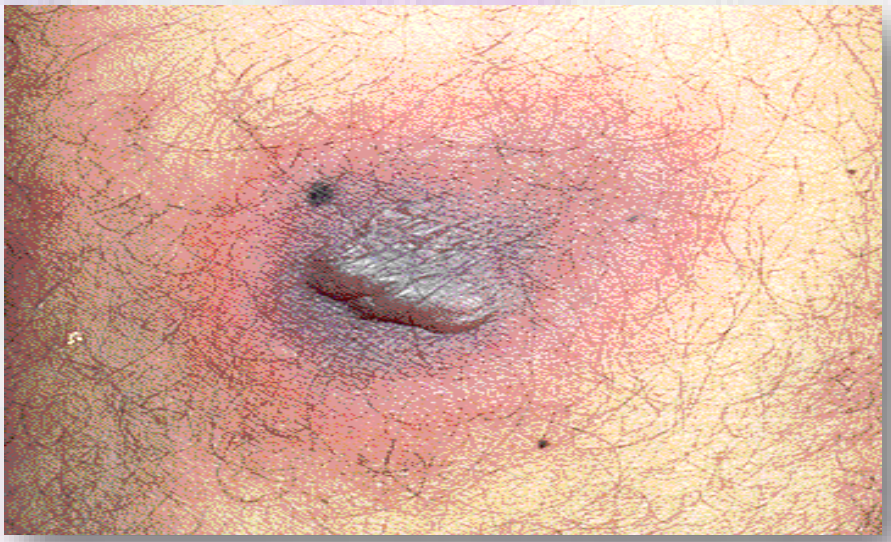
I. Decreased bone marrow function

- Aplastic anemia.
- Acute leukemia, myelodysplasia and myeloma.
- Marrow Infiltration with lymphoma, solid tumors and granulomas (tuberculosis).
- Megaloblastic anemia.
- Myelofibrosis (MF).

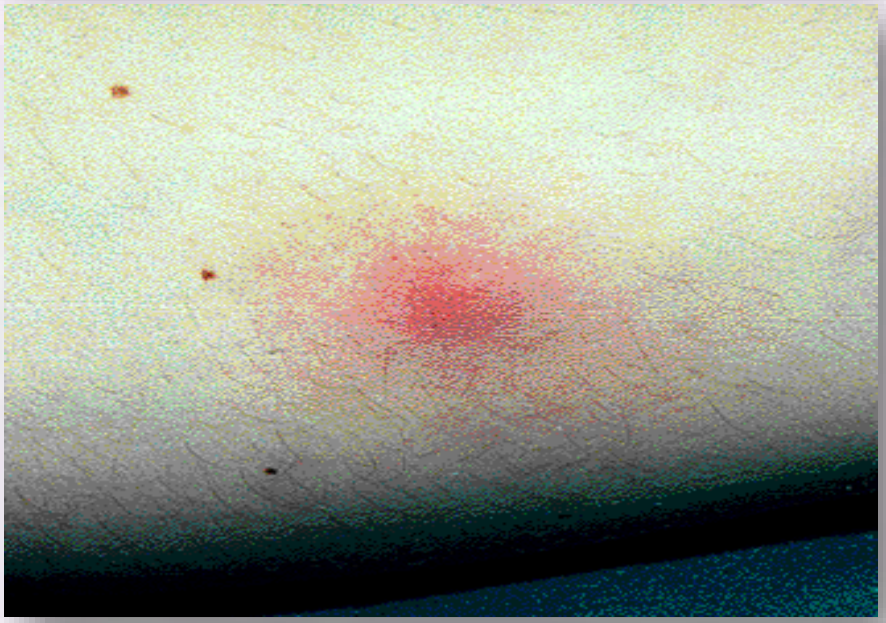
II. Increased peripheral destruction; Splenomegaly and hypersplenism.

❖Clinical features:

- Features of anemia.
- Infections; due to neutropenia, particularly of the mouth and throat, are common and generalized infections are frequently life-threatening.
- Features of thrombocytopenia (usual the presenting features); the most frequent hemorrhagic manifestations; bruising, bleeding gums, epistaxis and menorrhagia.
- The lymph nodes, liver and spleen are not enlarged.

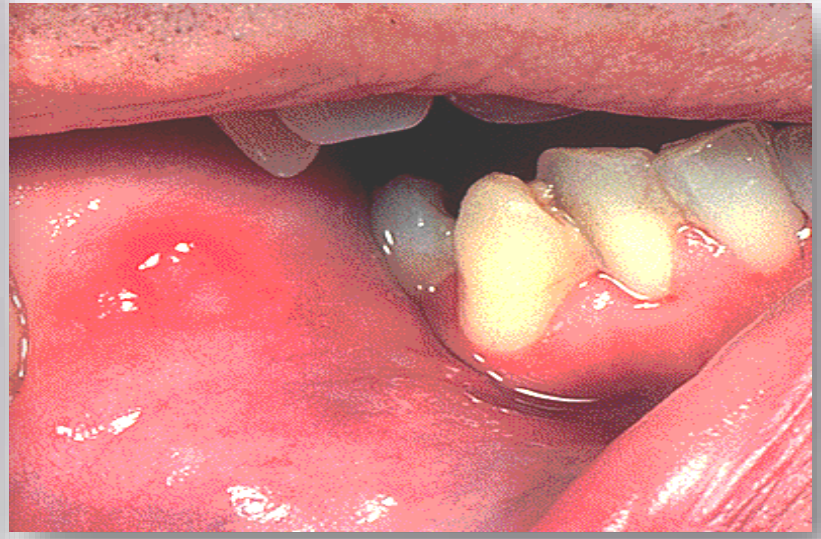


Skin infection;
Pseudomonas Pyocyanea



Skin infection Candida Albicans

Buccal infection Herpes simplex

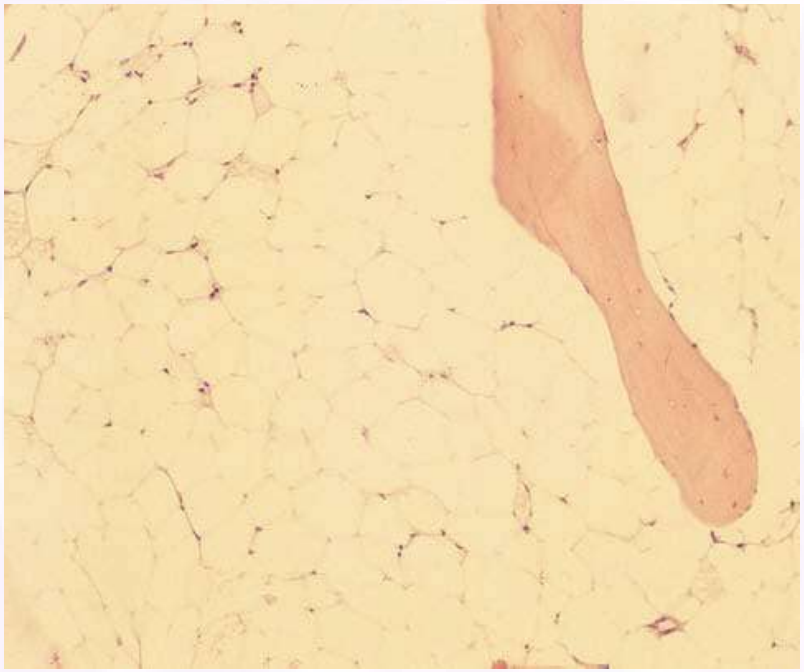


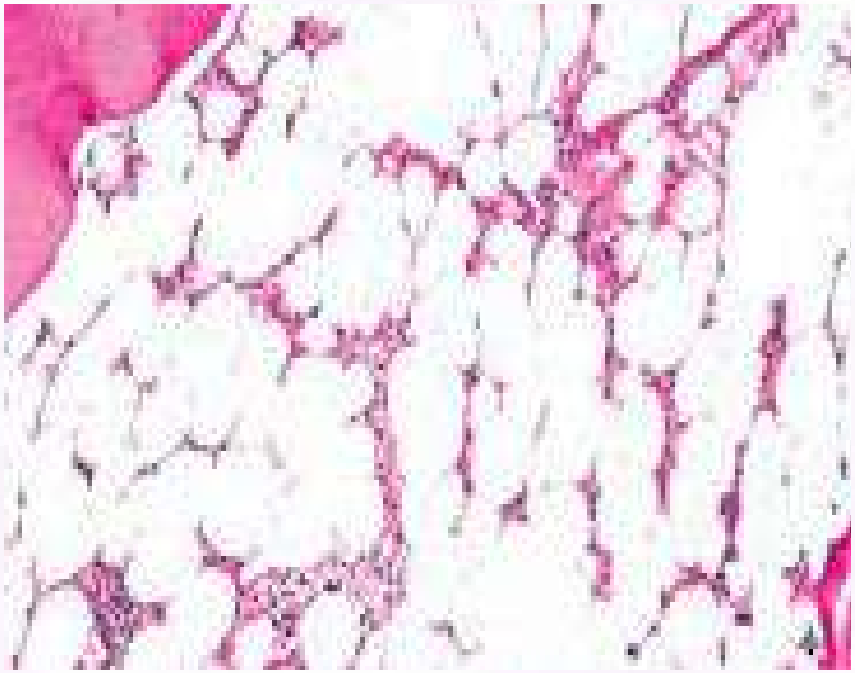
❖Laboratory findings:

- Anemia; normochromic or macrocytic.
- Leucopenia with absolute neutropenia. Severe cases show neutrophils $<0.5\times10^9$/L (very severe $<0.2\times10^9$/L).
- Thrombocytopenia; always (platelets $<20\times10^9$/L).
- Reticulocyte count (corrected); extremely low.
- Blood film; no abnormal cells.
- Bone marrow aspirate; shows hypoplasia, with replacement of hemopoietic tissue by fat which comprises over 75% of the marrow.

BM Trephine biopsy; is essential to asses the hypocellularity

- Shows diffuse or patchy.
- Main cells are lymphocytes and plasma cells.
- Megakaryocytes; severely reduced or absent.





❖Treatment:

- Avoid the possible precipitating factor, especially radiation or drug.
- Assessment of the severity depends on; retic count, neutrophil, platelets count, and degree of hypocellularity.
- Supportive;

✓ Blood transfusion

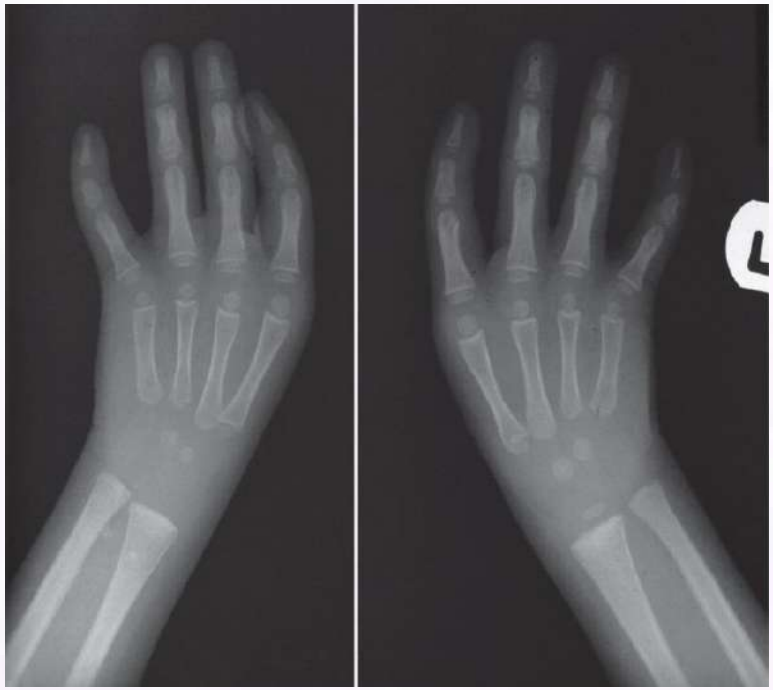
✓ Platelet concentrate

✓ Prevention and treatment of infections.

- Specific; antilymphocyte or antithymocyte globulins (ALG & ATG), ciclosporin, and androgens.
- Allogenic SCT is the curative treatment especially indicated in severely affected young patients.

FANCONI ANEMIA (FA)

- Group of congenital disorders characterized by association of growth retardation and skeletal anomalies in addition to AA.
- Consists of about 13 different gene abnormalities
- Usually presented at age of 5-10 years old
- AML may develop.
- The treatment usually by androgen and/or SCT.



شكراً جزيلاً

Thank
You
Merci
Gracias
Takk
aDank
BarakAllahuFiik
Mèsi
Chokrane
Kiitos
Xièxie
Dziakuju
Grazzi
TapadhLeat
Koszonom
Murakoze
WaadMahadsantahay
Buznyg
ThintKo
Blagodaram
Rahmat
Matondo
Mercé
TerimaKasih
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Tenki
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Barkal
GratiasAgimus
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