LYMPHOPROLIFERATIVE DISORDERS

Chronic Lymphocytic Leukemia-CLL
Hairy Cell Leukemia
Plasma Cell Disorders

CLL

CLL

- Chronic lymphocytic leukemia (CLL) is one of the chronic lymphoproliferative disorders (lymphoid neoplasms).
- It is characterized by a progressive accumulation of functionally incompetent lymphocytes, which are monoclonal in origin.
- CLL is identical disease with SLL at different stages

Epidemiology of CLL

- The most common type of lymphoid leukemia in the West-
  - 30% of all leukemias
- Median age 60yrs
  - 10% below the age of 50yrs
- Men are more affected- M:F= 2:1

Etiology and Pathogenesis

- Etiology
  - Unknown in the majority
  - Familial clusters well described
  - Radiation not related to increased incidence
- Pathogenesis
  - Defective immune surviellance
  - Clonal proliferation&
  - Accumulation of incompetent, long-lived CD5+ B-Cell
    - Over expression of BCL-2 & BCL-XL (antiapoptotic)

Clinical Features

- 25 %-asymptomatic (routine blood exam)
- Painless LN swelling
  - Cervical usually
  - Wax & wean
- Other features of immunodeficiency
  - Infection, respiratory
- Sxs of autoimmune phenomenon
  - Anemia & bleeding
  - Increased reaction to insect bite
- Sxs due to organomegaly
- B-symptoms

- B-Symtoms
  - Unintentional weight loss ≥ 10 percent of body weight within the previous six months.
  - Fevers of >100.5ºF (>38ºC) for ≥ 2 weeks without evidence of infection.
  - Drenching night sweats without evidence of infection.
  - Extreme fatigue

- Signs
  - Pallor
  - GeneralizedLAP
  - Hepatosplenomegaly
  - Skin
    - Bleeding
    - Vasculitis
    - Leukemic Cutis
  - Other organs
    - Waldeyer’s Ring
    - Membranoproliferative glomerulonephritis

Lab Features

- Anemia
  - AIHA
  - INFILTRATION
  - BLEEDING
- Lymphocytosis
  - SMUDGE / BASKET CELLS
- Granulocytes
- Thrombocytopenia
- Other tests
  - Organ function test
  - Uric acid & LDH
  - Coomb’s test
  - Serum protien Electrophoresis
  - CXR &CT scan

Dx of CLL

- Dx of CLL is based on
  - CBC & differential
  - Peripheral blood smear examination
  - Flowcytometry study
- BM examination is not required to establish the dx of CLL.
- Indications for BM examination in CLL
  - Doubtful cases
  - No Flowcytometry
  - Work up of Anemia & Thrombocytopenia
  - prognosis

Dx of CLL

- Diagnostic Criteria
  - The following 2 criteria must be met to dx CLL
    - Absolute lymphocyte count in the PB ≥ 5000/μL, with a preponderant population of mature appearing small lymphocytes
    - Demonstration of clonality of the circulating B-lymphocytes by flowcytometry

Dx of CLL

- Monoclonal B-cell lymphocytosis (MBL)
  - PB absolute lymphocytosis < 5,000/µL and
  - No LAP
- CLL versus Small Lymphocytic Lymphoma (SLL)
  - The same disease with identical markers/clonality
  - SLL is diagnozed
    - LAP

DDX in CLL

- MBL
- Infectious causes of lymphocytosis/ reactive
  - Viral
  - Autoimmune d/s, drugs & allergy
  - Splenectomy
  - Thyrotoxicosis, adrenal insufficiency
- PLL
- HCL
- Mantle cell lymphoma
- Splenic marginal zone lymphoma
- Lymphoplasmacytic lymphoma
- Follicular Lymphoma
- Large granular lymphocytic Leukemia
- Cutaneous T-cell lymphoma

Markers Useful in Distinguishing Chronic Lymphocytic Leukemias

Marker	B-CLL	PLL	HCL	T-CLL
S- Ig	**Weak**	**Strong**	**Strong**	**Negative**
CD2	-	-	-	++
CD3	-	-	-	++
CD4	-	-	-	+
CD5	++	±	-	++
CD7	-	-	-	++
CD8	-	-	-	+
CD19/20/24	++	++	++	-
CD23	++	±	-	-
CD22	±	++	++	-
CD10	-	±	-	-
CD25	-	-	++	-

Binet Staging System For Chronic Lymphocytic Leukemia	
STAGE	***DESCRIPTION***
A	***Two or less lymphoid bearing areas enlarged****
B	***Three or more lymphoid bearing areas enlarged***
C	***Presence of anemia (Hgb <10.0 g/dL) or thrombocytopenia (platelet count <100,000/microL)***
*** Five lymphoid bearing areas are possible: cervical, axillary, inguino-femoral, spleen, and**	

Rai Clinical Staging Systems

Level of Risk	Stage	Description
Low *	0	Lymphocytosis only (in blood and marrow)
Intermediate	I	Lymphocytosis plus enlarged nodes
	II	Lymphocytosis plus enlarged spleen or liver with or without enlargement of nodes
High *	III	Lymphocytosis plus anemia (hemoglobin <110 g/L) with or without enlarged nodes, spleen, liver
	IV	Lymphocytosis plus thrombocytopenia (platelets <100 × 109 /L) with or without anemia or enlarged nodes, spleen, liver

INDICATIONS FOR TREATMENT IN CLL

- Disease-related progressive symptoms (e.g., weight loss without trying, fever without overt infection, night sweats, weakness, or easy fatigability)
- Progressively worsening anemia or thrombocytopenia
- Autoimmune (Coombs-positive) hemolytic anemia or autoimmune thrombocytopenia

INDICATIONS FOR TREATMENT IN CLL

- Bulky lymphadenopathy that is getting progressively worse, and poses risk to the patient from pressure on underlying tissues, or causes significant cosmetic problems

- Massive splenomegaly that is worsening progressively or results in ***hypersplenism***

INDICATIONS FOR TREATMENT IN CLL

- Increased susceptibility to bacterial infections. This may result from marked
  - ***hypogammaglobulinemia***, in which case intravenous high-dose γ-globulin therapy has a proven protective effect.
  - ***Severe neutropenia or agranulocytosis*** may occur in CLL, and may play a major role in the development of bacterial sepsis

INDICATIONS FOR TREATMENT IN CLL

- Progressive hyperlymphocytosis.
  - It is not possible to set a rigid ***upper threshold for the blood lymphocyte count*** that must be met before starting therapy, but we do not allow this count to be more than 150 × 10^9 /L.
  - ***Hyperviscosity syndrome associated with hyperlymphocytosis*** in CLL can be catastrophic. The rate of increase of blood lymphocyte count is of importance;
  - a short ***doubling time (≤12 months***,

Prognostic features in chronic lymphocytic leukemia

Good prognostic features

- Low Rai or Binet clinical stage
- Interstitial or nodular pattern of lymphocyte infiltration in marrow
- Lymphocyte doubling time >12 months
- CD 38 negativity
- Mutated immunoglobulin Vh genes

Poor prognostic features

- High Rai or Binet stages
- Diffuse pattern of lymphocyte marrow infiltration
- Lymphocyte doubling time <12 months
- CD 38 positivity
- Unmutated immunoglobulin Vh genes

Prognostic features in chronic lymphocytic leukemia

Good prognostic features

- ZAP-70 negativity (low levels)
- Chromosome 13q14

Poor prognostic features

- ZAP-70 positivity (high levels)
- Del 11q23
- 17p-/p 53 abnormalities
- p 53 dysfunction or increased expression
- Increased levels of TNF-alpha, beta-2 microglobulin, IL-6, IL-8, IL-10, LDH, VEGFR-2, CD20, and CD52

Treatment of CLL

- Early stage & stable disease
  - Observation without Rx
  - Use of growth factors & IVIg
- Chemotherapy
  - Alkylating agent (Chlorambucil, Cyclophosphamide)
  - Nucleoside Analogues(purine analogues) – Fludarabine, Cladribine
- Monoclonal Antibodies
  - Rituximab (against CD20)
  - Alemtuzimab (against CD52)
- Combination Chemotherapy
  - Fludarabine + Cyclophosphamide (FC)
  - Fludarabine + Rituximab (FR)
  - Fludarabine + Cyclophosphamide + Rituximab(FCR)

- Resistant Disease
  - CVP/ CHOP +/- Rituximab
  - HSCT
- AIHA & thrombocytopenia
  - Steriods
  - Rituximab & combination chemotherapy
- Radiation Therapy
- Stem cell transplantation
- Special conditions
  - Ritcher's Transformation
    - Like diffuse large B-cell lymphoma
  - Prolymphocytic Leukemia

HIARY CELL LEUKEMIA

General Remarks about HCL

- Hairy cell leukemia (HCL) is an uncommon chronic B-cell lymphoproliferative disorder originally termed , in 1920
  - "leukemic reticuloendotheliosis"
- It was described as a distinct clinical entity by Bouroncle and colleagues in 1958,
- Named HCL in the 1960s because of
  - the prominent irregular cytoplasmic

- HCL is an uncommon malignancy
  - 2 percent of all leukemias
  - 600 to 800 new cases diagnosed/ year (USA)
- The median age at onset is 52
- Strong male predominance of about four to one.
- The incidence is about three times higher in caucasians than in blacks

- Pathogenesis is largely unknown
- Etiology
  - Unknown
  - Associated with exposure
    - Ionizing radiation
    - EBV
    - Organic Chemicals
    - Woodworking
    - Farming
    - Familial cases

Classic Presentation of a Patient with Hairy Cell Leukemia

Middle-aged man

Splenomegaly, often more than 5 cm below the left costal margin

Pancytopenia

Bone marrow cannot be aspirated ("dry tap")

Tartrate-resistant phosphatase (TRAP)-positive circulating hairy cells

Bone marrow trephine biopsy showing mononuclear cells separated by clear cytoplasm

Initial Evaluation in HCL

History and physical examination
Complete blood cell count, differential cell count
Review of peripheral blood smear
Serum chemistries
Bone marrow aspirate and biopsy
Tartrate-resistant acid phosphatase (TRAP) stain
Immunophenotyping of peripheral blood or bone marrow aspirate

DDX in HCL

Prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia variant
Chronic lymphocytic leukemia
Low-grade lymphoma
Agnogenic myeloid metaplasia
Systemic mastocytosis

Treatment of HCL

- OBSERVATION
- Indications for treatment
  - Anemia
  - Granulocytopenia/neutropenia
  - Thrombocytopenia
  - Symptomatic splenomegaly +/- LAP
  - Autoimmune Syndromes

- Therapeutic options
  - Cladribine
  - Pentostatin
  - Interferon –α
  - Splenectomy
  - Steriods
    - Vasculitis
    - Autoimmune conditions