# Presentation

of

CML

## Presented By

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# CHRONIC MYELOID LEUKEMIA (CML)

- **Chronic myeloid leukemia** (**CML**), also known as **Chronic myelogenous leukemia**, is a cancer of the white blood cells.

- It is a form of leukemia characterized by the increased and unregulated growth of myeloid cells in the bone marrow and the accumulation of these cells in the blood

# CML

**CML is a clonal bone marrow stem cell disorder in which a proliferation of mature granulocytes neutrophils, eosinophils and basophils and their precursors is found.**

# HISTORY

- *In 1845, Bennett in Scotland and Virchow in Germany described splenic enlargement, severe anemia, and leukocytosis at autopsy*
- *Virchow proposed the term leukämie*

- *In 1878, Neumann proposed –marrow origin for*
- *leukemia –myelogene (myelogenus)*
- *Nowell and Hungerford in 1960 identified the culprit gene at the Perelman School of Medicine, Philadelphia*
- *Dr. Rowley identified the BCR-ABL translocation*
- *1998 –Discovery of targeted TKI therapy*

# Type

- It is a type of myeloproliferative neoplasm associated with a characteristic chromosomal translocation called the Philadelphia chromosome.

# EPIDERMATALOGY

- **Annual incidence: 1 to 2 cases per 100,000**
- **15% – 20% of all adult leukemias**
- **Incidence increases significantly with age**
  - **Median age: ~ 55 years**
  - **Prevalence increasing due to current therapy**
  - **Most patients present in CP, 85%**
  - **50% of CML patients are asymptomatic at diagnosis**
- **Risk factors**
  - **Exposure to ionizing radiation, the only known**

# Epidermatalogy

- Sparse Indian data - 0.8–2.2/lakh in men and 0.6– 1.6/lakh in women
- 50-70% of leukemias in India
- Male predominance (1.4:1)
- Average age at presentation – 50 yrs

# SIGNS AND SYMPTOMS

- The way CML presents depends on the stage of the disease at diagnosis as it has been known to skip stages in some cases

- Most patients (~90%) are diagnosed during the chronic stage which is most often asymptomatic. In these cases it may be diagnosed incidentally with an elevated white blood cell count on a routine laboratory test.

# MOLECULAR GENETICS OF CML

- The Philadelphia chromosome was originally detected by workers in Philadelphia.
- The first genetic abnormality to be associated with a human cancer.
- The result of a balanced translocation between chromosomes 9 and 22.
- Derivative chromosome 22 is significantly smaller
- Ph chromosome is present in *hematopoietic cells* from patients with CML.
- Therefore, the Ph chromosome is acquired and **NOT** inherited through the germ line.

# Molecular Genetics of CML

- The development of chronic phase CML appears to be a direct result of the BCR-ABL1 activity, which promotes its development by allowing:
  1. **Uncontrolled proliferation of transformed cells**
  2. **Discordant maturation**
  3. **Escape from apoptosis**
  4. **Altered interaction with the cellular Matrix**
- The progression of CML from chronic phase to accelerated face or blast crisis is a complex, multistep process (may be related to GMP).
- Also, it appears to involve the constitutive expression of the BCR-ABL1 tyrosine kinase.

# FACTS

- It can also present with symptoms indicative of hepatosplenomegaly and the resulting upper quadrant pain this causes.

- The enlarged spleen may put pressure on the stomach causing a loss of appetite and resulting weight loss. It may also present with mild fever and night sweats due to an elevated basal level of metabolism

# Risk factors

- CML is more common in males than in females (male to female ratio of 1.4:1) and appears more commonly in the elderly with a median age at diagnosis of 65 years.
- Exposure to ionising radiation appears to be a risk factor, based on a 50 fold higher incidence of CML in Hiroshima and Nagasaki nuclear bombing survivors.
- The rate of CML in these individuals seems to peak about 10 years after the exposure.

# CLINICAL MANIFESTATIONS

- Asymptomatic in 20-50% of patients
- Fatigue 34%, weight loss 20%, excessive sweating 15%, abdominal fullness 15%, bleeding episodes 21% (platelet dysfunction).
- Abdominal pain in the LUQ (enlarged spleen)
- Tenderness over the lower sternum.
- Acute gouty arthritis
- Findings: Splenomegaly, anemia, WBC > 100,000, platelet count > 600,000

# CLINICAL FEATURES

## Symptoms

***At diagnosis – 70% Symptomatic***

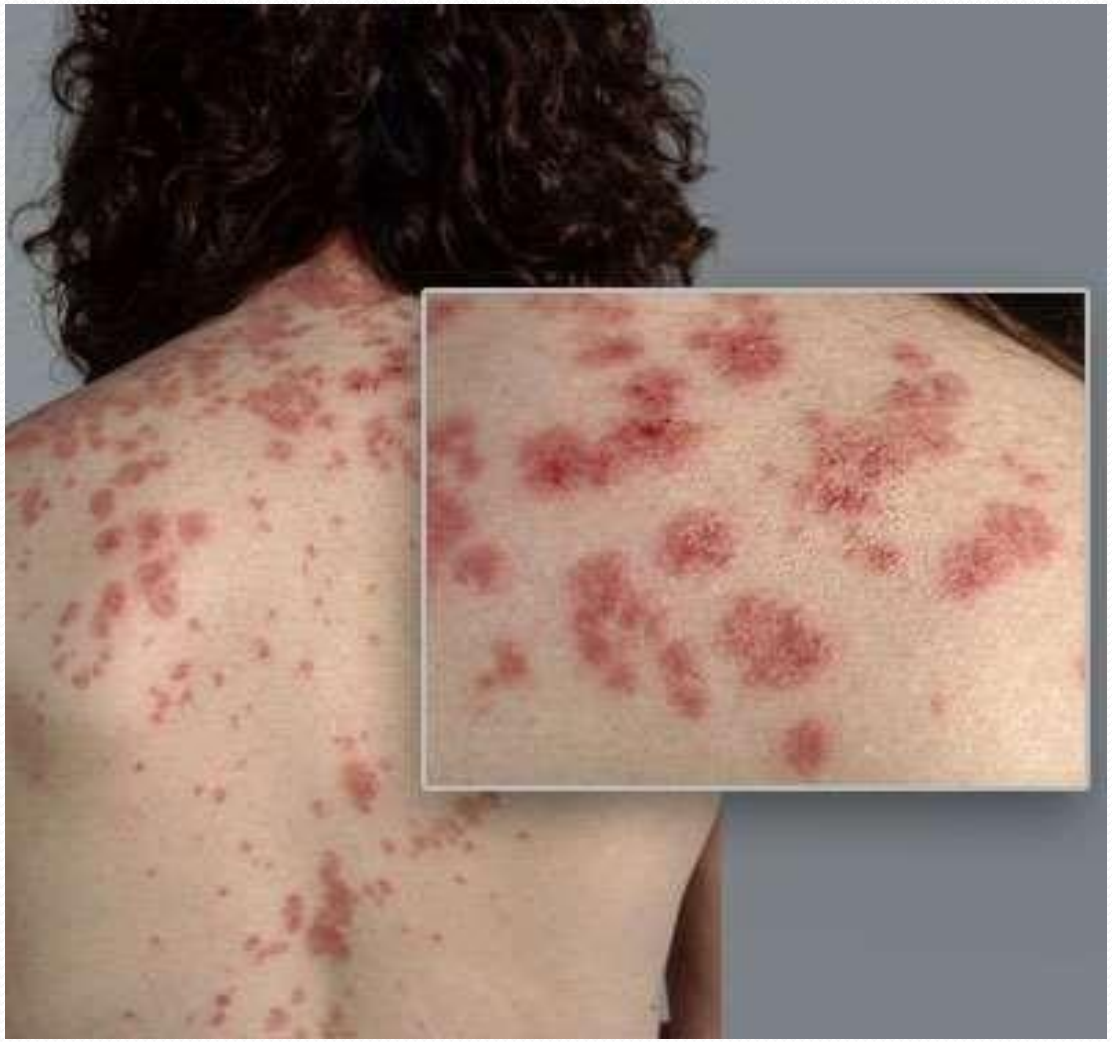
- ***Easy fatigability***
- ***Loss of sense of well-being***
- ***Decreased tolerance to exertion***
- ***Anorexia***
- ***Abdominal discomfort***
- ***Early satiety***
- ***Weight loss***
- ***Excessive sweating***

# UNCOMMON SYMPTOMS

1. ***Night sweats***
2. ***Heat intolerance***
3. ***Gouty arthitis***

- ***Left upper-quadrant and left shoulder pain***
- ***Urticaria***
- ***Hyperleukocytic Syndrome — dyspnea, tachypnea, hypoxia, lethargy, slurredspeech***

*Acute febrile neutrophilic dermatosis (Sweet syndrome)*



# BONE MARROW PATHOLOGY

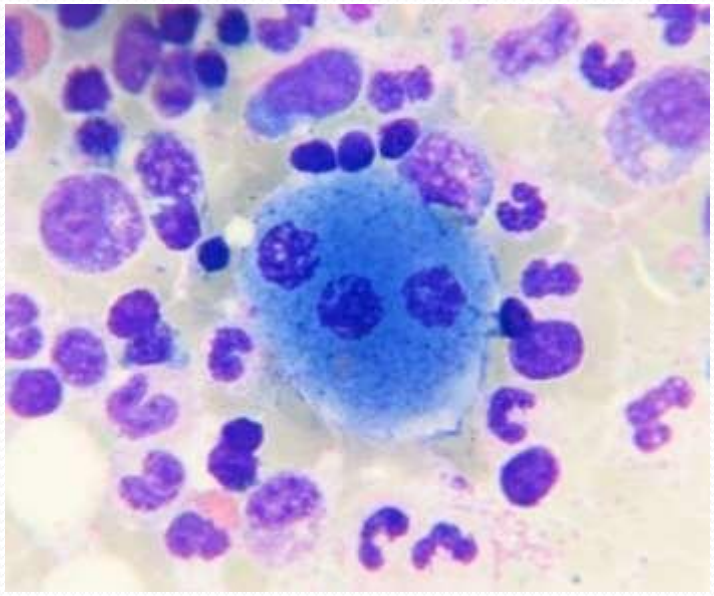
- Granulocytic maturation pattern same as in the peripheral blood
- Increased reticulin fibrosis and vascularity
- Erythroid islands are reduced in number and size
- Dwarf megakaryocytes
- Pseudo-Gaucher's cells and Sea Blue histiocytes (markers of increased cell turnover)
- Iron-laden macrophages are reduced or absent

# DIAGNOSIS

- *Blood counts and blood smear*
- Hemoglobin concentration isdecreased
- Nucleated red cells in blood film
- The leukocyte count above 25,000/µl (even > 1,00,000/µl),
- Hypersegmented neutrophils
- The basophil and eosinophil counts are increased
- (Absolute)
- The platelet count is normal or increased
- Blast cells ~3 %(<10% in the chronic phase)

# Bone Marrow studies

- Mitotic figures are increased
- Macrophages that mimic Gaucher cells*
- Macrophages - engorged with lipids - yield ceroid pigment - imparting a granular and bluish cast - *sea-blue histiocytes*
- Increased reticulin fibrosis (Collagen type Ⅲ)*
- Angiogenesis



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# Peripheral Blood Pathology

- Leukocytosis (median of 100,000)
- Differentiation shows virtually all cells of neutrophilic series
- Blasts < 2%
- Myelocytes more than metamyelocytes (a classic finding in CML)
- Neutrophils cytochemistry is abnormal – low LAP score
- Basophilia in 90% of cases
- Thrombocytosis. If low platelets – consider an other

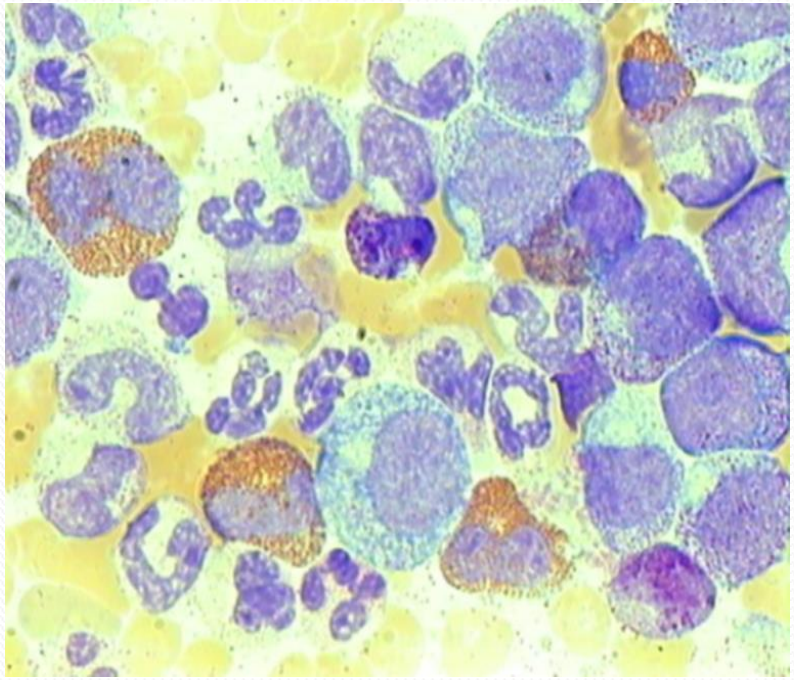
# COURSE OF THE DISEASE

- CML has 3phases

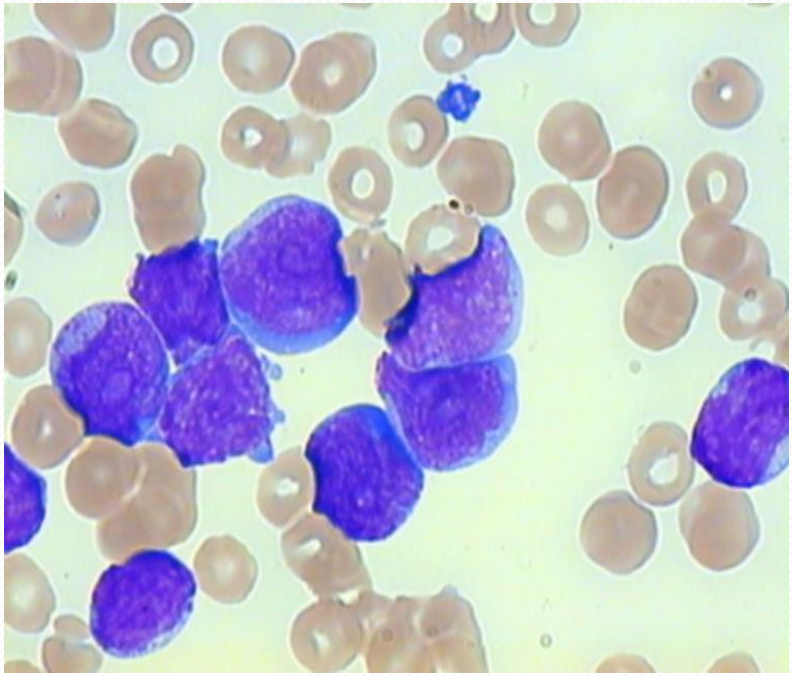

## Chronic Phase

- Most patients are asymptomatic
- Incidental leukocytosis/splenomegaly
- Bleeding and infectious complications are uncommon in the chronic phase

# MOST CML PATIENTS ARE DIAGNOSED IN THE CHRONIC PHASE

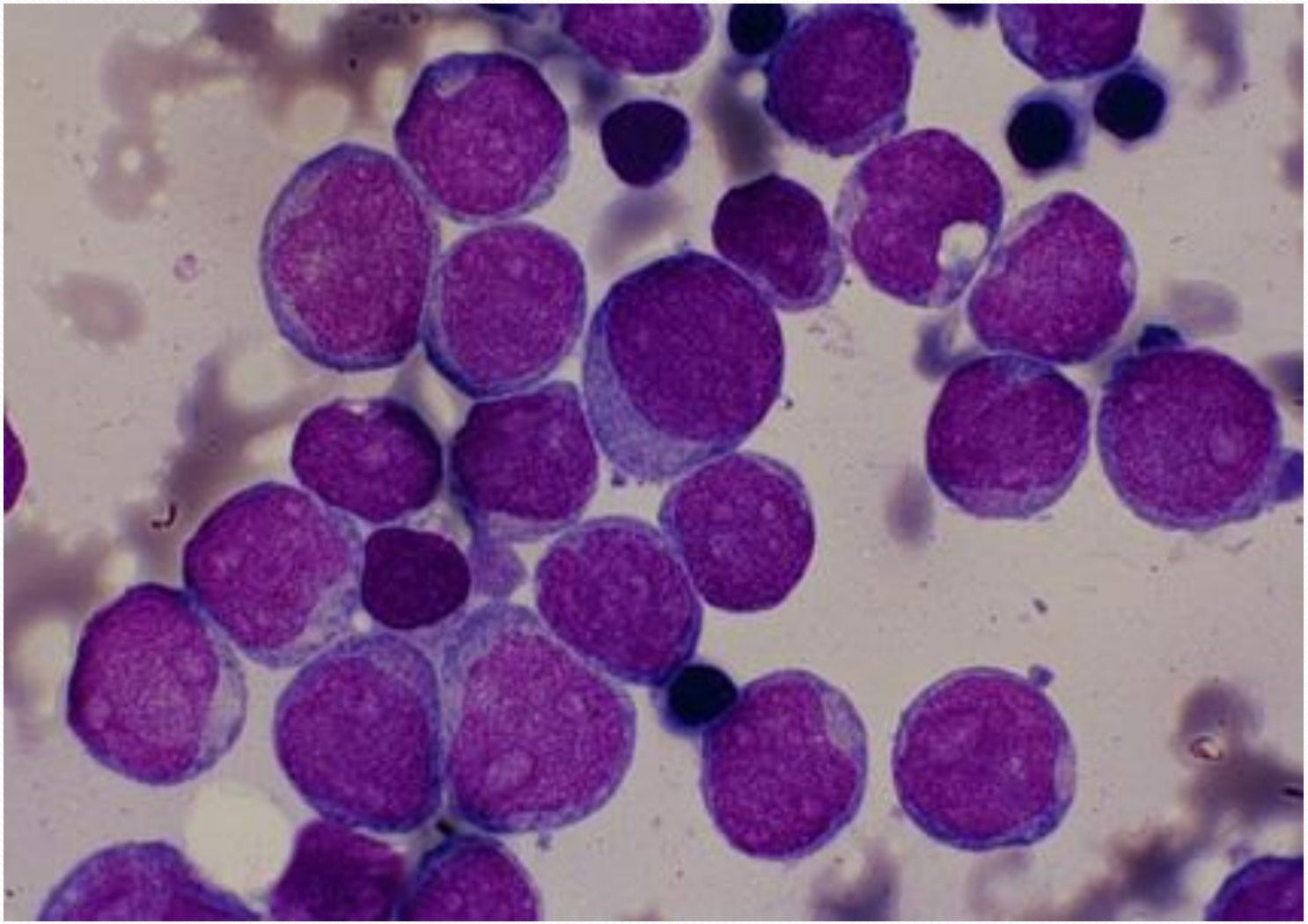


Chronic phase



Blastic phase

# Blast Phase CML – Bone Marrow



# ACCELERATED PHASE CML

- 10-19% blasts in the peripheral blood or bone marrow
- Peripheral blood basophils ≥20%
- Platelets < 100,000/microL, unrelated to therapy
- Platelets > 1,000,000/microL, unresponsive to therapy
- Progressive splenomegaly and increasing WBC, unresponsive to therapy
- Cytogenic evolution

# BLASTIC PHASE CML

**Blast crisis is generally refractory to treatment, occurs approximately 3-5 years after the diagnosis of CML and 18 months after the onset of accelerated face**

- Blasts in the peripheral blood ≥20% or in the bone marrow ≥30%
- Large foci or clusters of blasts on the bone marrow biopsy
- Presence of extramedullary blastic infiltrate (e.g., myeloid sarcoma, also known as granulocytic sarcoma or chloroma)

# Pregnancy and TKIs

- All TKIs could be teratogenic during pregnancy
- Women are advised not to become pregnant while on TKIs (any TKI)
- Best effective contraception is the barrier
- Woman taking TKIs are advised to avoid to breast-feeding

# Prognosis

- Improved dramatically since the incorporation of tyrosine kinase inhibitors into the initial treatment
- SEER database.  5138 patient's, year 2000 and 2005
  - 15-44 years – OS 72 versus 86%
  - 45-64 years – OS 68 versus 76%
  - 65-74 years – OS 38 versus 51%
  - 75-84 years – OS 19 versus 36%
- Stage of disease at the time of diagnosis is the strongest single predictor of outcome.


Thanks For Your
Attention