CHRONIC LEUKEMIA

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Types of Leukemia

	Acute – no maturation	Chronic – maturation
Lymphocytic	ALL	CLL
Myeloid	AML	CML

The peripheral blood white cell count in leukemia

	White Cell Count	Differential White Cell Count
Acute	Low, normal or high	If high, blast cells predominate. If normal or low, can be very few blasts.
Chronic	High	Mature cells predominate. Blasts less than 10%.

Chronic Leukemias

Increased proliferation and/or accumulation of leukocytes in the peripheral blood and bone marrow.

There are two types :

1- chronic myeloid leukemia.
2- chronic lymphoid leukemia.

Chronic Myeloid Leukemia

- ✓ A clonal stem cell disorder of hemopoietic stem cells that lead to accumulation of myeloid cells.
- ✓ A two-phase disease, Chronic and Accelerated phas

Types of chronic ML:

Type	name
1	(CML,Ph+)(chronic granulocytic leukemia)
2	(CML,Ph-)
3	Juvenile CML
4	Chronic neutrophilic leukemia.
5	Esinophilic leukemia
6	Chronic myelomonocytic leukemia

CML – pathology :

- ✓ Chronic phase :
- ✓ Accelerated phase:
- ✓ Blast phase:

Chronic Phase :

- ❖ **Accumulation of myeloid cells**
  - ✓ bone marrow
  - ✓ peripheral blood
  - ✓ spleen and liver
  - ✓ elsewhere

Accelerated Phase :

- ❖ Further genetic changes in the stem cell leading eventually to acute transformation (i.e. acute leukemia)

Blast phase :

- ❖ Acute leukemia → sever constitutional symptoms, infection, bleeding, and possible leukostasis

❖ The Philadelphia Chromosome :

- ✓ Is the chromosome which result from the t(9;22)(q34;q11)⇒part of the Abelson proto-oncogene ABL is moved to the BCR gene on chromosome 22 & part of chromosome 22 moves to chromosome 9.
- ✓ The abnormal chromosome 22is the Ph.

❖ CML - Clinical Features of **Chronic Phase** :

- ✓ Peak age 20 to 40 years.
- ✓ Often found by chance
- ✓ 20 – 40 % of patients are asymptomatic at diagnosis .

Symptoms related to hyper metabolism:

- ✓ weight loss, fatighe, malaise, anorexia or night sweats
- ✓ Gout or renal impairment caused by hyperuriceamia

Bone marrow failure:

- ✓ Anemia.
- ✓ Bruising ,epistaxis,menorrhagia or hemorrhage from any site because of platelet dysfunction**.**

Organ infiltration:

- ✓ Splenomegally almost always present and is frequently massive.
- ✓ Rare symptoms include visual disturbance.

❖ CML - **Accelerated Phase**

- ✓ Inevitable (without treatment)
- ✓ Occurs at median 3 years from diagnosis in untreated patients
- ✓ Usually blast crisis (2/3 myeloblastic, 1/3 lymphoblastic)
- ✓ Rapidly fatal despite treatment

CML – Diagnosis :

- ***Blood count***

CBC:

- ✓ Wbc is usually >50X10/l & some times >500X10/l.
- ✓ Normocytic normochromic anemia.
- ✓ Platelets ⇓⇒⇑.

Peripheral blood film:

- ✓ High circulating basophil.

Neutrophil alkaline phosphatase score is invariably low.

BM :is hyper cellular with granulopoietic predominance.

- ***Genetic analysis***

***Cytogenetics*:** ph chromosome.

- ✓ Serum vitamin B12 & vitamin b12-binding capacity are⇑.
- ✓ Serum uric acid is usually⇑.

CML – Treatment

- ✓ Imatinib mesylate (Gleevec, Glivic) (Tyrosine kinase inhibitor)
- ✓ Allogeneic transplantation
- ✓ Hydroxyurea

CML - Prognosis (median survival years)

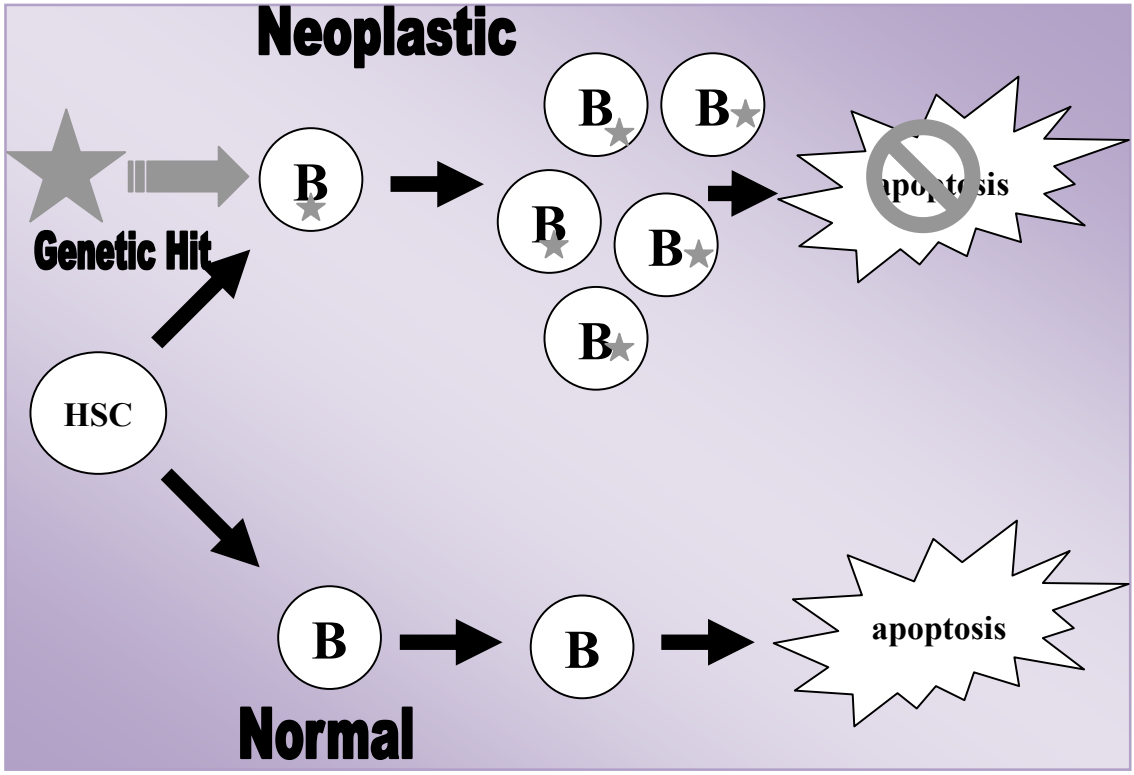
- ✓ Usually shows excellent response to chemtherapy in the chonic phase.
- ✓ Death usually occur from terminal acute trasformation ,hemorrhage or infection.
- ✓ Imatinib mesylate – median not reached (at least 5 years and probably much more)

1. Stem cell Transplant – cure but significant mortality and morbidity
2. Interferon +/- Cytarabine
3. Hydroxyurea

- ✓ Poor prognostic factors: ↑ age, ↑ platelet count, ↑ spleen size, ↑percentage of blasts.

Chronic Lymphocytic Leukemia

- ✓ Clonal Expansion with gradual accumulation of neoplastic of mature, functionally defective lymphocytes and failure of apoptosis
- ✓ In the West = 30% of the leukemias, 95 % B-Cell
- ✓ In Asia, 5 % of the Leukemias, 95 % T-Cell
- ✓ CLL is the most common of the chronic lymphoid leukemias." Commonest leukemia in adults"
- ✓ Approximately 25% of all leukemias
- ✓ Peak incidence between 60-80yrs.
- ✓ M : F = 2 : 1
- ✓ It is characterize by chronic persistent lymphocytosis which later infiltrate different organs.
- ✓ Does not affect children



clinical presentation :

- ✓ The disease occurs in older subject, rare before 40yrs.
- ✓ Many cases discover routinely.
- ✓ Symmetrical enlargement of superficial lymph node is the most frequent clinical sign.
- ✓ Features of autoimmune hemolytic anemia.
- ✓ Splenomegaly & hepatomegaly usual in later stage.
- ✓ Repeated bacterial or fungal infection.
- ✓ Thrombocytopenia.

CLL – Rai Staging System

- ✓ Stage 0 = Lymphocytosis > 10000,.
- ✓ Stage 1 = Lymphocytosis + Lymphadenopathy,
- ✓ Stage 2 = lymphadenopathy + splenomegaly and ? Or hepatomegally,
- ✓ Stage 111 = Lymphocytosis + Anemia,
- ✓ Stage 1V = Lymphocytosis + Thrombocytopenia,

B-Binet Classification:

Stage	Organomegally	Hb	Platelet.
A (50-60%)	0,1,or2areas		
B (30%)	3,4,or 5areas	≥10	≥100
C (<20%)	Not considered	<10	and /or <100

Immune Defects

1. Defective cellular immune function, with imbalanced T4 : T8
2. Hypogamaglobulinemia,
3. Autoimmune disease (hemolytic anemia ,thrombocytopenia etc)

CLL – Complications

- Failure of humoral and cellular immunity
  - Opportunistic infection common
    - eg shingles, pneumocystis, bacteria, fungi

- Autoimmune disease
  - warm autoimmune hemolytic anemia
  - autoimmune thrombocytopenia
  - pure red cell aplasia (antibodies against precursors of RBCs)

Warm Autoimmune → IgG ,
Cold Autoimmune → IgM

- Increase in blood lymphocyte count
- Demonstrate presence of a B-lymphocyte clone of appropriate immunophenotype
  - Surface marker analysis (CD 19, CD 20, CD 5 positive)
  - Immunoglobulin gene studie

Investigations :

CBC

- ✓ Wbc:↑.
- ✓ Diff: lymphocytosis ,the absolute lymphocyte count is>5x109/l and may be up to 300x109/l or more
- ✓ Anemia: normocytic normochromic anemia is present in later stages, autoimmune haemolysis.
- ✓ Platelets : thrombocytepenia may occur.

Blood film

- ✓ 70-99% of white cells mature lymphocyte.
- ✓ ***Smudge cells.***

Immunophenotyping

- ✓ Shows that the lymphocyte are B cells(CD19)expressing one form of light chain(κ orλ only)cells are also CD5&CD23+ve.

Bone marrow aspiration

- ✓ Lymphocytic replacement of normal marrow.

Immunoglobulin electrophoresis

- ↓ of Ig more marker with advance disease

Cytogenetic

- ✓ The 4 most common abnormalities are; deletion of13q14,trisomy 12,deletion of11q23&structural abnormality of 17p involving the p53 gene.

CLL - Principles of Treatment

- ❖ Since cure is rare,the treatment aim is only symptoms control.
- ❖ Indication for treatment:
  - ✓ Troublesome organomegaly.
  - ✓ Hemolytic episodes.
  - ✓ Bone marrow suppression.
- ❖ No treatment is needed for asymptomatic patients without marrow failure.
- ❖ Control of the disease with chemotherapy is the goal in symptomatic patients

Treatment :

1-chemotherapy:

- ✓ *Chlorambucil:* kill abnormal lymphocytes only.
- ✓ 6mg/m2 daily for 10 days monthly for 2-4 month after which remission will be obtain.
- ✓ *Fludarabine*: more effective as single agent.
- ✓ *Corticosteroid* : indicated in bone marrow failure,also indicated in autoimmune hemolytic anemia and thrombocytopenia.

2-Radiotherapy:

Is useful in reducing the size of lymphnode not responsive to chemo.

3-Monoclonal antibody:

Both Campath IH(anti CD52)and Rituximab(anti CD20)produce response in proportion of patient.

4-Splenectomy :

For immune-mediated cytopenia or painful bulky splenomegally.

5-immunoglobulin replacement:

250mg/kg /month by IV for patient with hypogammaglobulinemia and recurrent infection.

6- Stem cell transplant:

Under clinical trial.

CLL - Median Survival (years)

- ✓ Early - lymphocytosis alone (>10)
- ✓ Intermediate - plus lymphadenopathy, or enlargement of liver or spleen (7)
- ✓ Late - marrow failure (1.5)

][COMMON MCQS][

❖ All cause of huge spleen Except:

a. CML
b. lieshmania
c. mononucleosis

❖ The following statement are true regarding CLL:

a. is often discovered incidentally when blood test for other reasons (T)
b. lymphadenopathy is often generalized (T)
c. the commonest cause of mortality is infection (T)
d. no treatment for stable, asymptomatic stage A disease (F)
e. overall prognosis is better than any other leukemia (F)

IN TIME, WE HATE THAT WHICH WE OFTEN FEAR !!
SHAKESPEAR

Done by
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