Chronic Lymphocytic Leukemia

- Most common leukemia
- Usual age > 50 yrs
- Increased proliferation and progressive accumulation of neoplastic, immunologically incompetent, clonal lymphocytes
  - B cell origin > 99%
Clinical Features of CLL

• Highly variable presentation
  – Asymptomatic, or vague, non-specific complaints
  – Recurrent infection 10% (often pneumococcus)

• Signs
  – Lymphadenopathy (60%)
  – Splenomegaly (50%)
  – Hepatomegaly (< 40%)

Clinical Features of CLL

• Laboratory
  – blood and marrow lymphocytosis
  – B cell monoclonality:
    – κ vs λ surface light chain
    – single Ig gene rearrangement
  – hypogammaglobulinemia

• Prognosis
  – Mean survival = 50-60 months
  – Range = few months to > 20 yrs

Immunological Abnormalities in CLL

• Disturbed Ab production
  – Hypogammaglobulinemia (50%) → bacterial infection
  – Monoclonal Ig paraprotein in serum (10%)
  – Autoantibodies (10%)

• Minor impairments in cell-mediated immunity

• Neoplastic lymphocytes
  – Monoclonal surface Ig
  – Abnormal response to Ig challenge

Complications of CLL

Recurre nt inf ect io ns
Immune hem olysis
Immune thrombocytopenia
Progressive disease
Rai Staging System for CLL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Features</th>
<th>Median survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lymphocytosis</td>
<td>13</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis + lymphadenopathy</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis + splenomegaly</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis + anemia</td>
<td>1-2</td>
</tr>
<tr>
<td>V</td>
<td>Lymphocytosis + thrombocytopenia</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Treatment of CLL

- No evidence that therapy prolongs survival
- Asymptomatic: watch and wait
- Symptomatic:
  - Radiation for local complications
  - Chemotherapy: fludarabine, alkylators, combinations
  - Monoclonal antibodies (eg, Campath)
  - Stem cell transplantation

Classical Diagnostic Features of Myeloma

- Plasmacytosis in marrow
- Monoclonal protein in serum or urine
- Lytic disease of bone

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Marrow Plasmacytosis in Myeloma

- Plasma cells > 10%
- Usually much higher
- Often present in ‘sheets’
- Alternatively, biopsy-proven plasmacytoma
- Other causes of plasmacytosis:
  - Inflammation, cirrhosis, AIDS

Multiple Myeloma

- Clonal malignancy of plasma cells
- Increasing incidence
- Blacks:whites 2:1
- Age range 20-100 yrs (peak age 70 yrs)
- Cause unknown
  (Environmental/Genetic factors)
Diagnosis of Myeloma: Monoclonal Proteins

- 75-80% have serum monoclonal Ig
  (M-component, paraprotein, or 'spike' on electrophoresis)
- 10-20% make light chains only → rapid renal excretion → no paraprotein on serum protein electrophoresis
- Non-secretory myeloma rare (<1%)
- Other causes of monoclonal proteins
  (eg, CLL, lymphoma, benign monoclonal gammopathy)

Protein Electrophoresis (PEP):
- Apply serum or urine
- Stain
- Scan
- Proteins separated according to charge and size
**Bone Disease in Myeloma**

- Unbalanced osteoclast activity

- Radiographic manifestations
  - Osteoporosis almost invariable
  - Usually multiple lytic lesions
  - Axial skeleton involved (active marrow)
  - Osteoblastic reaction minimal

- Hypercalciuria and hypercalcemia
Benign Monoclonal Gammopathy

• Monoclonal Ig as isolated finding
• More common than myeloma
• No bone disease, anemia, renal dysfunction
• Most remain stable
• About 10% eventually develop classical myeloma

Myeloma at Presentation

• Early - asymptomatic, incidental diagnosis
  Paraprotein on electrophoresis
  Mild marrow plasmacytosis
  Solitary plasmacytoma (10% of cases)

• Late - symptomatic
  Bone pain (usually lower back)
  Pneumococcal infection
  Systemic symptoms (eg, weakness, weight loss)
  Related to anemia, renal failure, hypercalcemia
Hyperviscosity Syndrome

- Due to aggregating paraprotein

- Pathogenesis
  - Circulatory insufficiency, abnormal hemostasis

- Manifestations
  - Bleeding
  - Dyspnea (congestion on CXR)
  - Encephalopathy and visual disturbances

Immunological Features of Myeloma

- Monoclonal Ig and/or monoclonal light chain

- ↓ Levels of normal Ig’s (hypogammaglobulinemia)

- Cellular immune responses usually preserved

- Bacterial infections common
  
  Early: S pneumoniae
  
  Late: S aureus, Gram negative rods
Amyloidosis in Myeloma

- Due to light chain deposition in tissues
- Incidence: $\lambda$ amyloid > $\kappa$ amyloid
- Organs commonly involved:
  - Skin
  - Tongue and GI
  - Heart
  - Peripheral nerves
  - Kidneys
  - Soft tissues
- No effective therapy, except stem cell transplant
### Therapy for Myeloma

- Biphosphonates (pamidronate, zoledronate)
- Radiotherapy
- Corticosteroids and conventional chemotherapy
- Thalidomide (anti-angiogenesis)
- Bortezomib (proteasome inhibitor)
- Stem cell transplantation