CHRONIC MYELOPROLIFERATIVE NEOPLASMS

- Clonal hematopoietic stem cell disorder
- Proliferation of one or more myeloid cell lineages
- Normal differentiation with increased cell proliferation –excess of maturing and mature cells
- Progress to bone marrow failure/acute leukemia

- Relative predominance of any one series

wbc- CML

Rbc- PCV

platelet- ET

FEATURES COMMON TO CMPN

- Increased Proliferative Drive In The Bone Marrow
- Homing Of Neoplastic Stem Cells To Secondary Hematopoietic Organs- **Extramedullary Hematopoiesis**
- Transformation To Spent Phase- Myelofibrosis And Pb Cytopenias
- Transformation To Acute Leukemia

CLASSIFICATION -WHO

- **Chronic myelogenous leukemia(CML)**
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia
- **Polycythemia vera**
- Chronic idiopathic myelofibrosis
- **Essential thrombocythemia**
- CMD- unclassified

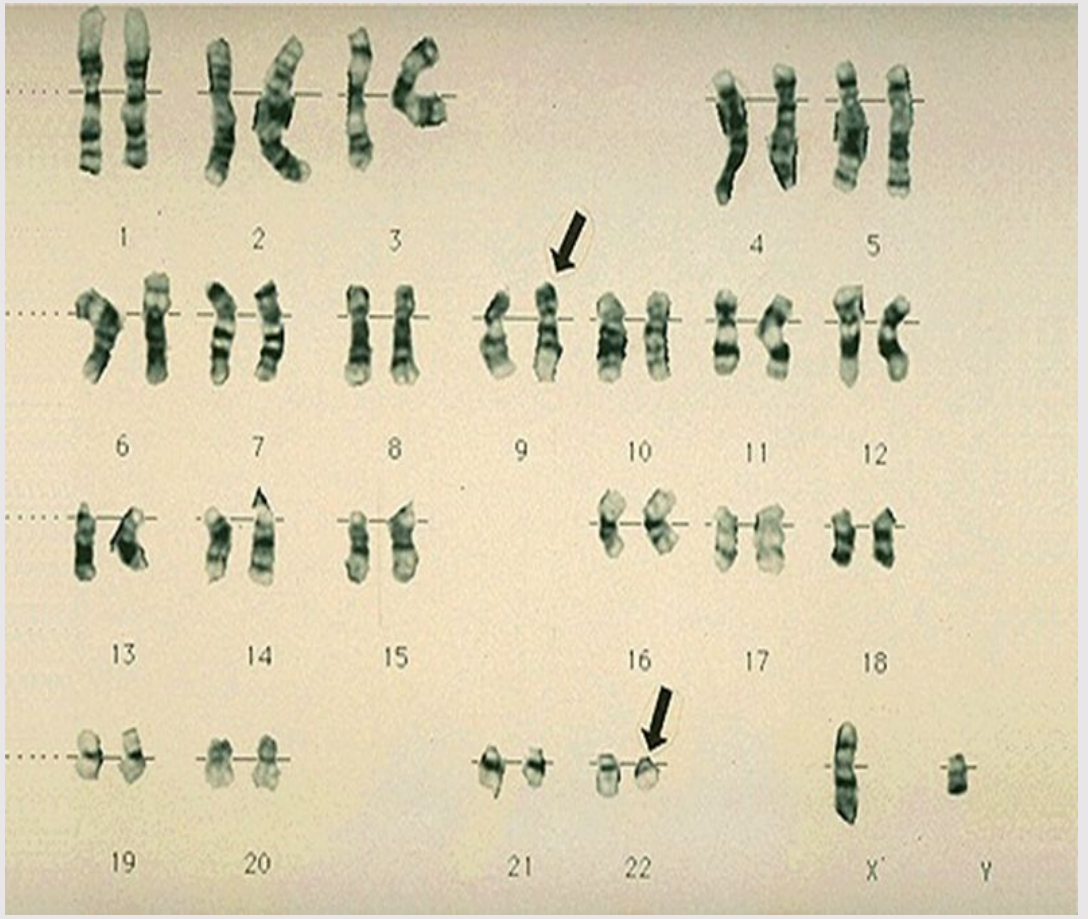
Chronic myelogenous leukemia

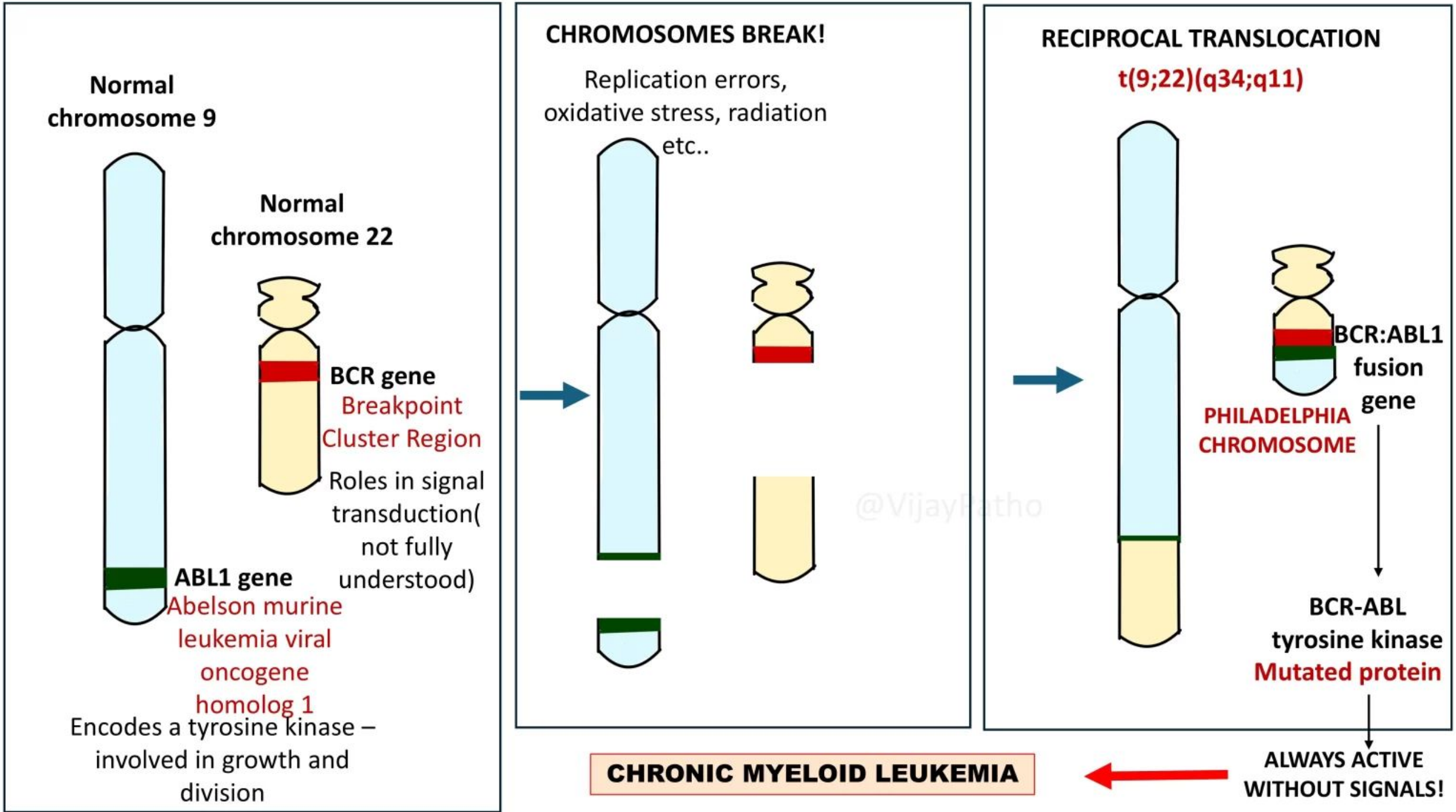
- Most common
- 1-1.5 cases per 1 lakh
- 5^{th}-6^{th} decade , peak 65 yrs
- Males

ETIOLOGY

- Exact aetiology- not known
- VARIOUS FACTORS- CHROMOSOMAL ABERRATIONS OF Ph CHROMOSOME
- Ionising radiation
- HLA CW3,HLA CW4

Translocation t(9;22)(q34;q11)




Normal chromosome 9
Normal chromosome 22
BCR gene
Breakpoint Cluster Region
Roles in signal transduction(not fully understood)
ABL1 gene
Abelson murine leukemia viral oncogene homolog 1
Encodes a tyrosine kinase – involved in growth and division
CHROMOSOMES BREAK!
Replication errors, oxidative stress, radiation etc..
RECIPROCAL TRANSLOCATION
t(9;22)(q34;q11)
BCR:ABL1 fusion gene
PHILADELPHIA CHROMOSOME
BCR-ABL tyrosine kinase
Mutated protein
ALWAYS ACTIVE WITHOUT SIGNALS!
CHRONIC MYELOID LEUKEMIA

PATHOGENESIS

- Genetic translocation – Reciprocal translocation b/w Ch 9:22
- BCR/ABL **chimeric fusion gene** – Philadelphia chromosome
- Mutation and activation of **tyrosine kinases**
- aberrations in downstream signalling pathway (like JAK/STAT, RAS/MEK) –uncontrolled cell growth, division, and increased survival
- **Clonal Expansion & Impaired Maturation-** growth factor independence
- Fibrosis – due to PDGF , TGF released by megakaryocytes & other cells

PHILADELPHIA CHROMOSOME

- Genetic abnormality on **Chromosome 22**
- Unusually short chromosome 22 (Ph chromosome) and unusually long chromosome 9 due to Reciprocal translocation b/w Chr 9 & 22
- t (9;22)
- Movement of ABL gene on Chr 9 to BCR gene on Chr 22 producing a fusion gene called BCR-ABL1 gene.
- The translocation produces abnormal protein called p210 or p190.
- Expressed in all blood cells except in T lymphocytes & few B cells.
- 2-5% of child ALL, 25% of adult ALL & some AML are also Ph Positive.

MORPHOLOGY

- Chronic phase – massive leukocytosis
  blasts<5%

- Blast transformation – blast >20 %

BLOOD PICTURE

- Moderate anaemia: 8 to 11 gm/dl
- Markedly elevated WBC count with full spectrum.

  Counts up to 500 X 10^9 /L

  myelocyte bulge -20-40%

  basophilia

  eosinophilia
- Myeloblasts < 5%.
- PLT count may be normal, decreased or increased.
- Decreased LAP score. (Increased in Leukemoid rn.)

PERIPHERAL BLOOD PICTURE

- **Rbc** normochromic normocytic or hypochromic microcytic

  Polychromatic cells and nucleated red cells.

- **WBC** count markedly elevated with significant shift to left.

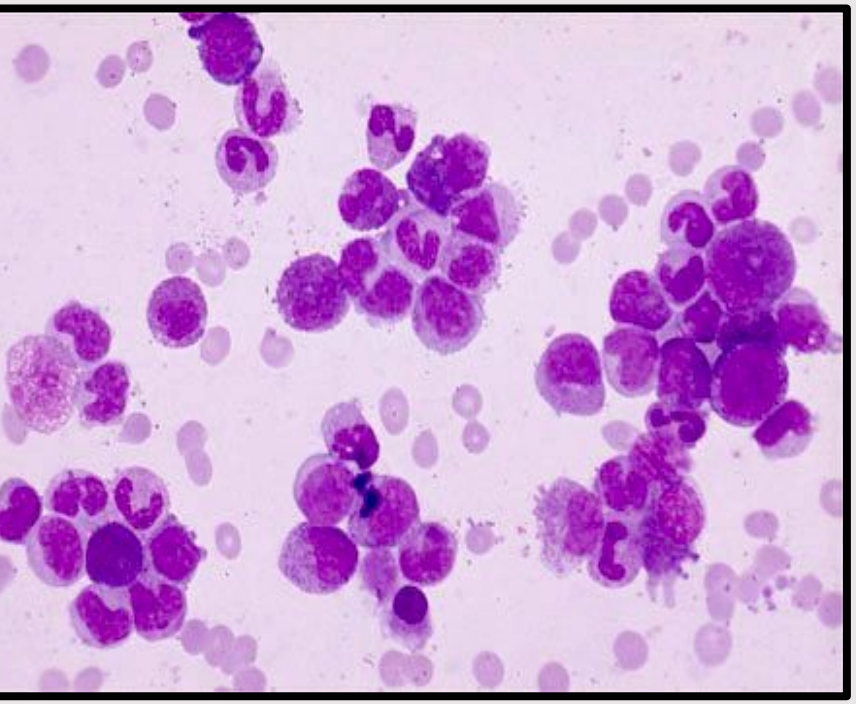
  Segmented neutrophils & myelocytes constitute majority of cells.

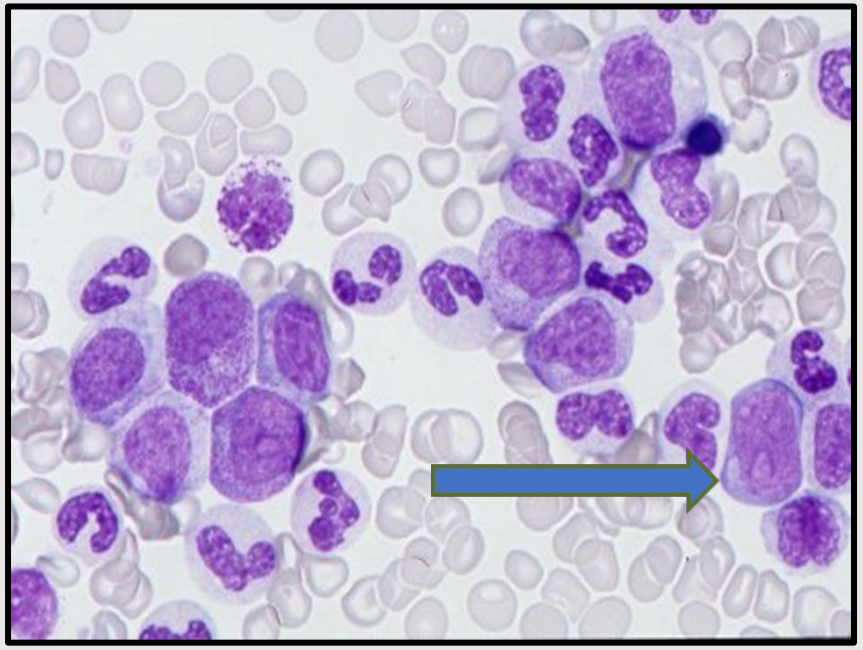
  Monocytes, Basophils, eosinophils are also increased.

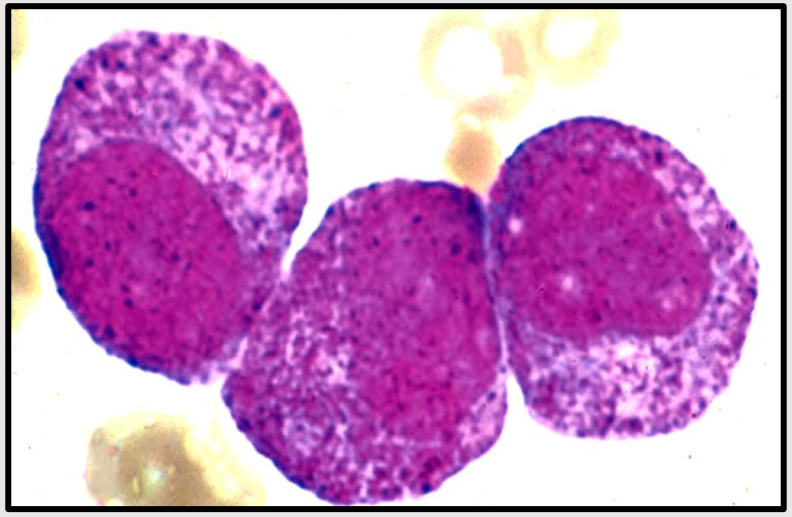
  Basophilia & eosinophilia.

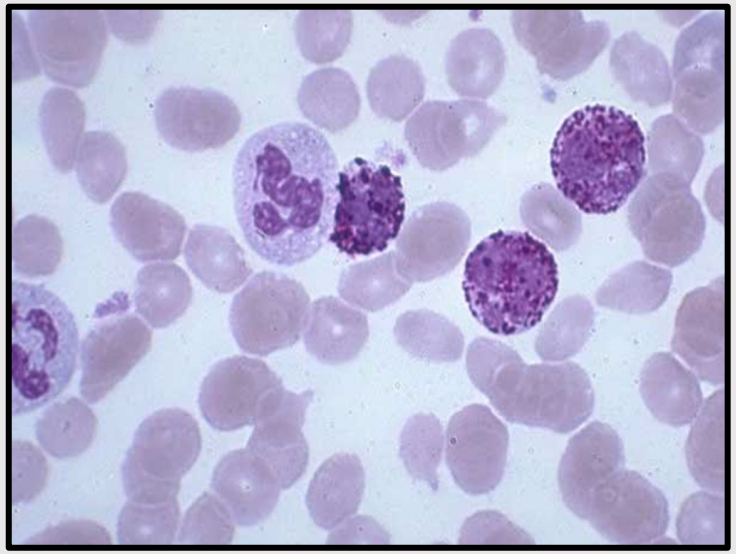
- **Platelets** normal or increased.

PERIPHERAL BLOOD PICTURE





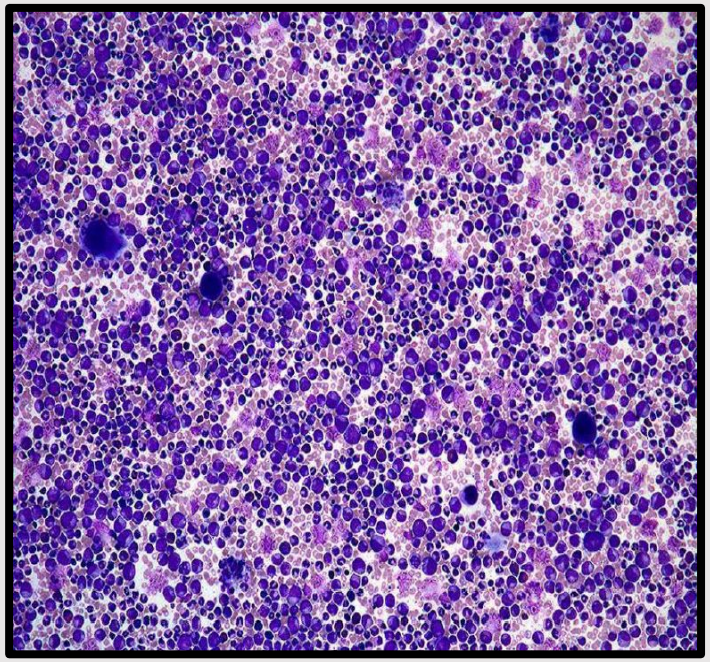


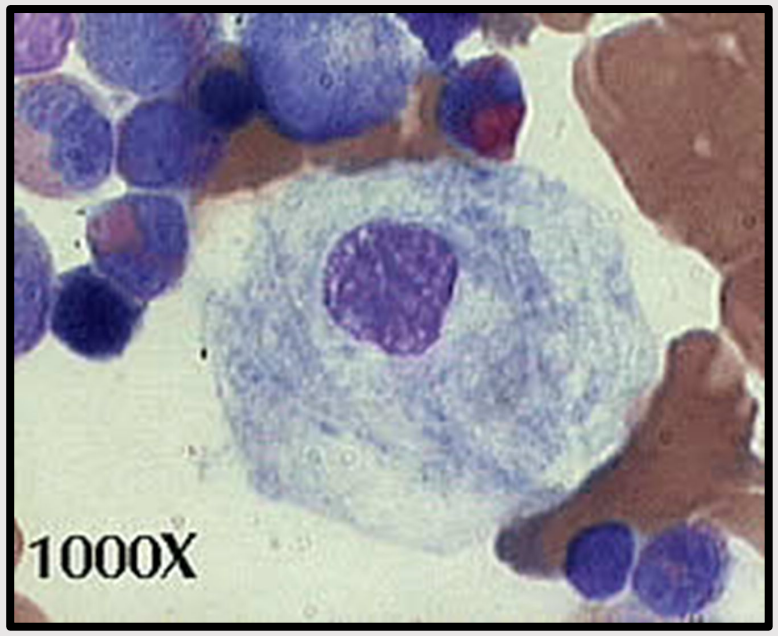


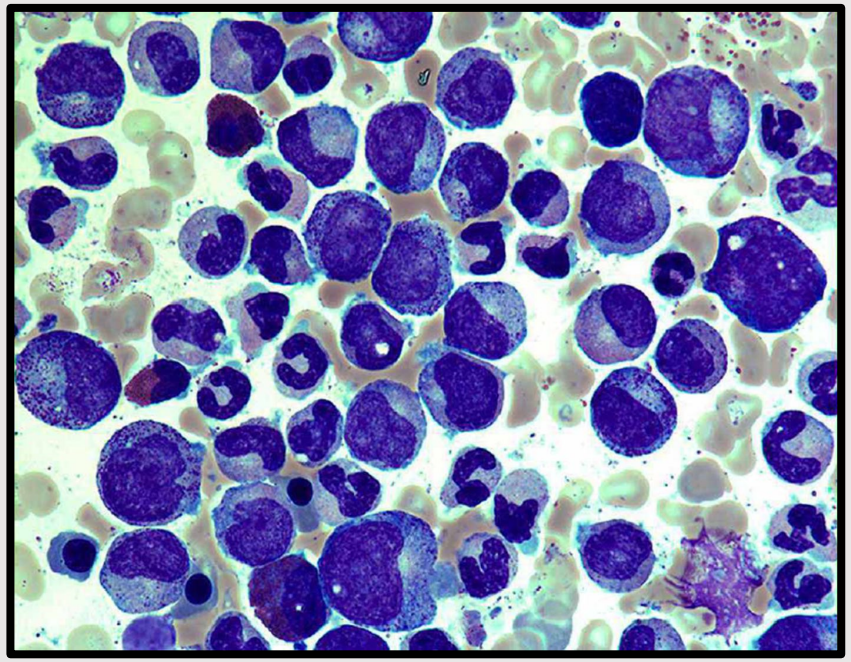
Bone marrow findings

- Hypercellular
- Marked M:E ratio 15:1 to 32:1
- Proliferation of neutrophilic precursors
- Eosinophilic and basophilic precursors increased
- Blast <5%
- MK- hyperplasia- **dwarf** MK
- Erythropoiesis – decreased
- Pseudo –Gaucher cells/sea blue histiocytes

Bone marrow findings







Lab Investigations

- Routine –Hb N/↓, TC & Platelet - Markedly increased
- Peripheral blood
- Bone-marrow aspiration/ biopsy
- Cytogenetic analysis(Karyotyping)-Ph chromosome
- FISH
- RT-PCR
- LAP score

BLAST TRANSFORMATION

- Blasts >/=20 % in peripheral blood
- Extra medullary blast proliferation(granulocytic sarcoma)
- Large foci of blasts in BM
- Anaemia + thrombocytopenia

CLINICAL FEATURES

- Weakness, fatigability, weight loss, tiredness, anorexia
- Dragging sensation in the abdomen, luq pain
- Mild to moderate anemia
- Visual disturbances and venous thrombosis
- Pallor
- Hepatoslenomegaly
- Priapism
- Sternal tenderness

Differential diagnosis

LEUKEMOID REACTION

Blood picture resembling leukemia in a person who doesn’t have leukemia

TLC can go upto 1 lac;myelocytes and even myeloblast can be seen

Types- myeloid and lymphoid

Causes

- Bacterial infection
- Pertussis
- IMN
- CMV
- TB
- a/c hemolytic anaemia
- Malignancy

Differential diagnosis

PS: absence of eosinophilia and basophilia

BM- fat spaces maintained

NAP score ▲▲▲

Molecular study: absence of bcr-abl fusion gene

DIFFERENTIAL DIAGNOSIS

- Myeloid Leukemoid Reaction

Particulars	CML	Leukemoid Reaction
Age	Adults	Any Age
Cause	Neoplastic	Infection
Biochemical	Low LAP Score	High LAP Score
Peripheral Blood	WBC count- markedly elevated Nucleated RBC- ++ Blast 0-2% E&B ++ Platelets- Increased	WBC count- moderately elevated Nucleated RBC- +/- Blast 0% E&B-Nil Platelets- Normal

Treatment

- Imatinib, dasatinib, nilotinib – TKI ;bcr-abl TK inhibited
- Alpha interferon
- Hydroxyurea
- Busulphan

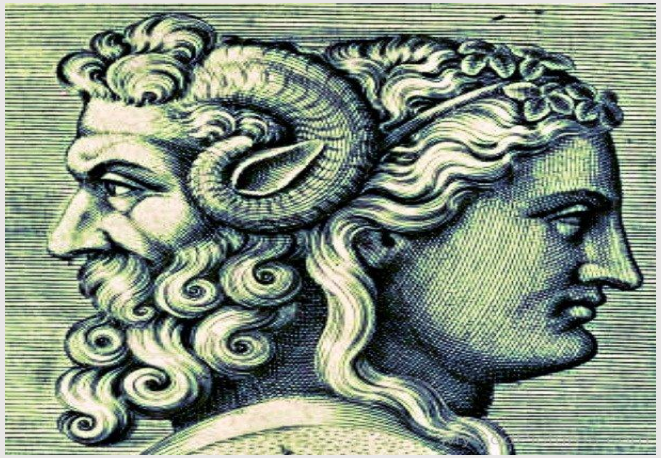
- Bone marrow transplantation

ESSENTIAL THROMBOCYTHEMIA

- Clonal MPN characterized by marked megakaryocytic hyperplasia with resultant thrombocytosis >4.5 lac/cumm

Cytogenetics/pathogenesis

- JAK2 /JAK-STAT mutations in 50% of cases



- Other causes of reactive thrombocytosis to be excluded

- Can progress to acute leukemia or myelofibrosis

Clinical features

- 50-60 years
- M=F
- Painful burning sensation of soles and toes ,pain aggravated on standing/warming
- Arterioles occluded by platelets- late stage gangrene
- Mild to moderate splenomegaly
- Hepatomegaly

- Portal vein thrombosis
- Retinal artery occlusion
- MI
- Pulmonary embolism
- Headache, vertigo

Lab findings

- BRE- thrombocytosis

  mild leukocytosis
- PS- giant /agranular platelets

  size variation- microthrombocyte,bizarre forms

  mild eosinophilia/basophilia

  neutrophilia with mild STL

  NC NC RBC

Bone marrow

- Normocellular with marked MK hyperplasia
- MK clusters
- Giant MK – characteristic
- MK in sinusoids and paratrabecular area

Polycythemia vera

- Clonal MPN with increased red cells , blood volume and splenomegaly
- JAK-STAT mutation in 95% cases
- Panmyelosis with associated thrombocytosis and leucocytosis

Phases

- Pre polycythemic phase
- Overt polycythemic phase
- spent/myelofibrosis phase

Clinical feature

- M>F
- Old age (55-80 yrs)
- Ruddy skin of face
- Intense itching
- Thrombosis/claudication
- Portal vein /splenic vein thrombosis
- Budd chiari s/d

Lab diagnosis

- Hb- 18-24 g/dl
- RBC count- 6.5- 10 million/cumm
- PCV->55 %
- PS-NCNC RBC

  nucleated RBC

- WBC- 20000-50000
  mild STL
- NAP increased
- PLT- 5-9 Lacs/cumm
- ESR- decreased
- S.EPO- decreased
- BM- hypercellular

Chronic Lymphocytic Leukemia

CHRONIC LYMPHOCYTIC LEUKEMIA

- Elderly age
- Exclusively a disease of older adults. Rarely below the age of 40 yrs.
- Defect in the committed stem cell.
- Counterpart lymphoma in tissue is SLL.
- Splenomegaly, Hepatomegaly.
- Common B cell (CD5 +ve)
- More common in Males

CHRONIC LYMPHOCYTIC LEUKEMIA

- Anemia, fever & bleeding – slow over years.
- Lymphocytosis & Lymphadenopathy
- Absolute lymphocytosis >5k / cumm
- Lymphadenopathy is common.
- Incidental finding on PS examination.
- Small round B lymphocytes — blood, bone marrow & lymph nodes

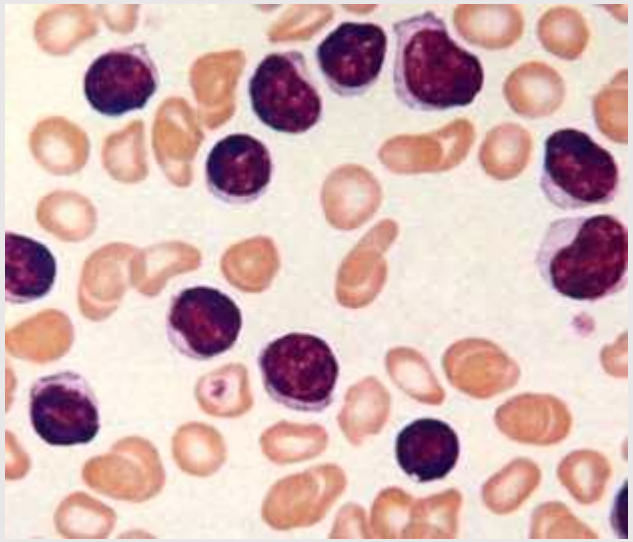
PERIPHERAL BLOOD FINDING

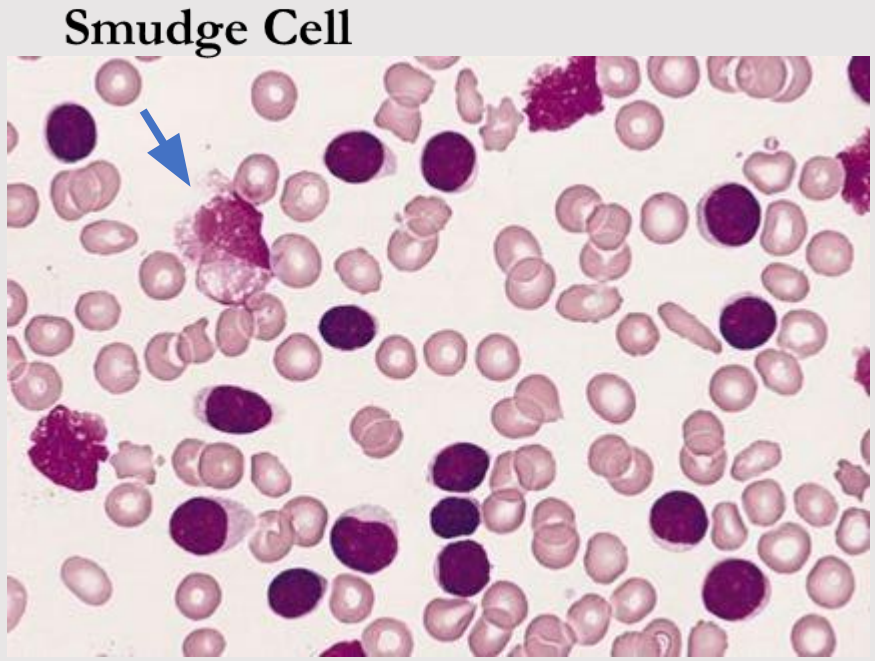
- Monotonous population of Lymphoid cells
- Have scant cytoplasm, small round nuclei with condensed chromatin and inconspicuous nucleoli
- SMUDGE Cells – Fragile leukemic cells with disrupted cytoplasm and consists largely of nuclear material only

MARROW FINDINGS

- Lymphocytes > 30% of all cells in BM smears
- Morphology similar to PS lymphoid cells
- BM trephine show 3 patterns of infiltration
  1. Focal
  2. Interstitial
  3. Diffuse

PERIPHERAL BLOOD PICTURE





CLINICAL COURSE

- Can transform to High grade Neoplasm
- Pro-Lymphocytic transformation
  - Small B-cells are transformed to pro-lymphocytes
  - Cells with moderate basophilic cytoplasm, coarse chromatin and prominent single nucleoli
- Richter syndrome
  - Transformation to DLBCL

DIFFERENTIAL DIAGNOSIS

- Lymphoid Leukemoid Reaction

Particulars	CLL	Lymphoid Leukemoid Reaction
Age	Older Adults	Any Age
Cause	Neoplastic	Infective- Tuberculosis and Pertussis
Peripheral Blood	WBC count- markedly elevated Nucleated RBC- +/- Monotonous population of Lymphoid cells	WBC count- moderately elevated Nucleated RBC- +/- Heterogenous population of Lymphoid cells