<table>
<thead>
<tr>
<th>Disease</th>
<th>Usual phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute leukemia</td>
<td>precursor</td>
</tr>
<tr>
<td>chronic leukemia</td>
<td>differentiated</td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
</tr>
<tr>
<td>myeloma</td>
<td></td>
</tr>
</tbody>
</table>

- **Pre-B-cell**
- **B-cell**
- **Transformed B-cell**
- **Plasma cell**

**Ig**

- **Surface**
- **Secreted**

**Major malignant counterpart**

- **B-ALL**
- **CLL**
- **Macroglobulinemia**
- **Myeloma**

**Major immunological abnormality**

- ↓ Gamma globulins
- Monoclonal IgM
- Monoclonal Ig or light chain
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:
    - \( \kappa \) vs \( \lambda \) surface light chain
    - single Ig gene rearrangement
  - hypoimmunoglobulinemia

- **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**

- Recurrent infections
- Immune hemolysis
- 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
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)
Classical Diagnostic Features of Myeloma

• Plasmacytosis in marrow

• Monoclonal protein in serum or urine

• Lytic disease of bone

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
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):
Proteins separated according to charge and size

Apply serum or urine

Origin

Stain

Scan

γ
β
α₂
α₁
albumin
globulins
Serum Protein Electrophoreses in 2 Patients with Myeloma

#1

Stain

Scan

γglobulins β α2 α1 albumin

#2

Stain

Scan

γglobulins β α2 α1 albumin
Immunofixation Electrophoresis

Patient with Monoclonal IgGκ Immunoglobulin

Patient Without Monoclonal Protein
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 electropheresis
  - Mild marrow plasmacytosis
  - Solitary plasmacytoma (10% of cases)

- Late - symptomatic
  - Bone pain (usually lower back)
  - Pneumococcal infection
  - Systemic symptoms (e.g., 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: λ amyloid > κ 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 and lenalidomide (anti-angiogenesis)
- Bortezomib (proteasome inhibitor)
- Stem cell transplantation