THE CHRONIC LEUKEMIAS

CHRONIC LYMPHOID LEUKEMIA
CHRONIC MYELOID LEUKEMIA

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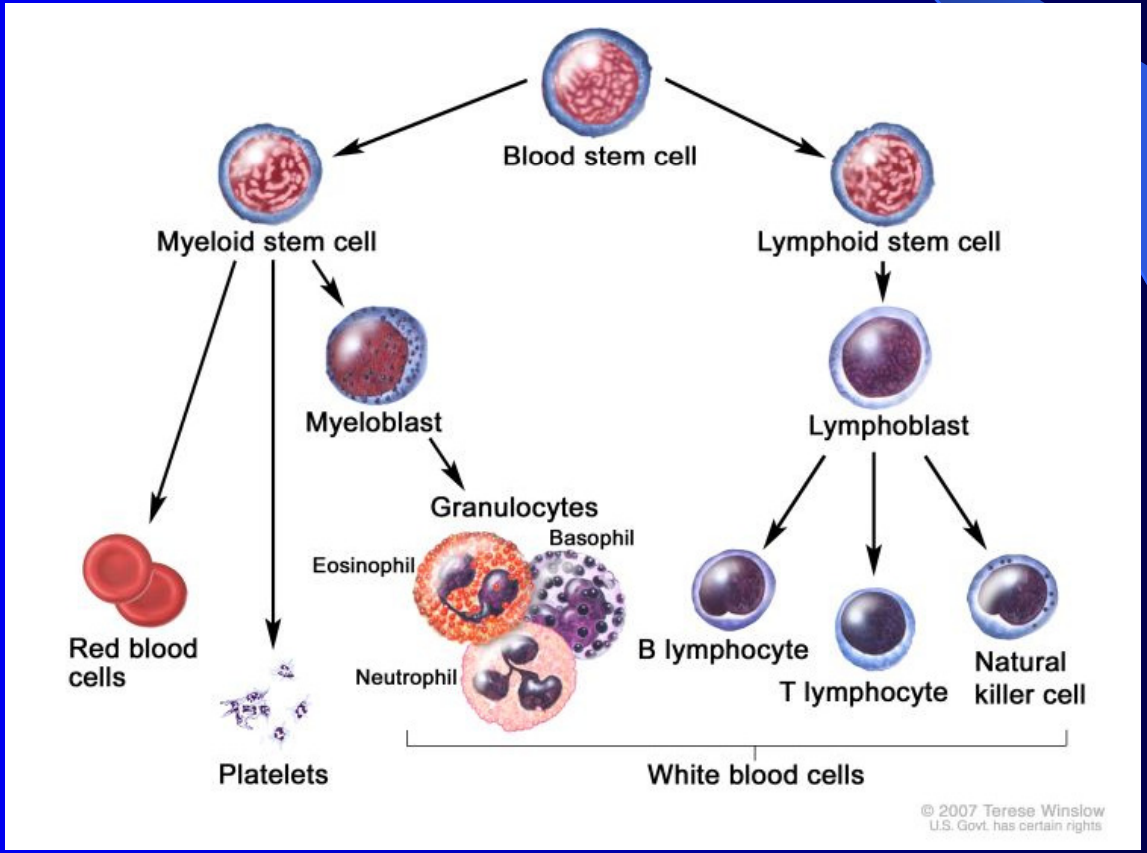
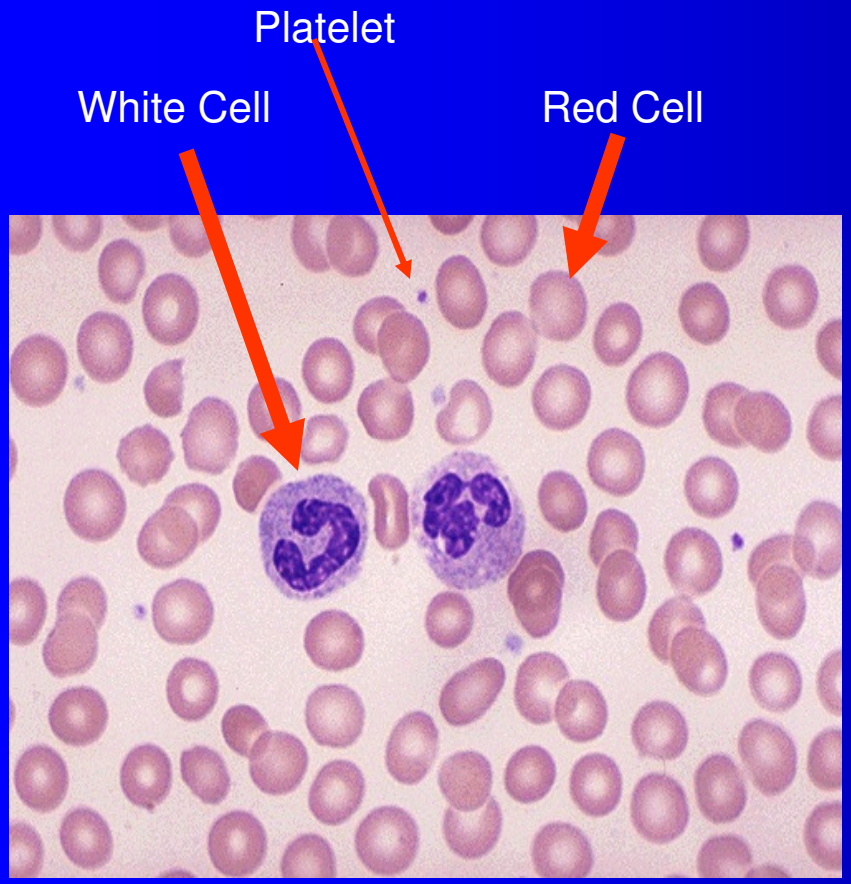
Lecturer

What are the Chronic Leukemias?

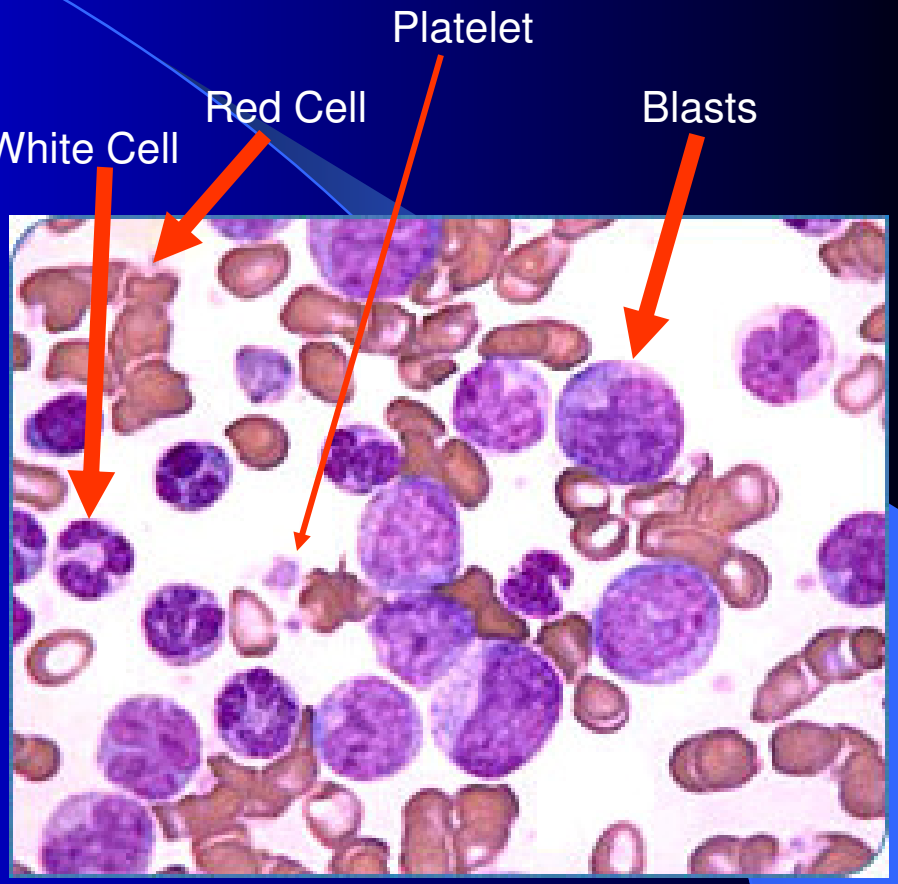
Neoplasms of either the myeloid or lymphoid lineage which are capable of differentiation to mature cells.



Pictures Of Blood



Normal human blood



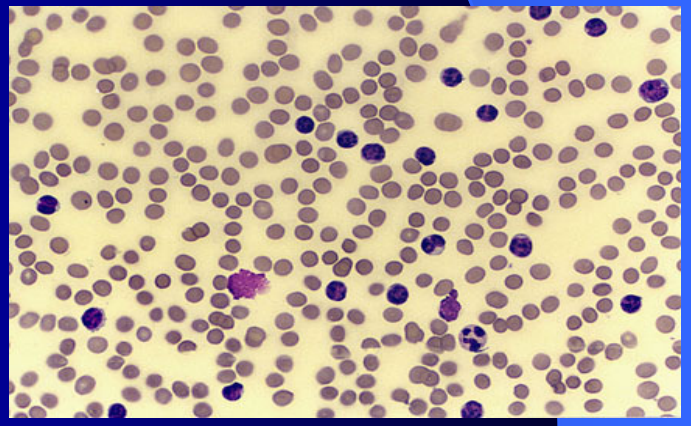
Blood with leukemia

Acute versus Chronic Leukemia

	White Cell Count	Chronic – maturation beyond blast
Acute	Low, normal or high	Blasts predominate if WBC high
Chronic	High	maximum 10% blasts

Chronic Lymphocytic Leukemia

- Monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes.
- Most common form of leukemia found in adults in Western countries
- Extremely rare in India, 1.95–8.8% of all leukemias.
- Sex: M > F, 1.7:1.
- Age: primarily affects elderly individuals, majority > 55 years.



Peripheral smear in CLL, small lymphocytic variety.

Pathophysiology

- The cells of origin in the majority of CLL are clonal B cells arrested in the B-cell differentiation pathway, intermediate between pre-B cells and mature B cells.
- Morphologically in the peripheral blood, these cells resemble mature lymphocytes.
- An abnormal karyotype is observed in the majority of patients with CLL.
- The most common abnormality is deletion of 13q, >50%

Mortality / Morbidity

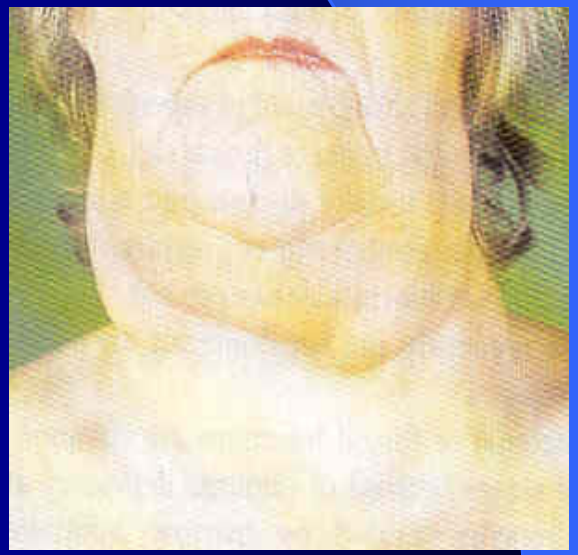
- The natural history is heterogeneous
- Some patients die rapidly, within 2-3 years of diagnosis
- The majority of patients live 5-10 years
- Initial course that is relatively benign but followed by a terminal, progressive, and resistant phase lasting 1-2 years.
- During the later phase, morbidity is considerable, both from the disease and from complications of therapy

History

- Onset is insidious
- 25-50% will be asymptomatic at time of presentation.
- Predisposition to repeated infections such as pneumonia, are most common presenting symptom, 87% of symptomatic at time of diagnosis.
- Early satiety and/or abdominal discomfort (enlarged spleen)
- Mucocutaneous bleeding and/or petechiae (thrombocytopenia)
- Tiredness and fatigue (anemia)
- Fevers, chills, night sweats, weight loss
- autoimmune hemolytic anemia (10 %)

Physical

- Localized or generalized lymphadenopathy (80-90%)
- Splenomegaly (30-54%)
- Hepatomegaly (10-20%)
- Petechiae
- Pallor



Causes

- Exact cause uncertain.
- Protooncogene bcl2 is known to be overexpressed, which leads to suppression of apoptosis in the affected lymphoid cells.
- Is an acquired disorder
- Reports of truly familial cases are exceedingly rare

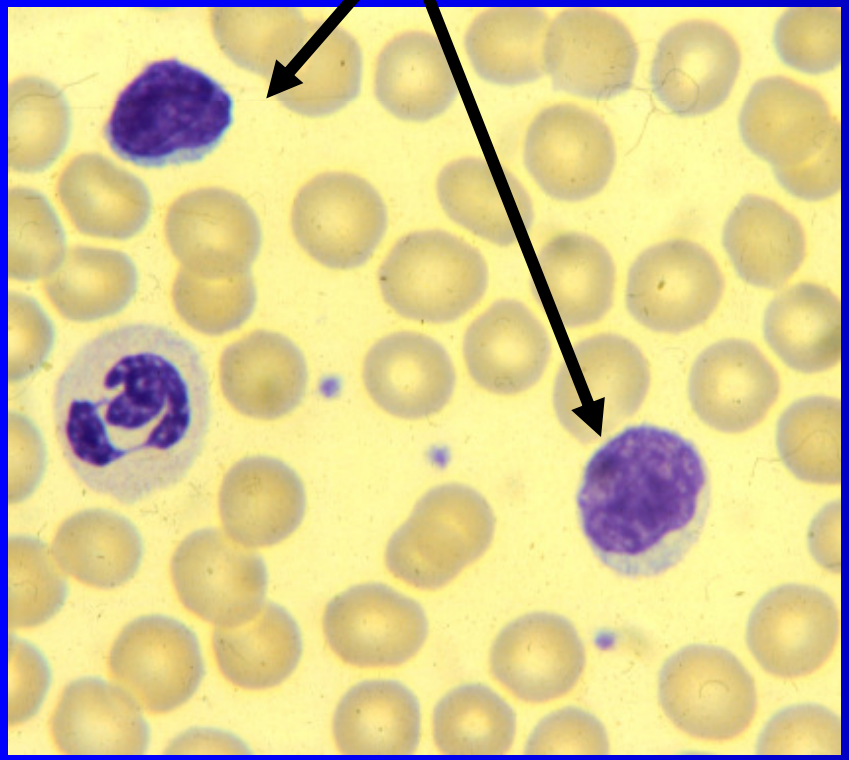
Laboratory Studies

- PBF to confirm lymphocytosis. It usually shows the presence of smudge cells, which are artifacts due to damaged lymphocytes during the slide preparation
- CBC show absolute lymphocytosis with more than 5000 B-lymphocytes/μL for longer than 3 months
- Large atypical cells, cleaved cells, and prolymphocytes are also often seen
- Peripheral blood flow cytometry is the most valuable test to confirm presence of circulating clonal B-lymphocytes

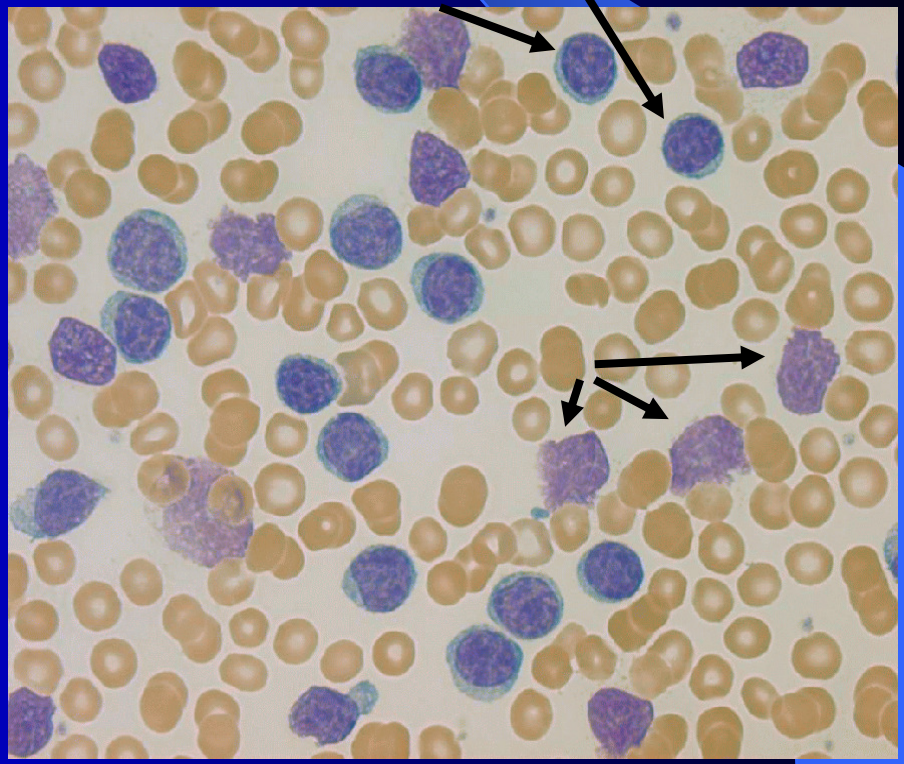
Normal

CLL

lymphocytes



lymphocytes



CLL - blood count

WBC x 10^9/L	150	[4-11]
Hb g/L	9.8	[12-16]
MCV fl	87	[79-98]
Platelets x 10^9/L	48	[150-450]
Neuts x 10^9/L	1.5	[2-7.5]
Lymphs x 10^9/L	130	[1.5-4]
Monos x 10^9/L	0.5	[0.2-0.8]
Eos x 10^9/L	-	[0-0.7]
Basos x 10^9/L	-	[0-0.1]
Smudge Cells x 10^9/L	28	[0]

lymphocytosis with smudge cells: appearances suggest CLL

- FISH can identify certain chromosomal abnormalities of CLL with prognostic significance.
- Deletion in the short arm of chromosome 17 tend to have a worse prognosis, as well as resistance to therapy with alkylating agents and purine analogues.
- Deletions in the long arm of chromosome 11 have a worse prognosis. May benefit from treatment with monoclonal antibody alemtuzumab.
- IgV_H status has shown potential as a prognostic marker for CLL

Procedures

- BMA & BMBx with flow cytometry is not required in all cases of CLL
- May be necessary in selected cases to establish the diagnosis
- LNBx if lymph nodes begin to enlarge rapidly in a patient with known CLL to assess the possibility of transformation to a high-grade lymphoma.
- When such transformation is accompanied by fever, weight loss, and pain, it is termed Richter syndrome.

Staging

Revised Rai-Sawitsky 3-stage system

divides patients into low-, intermediate-, and high-risk groups.

- Low risk – Lymphocytosis in the blood and marrow only
- Intermediate risk – Lymphocytosis with enlarged nodes in any site or splenomegaly or hepatomegaly
- High risk – Lymphocytosis with disease-related anemia or thrombocytopenia

Binet staging 3 stages system—Areas of involvement : head and neck lymph nodes (multiple sites counts as 1 area), axillary lymph nodes (bilateral counts as 1 area), inguinal lymph nodes (bilateral counts as 1 area), splenomegaly, and hepatomegaly.

- Stage A – Hb $\geq$ 10 g/dL, platelets $\geq$ 100 X 10^9/L, < 3 LN areas involved.
- Stage B – Hb and platelet as in stage A and $\geq$ 3 LN areas.
- Stage C – Hb < 10 g/dL or platelets < 100 X 10^9/L, or both.

- Patients with low risk or Binet A disease whose CLL is stable require only periodic follow-up.
- In multiple studies and meta-analysis, early initiation of chemotherapy has failed to show benefit, and it may increase mortality in patients with CLL.
- Treat with chemotherapy if the patient is symptomatic, or there is evidence of rapid progression of disease shown by:
  - Weight loss of >10% over 6 months
  - Extreme fatigue
  - Fever related to leukemia for > 2 weeks
  - Night sweats for > 1 month
  - anemia or thrombocytopenia
  - Autoimmune anemia or thrombocytopenia not responding to glucocorticoids
  - Progressive or symptomatic splenomegaly
  - Massive or symptomatic lymphadenopathy
  - Progressive lymphocytosis (inc of > 50% in 2 months or doubling time < 6 months)

- **Pentostatin** Inhibits adenosine deaminase that may inhibit DNA or RNA synthesis causing cell death.
- **Chlorambucil** Nitrogen mustard derivative with bifunctional alkylating activity, interfering with DNA replication and RNA transcription and translation.
- **Fludarabine** Nucleoside analogues is currently the most commonly used first-line therapy
- Fludarabine and cyclophosphamide combination has shown higher response rates
- **Lenalidomide** is an immunomodulatory drug utilized in treatment of patients with relapsed and refractory cases

Monoclonal Antibodies

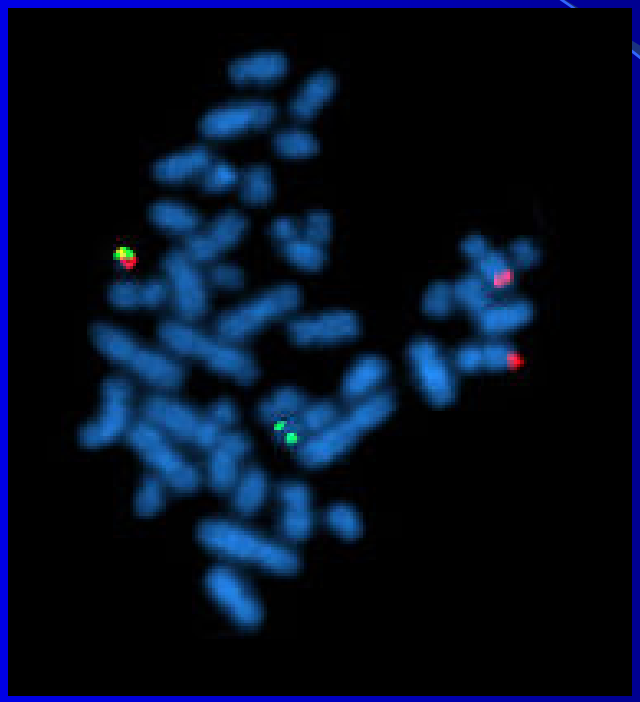
- **Alemtuzumab** directed at CD52; approved for use as both first-line agent and for in patients with fludarabine-refractory disease
- **Rituximab** directed at CD20; as single agent only partial responses of short duration; main role in combination chemotherapy.
- **Ofatumumab** Anti-CD20 inhibits B-cell activation in early stages. Indicated for cases refractory to fludarabine and alemtuzumab.

- **Bone marrow transplantation** has been investigated in the therapy of CLL.
- Allogenic stem cell transplantation is the only known curative therapy.
- Extremely high WBC counts (>300,000/μL) may produce a hyperviscosity syndrome with altered central nervous system function and/or respiratory insufficiency.
- Leukocytapheresis and urgent therapy with prednisone and chemotherapy may be required.

Complications

- Hypogammaglobinemia and impaired T-cell function associated with CLL predispose patients to potentially serious infections.
- Anemia / Thrombocytopenia secondary to bone marrow involvement with CLL, splenic sequestration of red blood cells, and autoimmune hemolytic anemia
- **Richter syndrome** refers to the transformation of CLL into an aggressive large B-cell lymphoma (3-10% of cases).
- Patients often present with symptoms of weight loss, fevers, night sweats, muscle wasting, and increasing hepatosplenomegaly and lymphadenopathy.
- Lymph node biopsy is necessary for the diagnosis.
- Epstein-Barr virus/ Immunosuppression may play a role in transformation.

Chronic myeloid leukemia



The Philadelphia chromosome as seen by metaphase FISH

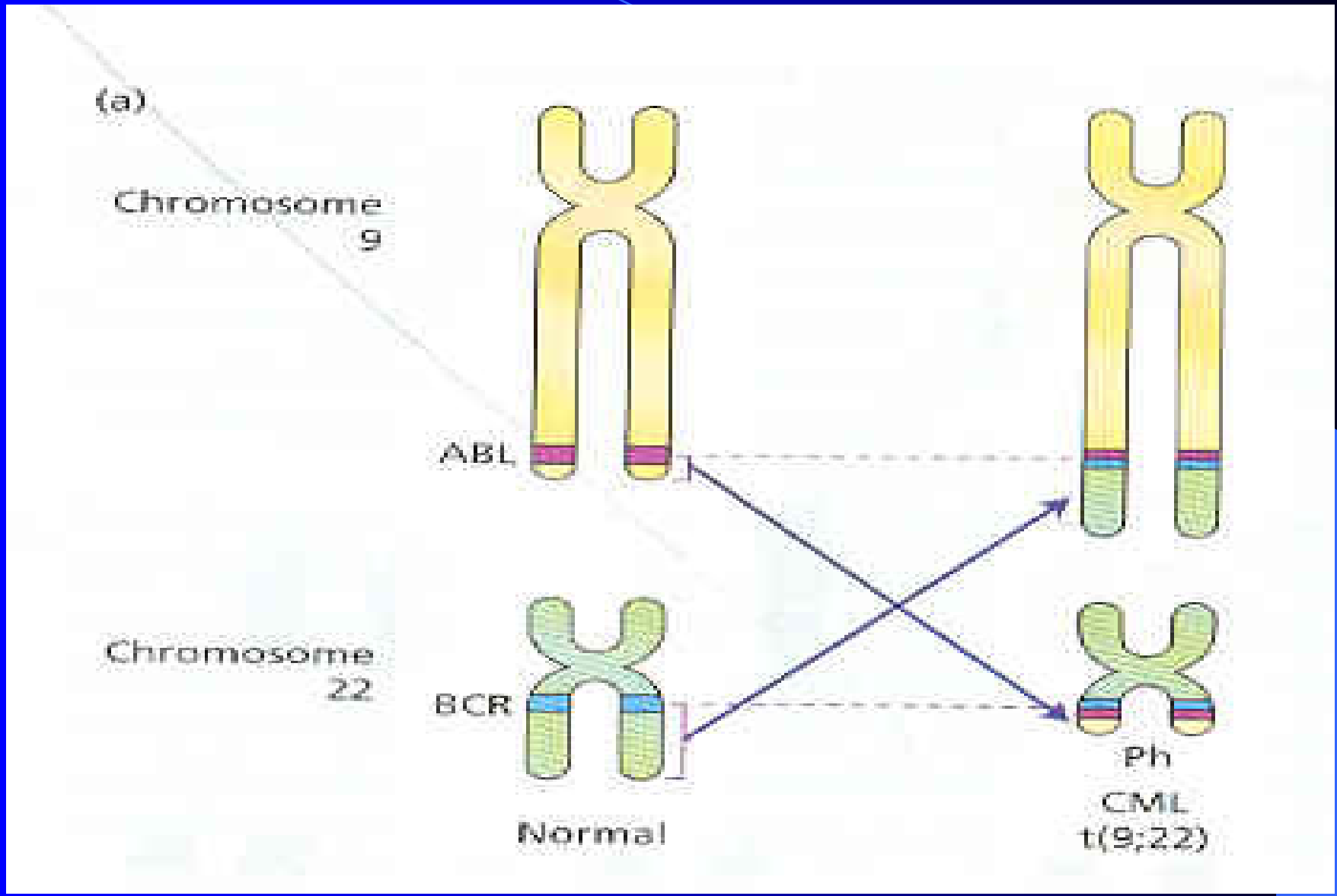
Chronic myeloid leukemia

- Myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate.
- Consequently, the peripheral blood cell profile shows an increased number of granulocytes and their immature precursors, including occasional blast cells.
- It is the commonest type of leukemia seen in India, accounting for 30% of all leukemia cases.
- It typically affects middle-aged individuals.
- *CAUSE: Unknown, exposure to irradiation, benzene*

Pathophysiology

- Acquired abnormality that involves hematopoietic stem cell.
- Characterized by a cytogenetic aberration consisting of a reciprocal translocation between the long arms of chromosomes 22 and 9; t(9;22). The translocation results in a shortened chromosome 22
- This translocation relocates an oncogene called abl from the long arm of chromosome 9 to the long arm of chromosome 22 in the BCR region. The resulting BCR/ABL fusion gene encodes a chimeric protein with strong tyrosine kinase activity.
- The expression of this protein leads to the development of the CML phenotype
- It is considered diagnostic when present in a patient with clinical manifestations of CML.

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



General course

- Most patients with CML present in chronic phase, characterized by splenomegaly and leukocytosis with generally few symptoms.
- This phase is easily controlled by medication.
- After an average of 3-5 years, CML usually evolves into blast crisis, marked by increase in bone marrow or peripheral blood blast count or by development of soft-tissue or skin leukemic infiltrates. Manifestations of blast crisis are similar to acute leukemia. Treatment results are unsatisfactory, and most patients succumb to the disease once this phase develops.
- In many patients, an accelerated phase occurs 3-6 months before the diagnosis of blast crisis. Clinical features in this phase are intermediate between the chronic phase and blast crisis.

History

- Manifestations - insidious and often discovered incidentally (CBC/ SPLEEN)
- Tiredness, fatigue, weight
- Patients often have symptoms related to enlargement of the spleen, liver, or both.
  - early satiety and decreased food intake, left upper quadrant abdominal pain
- Some may have low-grade fever and excessive sweating related to hypermetabolism

Physical

- Splenomegaly is the most common physical finding
  - Size of spleen correlates with peripheral blood granulocyte counts with largest spleens being observed in patients with high WBC counts.
- Hepatomegaly, usually part of extramedullary hematopoiesis occurring in spleen, occurs less commonly .
- Physical findings of leukostasis and hyperviscosity can occur in some patients, with WBC counts exceeding 300,000-600,000 cells/μL.
- Upon funduscopy, the retina may show papilledema, venous obstruction, and hemorrhages.

Diagnosis

- The diagnosis of CML is based on the histopathologic findings in the peripheral blood and the Ph1 chromosome in the bone marrow cells.
- Peripheral blood findings in patients with CML show typical leukoerythroblastic blood picture, with circulating immature cells from the bone marrow
- Increase in mature granulocytes and normal lymphocyte counts results in a total WBC count of 20,000-60,000 cells/μL.
- Mild increase in basophils and eosinophils is present and becomes more prominent during the transition to acute leukemia.
- These mature granulocytes, have decreased apoptosis resulting in cells with low or absent ALP

Diagnosis

- Early myeloid cells such as myeloblasts, myelocytes, metamyelocytes, and nucleated red blood cells are commonly present in the blood smear.
- The presence of the different midstage progenitor cells differentiates this condition from the acute myelogenous leukemias, in which a leukemic gap (maturation arrest) or hiatus exists that shows absence of these cells.
- Mild to moderate anemia (normochromic & normocytic)
- The platelet counts at diagnosis can be low, normal, or even increased

CML - blood count

WBC x 10^9/L	122	[4-11]
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Platelets x 10^9/L	843	[150-450]
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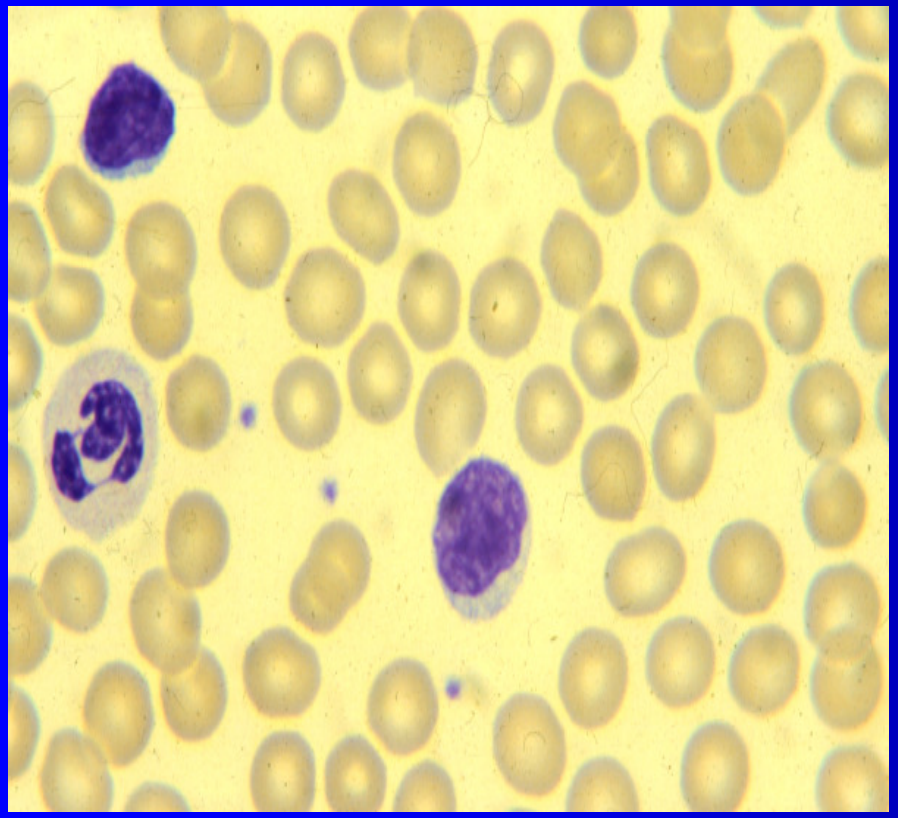
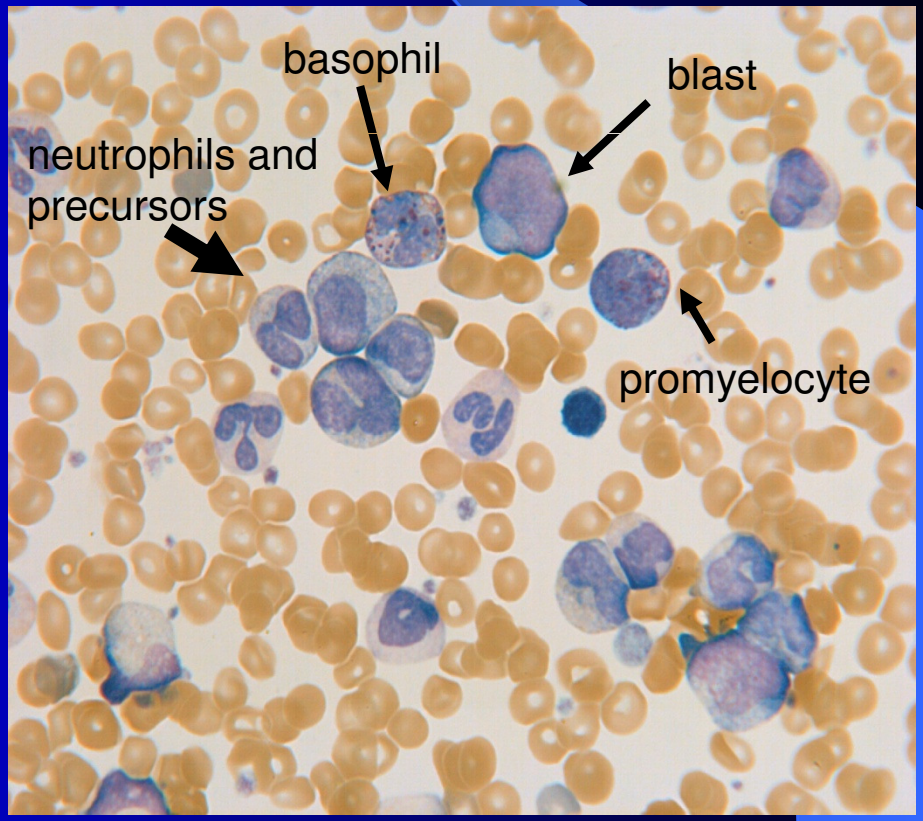
Eos x 10^9/L	1.0	[0-0.7]
Basos x 10^9/L	5.0	[0-0.1]
Metamyelocytes x 10^9/L	4.0	[0]
Myelocytes x 10^9/L	20.0	[0]
Promyelocytes x 10^9/L	4.0	[0]
Blasts x 10^9/L	2.0	[0]
Nucleated red cells x 10^9/L	2.0	[0]

Film Comment: *appearances suggest CML*

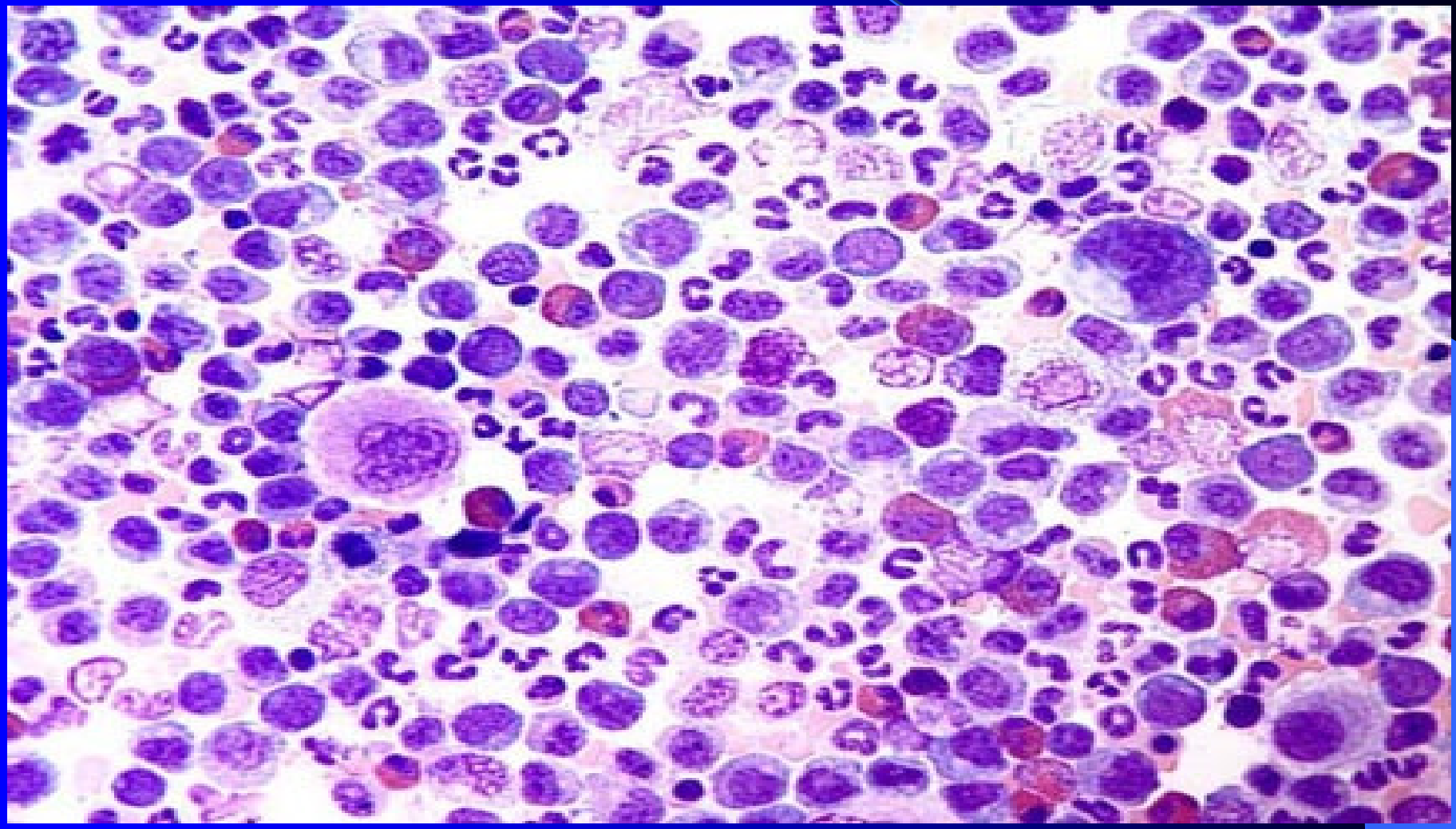
Normal

CML





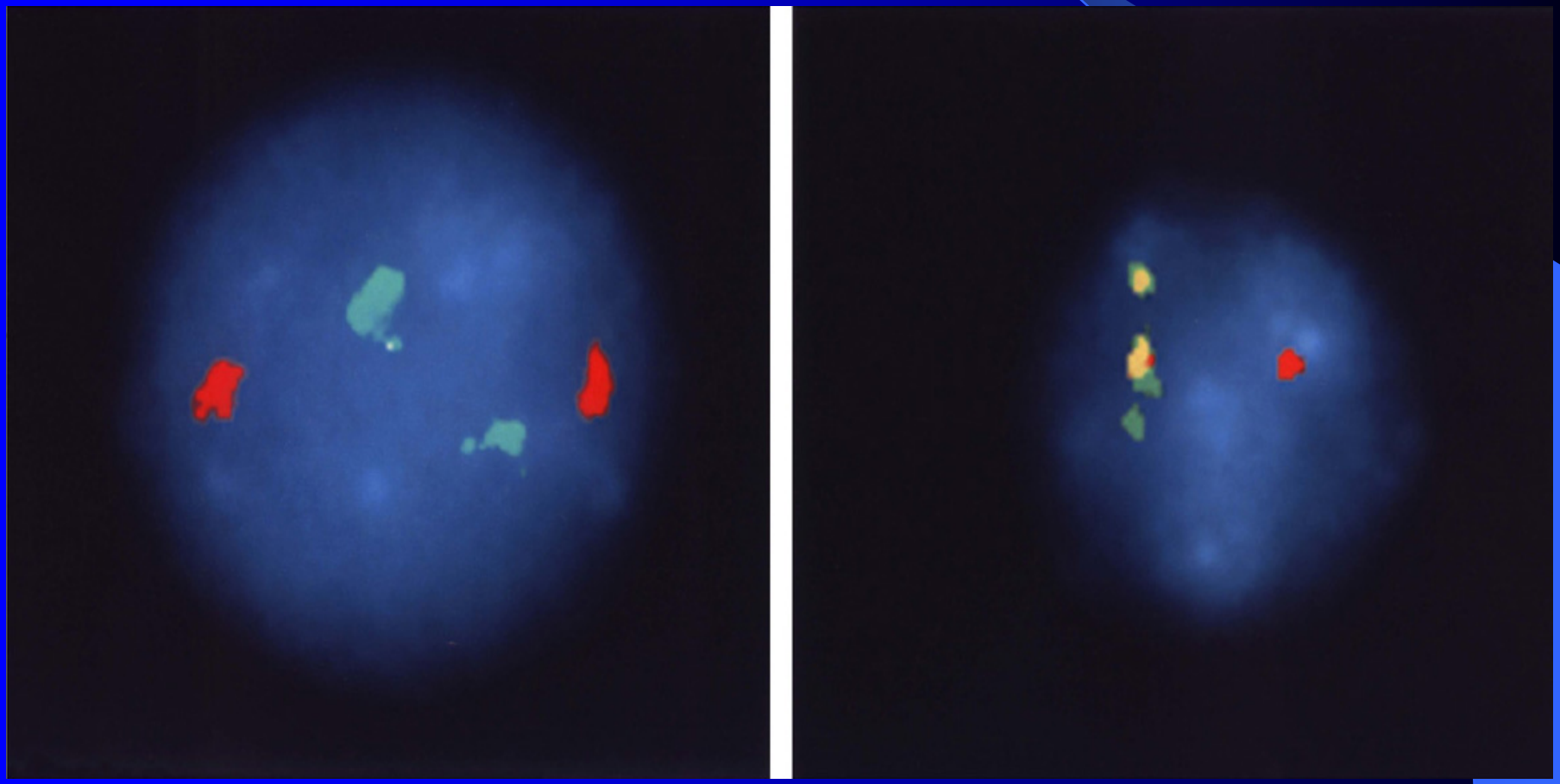
Bone marrow is hypercellular, clear dominance of granulopoiesis and its progenitor cells.
Megakaryocytes are prominent and may be increased.



Fluorescence in situ hybridization (FISH) uses labeled probes that are hybridized to either metaphase chromosomes or interphase nuclei, and the hybridized probe is detected with fluorochromes.

Using unique-sequence, double-fusion DNA probes for bcr (22q11.2) in red and c-abl (9q34) gene regions in green.

The abnormal bcr/abl fusion present in Philadelphia chromosome–positive cells is in yellow (right panel) compared with a control (left panel).



Accelerated phase (WHO criteria)

The patient is considered to be in the accelerated phase if any of the below are present.

- *10–19% myeloblasts in the blood or bone marrow*
- *>20% basophils in the blood or bone marrow*
- *Platelet count <100,000, unrelated to therapy*
- *Platelet count >1,000,000, unresponsive to therapy*
- *Cytogenetic evolution with new abnormalities in addition to the Philadelphia chromosome*
- *Increasing splenomegaly or white blood cell count, unresponsive to therapy*

Blast crisis

Blast crisis is diagnosed if any of following are present

- *>20% myeloblasts or lymphoblasts in the blood or bone marrow*
- *Large clusters of blasts in the bone marrow on biopsy*
- *Development of a chloroma (solid focus of leukemia outside the bone marrow)*

Positive for the Ph chromosome

- Acute lymphocytic leukemia
- Non lymphocytic leukemia
- Polycythemia vera
- Essential thrombocythemia
- Myelodysplastic syndrome

3-fold goals

- 1) to achieve a hematologic remission
- *normal CBC count and physical examination*
- 2) to achieve cytogenetic remission
- *normal chromosome returns with 0% Ph-positive cells*
- 3) to achieve molecular remission
- *negative PCR result for mutational BCR/ABL m-RNA*

- **Hydroxyurea**
- DOC for inducing hematologic remission in CML.
- **Busulfan**
- Potent cytotoxic drug causes profound myelosuppression.
- **Imatinib mesylate**
- inhibit tyrosine kinase activity of bcr-abl kinase in Ph-positive leukemia. DOC for maintenance
- **Dasatinib, Nilotinib**
- Multiple tyrosine kinase inhibitor. indicated for resistant to or intolerant of imatinib
- **Interferon alfa-2a or alfa-2b**
- inhibit propagation of Ph-positive hematopoietic clone, allowing return of normal cells in bone marrow

- For patients with chronic-phase CML, imatinib at 400 mg/d is the best candidate for primary therapy, because it induces a complete hematologic response in almost all patients and causes a high cytogenetic response rate. 2-year survival rate of 60%.
- Allogeneic BMT is currently the only proven cure for CML.
- Transplantation has been relegated to patients who do not achieve molecular remissions or show resistance to imatinib and failure to second-generation inhibitors such as dasatinib.
- BMT should be considered early in young patients (<55 y) who have a matched sibling donor
- Favorable results of vaccination were reported with the BCR/abl p210 fusion protein in patients with stable disease

Monitoring

- CBC, cytogenetics (or FISH), and quantitative RT-PCR for BCR/ABL mRNA.
- The more sensitive tests are done when the previous less sensitive tests become negative (cytogenetics and FISH)

The standard therapeutic milestones to be achieved in the patients are

(1) a complete hematologic response (normal CBC and no evidence of extramedullary disease) at 3 months,

(2) a minor cytogenetic response (36% to 65% Ph+) at 6 months,

(3) a major cytogenetic response (0% to 35% Ph+) at 12 months, and

(4) a complete cytogenetic response (0% Ph+) at 18 months.

Prognosis

Poor prognosis is associated with:

- older age
- symptomatic presentation
- poor performance status
- hepatomegaly, splenomegaly
- negative Ph chromosome or BCR/ABL,
- anemia, thrombocytopenia, thrombocytosis
- decreased megakaryocytes, basophilia, or myelofibrosis
- longer time to hematologic remission with therapy
- short duration of remission
- poor suppression of Ph-positive cells by chemotherapy or interferon


Thank You