Chronic Myeloid leukemia

- It is a clonal disorder of pluripotent stem cell.

- The diagnosis is assisted by the characteristic presence of the Ph chromosome

WHO Classification:

Chronic Myeloproliferative Disease

- **Chronic Myelogenous Leukaemia**
  [Ph chromosome, t(9;22)(q34;q11), BCR/ABL- positive]
- **Chronic Neutrophilic Leukaemia**
- **Chronic Eosinophilic Leukaemia**
  (and the hypereosinophilic syndrome)
- **Polycythaemia Vera**
- **Chronic Idiopathic Myelofibrosis**
  (with extramedullary haematopoiesis)
- **Essential Thrombocythaemia**
- **Chronic Myeloproliferative Disease, Unclassifiable**

Myelodysplastic / Myeloproliferative Diseases

- **Chronic Myelomonocytic Leukaemia**
- **Atypical Chronic Myeloid Leukaemia**
- **Juvenile Myelomonocytic Leukaemia**
- **Myelodysplastic/Myeloproliferative Disease, Unclassifiable**

Myeloid Disorders: Usual Features at Diagnosis

Diseae	BM Cellularity	%Marrow Blasts	Maturation	Morphology	Haemato-poiesis	Blood count (s)	Organomega
Myeloproliferatie disorder	Usually increased	Normal or slightly increased (<10%)	Present	Relatively normal	Effective	One or more myeloid cell lines increased	Common
Myelodysplastic syndromes	Usually increased, occasionally decreased	Normal or increased (<20%)	Present	Dysplasia of one or more myeloid lineage	Ineffective	Cytopenia (S)	Uncommon
Myelodysplastic/ myeloproliferative disease	Usually increased	Normal or increased (<20%)	Present	Dysplasia of one or more myeloid lineages frequent	Effective or ineffective; may vary among involved lineages	Variable	Common

Presenting Manifestations of CML:

- Male to Female ratio 1.4:1

- Most frequently between age of 40 to 60 y (it may occur in children and neonates and in the very old age)

Common

1. Anaemia (pallor, dyspnea, tackycardia)

2. Splenomegaly

Less Common

3. Symptoms due to the raised metabolic rate (e.g. Wt loss, lassitude, anorexia, night sweats)

4. Haemorrhagic Manifestations, especially bruising (due to abnormal platelet function)

Occasional

- Acute abdominal pain
- Bone or joint pains
- Menstrual disturbances
- Neurological symptoms
- Priapism
- Gout caused by hyperuricemia from excessive purine breakdown
- Skin disorder
- Disturbances of vision or hearing
- Accidental discovery on routine blood examination in up to 50% of the cases.

Evolution of the disease

Chronic Phase

Accelerated Phase

Blastic Transformation

(AML) (ALL)

Laboratory Investigations:

i. CBC and blood film:

1. Leukocytosis is usually > 50 x10^9/l and some times > 500 x 10^9/l ..

2. Increased circulating basophils

3. Normocytic/ normochromic anemia

4. Platelets count may be increased (most frequently) or decreased.

Blood Film→ a complete spectrum of myeloid cells is seen in the peripheral blood, the level of neutrophils and myelocytes exceed those of blast cells and promyelocytes

ii. Serum uric acid is usually raised

iii. Neutrophil Alkaline Phosphatase **(NAP)** score is low

iv. <u>Bone Marrow Examination:</u>

- It shows hypercellular marrow with marked granulpoietic hyperplasia and M: E ratio of 10:1

- Megakaryocytes normal or increased.

v. <u>Cytogenetic Studies:</u>

(Ph) chromosome [t (9 : 22)]

<u>vi. DNA restriction enzyme analysis:</u>

BCR-ABL (Breakpoint Cluster Region)

<u>Neutrophil Alkaline Phosphatase (NAP):</u>

- Found mainly in the neutrophils, and demonstrated by ***Azo die*** technique

- Over all score is obtained by assessing the stain intensity in 100 neutrophils with each scale from 0-4

- Possible score will range between 0-400

- NAP score: **low or zero in CML**

high in infections (leukomoid reaction) or Polycythemia RV

- NAP score (pls refer to slides **# 13-16** in the lecture)

0 Negative, No granules
1 Occasional, scattered granules
2 Moderate number of granules
3 Numerous granules

4 Heavy positivity with coarse granules overlying the cytoplasm

Accelerated Phase:

1. Blasts 10% to 19% of peripheral blood white cells or bone marrow cells

2. Peripheral blood basophiles at least 20%

3. Persistent **thrombocytopenia** (<100X109/L) unrelated to therapy or persistent **thrombocytosis** (> 1000X109L) unresponsive to therapy

4. Increasing spleen size and increase WBC count unresponsive to therapy

5. Cytogenetic evidence of clonal evolution (i.e. the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML)

6. **Megakaryocytic proliferation** in sizable sheets and clusters, associated with marked reticulin or **collagen fibrosis**, and/or severe **granulocytic dysplasia**, should be considered as suggestive of CML-AP

Blastic Phase (BP):

1. Blasts 20% or more of peripheral blood white cells or bone marrow cells

2. Extramedullary blast proliferation

3. Large foci or clusters of blasts in bone marrow biopsy

(Ph) chromosome [t (9: 22)]: (pls refer to slide **# 20** in the lecture or fig **13.1** in the book)

- Karyotype showing the t (9;22)(q34;q11).

- Translocation between chromosome 9 and 22, part of proto-oncogene **c-ABL** is moved to the **BCR** gene on 22 and part of chromosome 22 moves to chromosome 9

- The abnormal chromosome 22 is the Ph chromosome

- This result in the formation of chimeric gene that codes for a fusion protein of size 210 k Da with higher tyrosine kinase activity and plays an important rule in leukemogenesis (pls refer to slide **# 21** in the lecture).

- In minority of patients, Ph abnormality cannot be seen by microscopic karyotyping analysis and the same molecular rearrangement is detectable by more sensitive technique (by FISH) (pls refer to slide **# 22** in the lecture).

FAP Proposal

Guidelines for distinguishing
Chronic Granulocytic (CGL), atypical Chronic Myeloid (aCML) and Chronic Myelomonocytic Leukaemia (CMML):

Parameters	**CGL**	**aCML**	**CMML**
Basophiles	≥ 3%	<2%	<2%
Monocytes	<3%	3 – 10%	≥ 3 – 10% (Usually >10%)
Granulocytic Dysplasia	------	++	+
Immature granulocytes	>20%	10 – 20%	≤ 10%
Blasts	≤ 2%	>2%	<2%
Erythroids	-	-	+