Multiple myeloma (MM) & related disorders

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Plasma cell neoplasms

• Six major variants:

(1) Multiple myeloma

(2) Solitary plasmacytoma

(3) Lymphoplasmacytic lymphoma

(4) Heavy-chain disease

(5) Primary amyloidosis

(6) MGUS... = monoclonal gammopathy of undetermined significance...when we find M protein in normal elderly persons
MM, overview

• Mean age: 70 years

• More in males and Africans

• Principally involves the bone marrow

• Causes lytic lesions throughout the skeleton

• Median survival: 4-6 years
• Production of M protein
  ...mainly of IgG type

• In 15-20%: only lambda or kappa light chains are produced
  ...excreted in urine...called: Bence Jones proteins

• More commonly both light chains and complete immunoglobulins
Solitary plasmacytoma

• When it forms only a mass in bone or soft tissue

• Transform into multiple myeloma (bone marrow and blood involvement) over 5-10 years

• Modestly elevated M proteins are present in some cases at diagnosis

• Those of soft tissues: less likely to transform
As with most other B cell malignancies, myelomas often have chromosomal translocations involving the \textit{IgH} locus on chromosome 14 and various other genes, including cyclin D1, fibroblast growth factor receptor 3, and cyclin D3 genes. Late in the course, translocations involving \textit{MYC} are sometimes also observed. As might be surmised from this list of genes, dysregulation of D cyclins is common in multiple myeloma.
MM, bone lytic lesions

- The characteristic bone resorption results from the secretion of certain cytokines (e.g., IL-1β, tumor necrosis factor, IL-6) by myeloma cells.

...These cytokines stimulate production of another cytokine called RANK-ligand, which stimulates the differentiation and absorptive activity of osteoclasts.
MM, immunosuppression

• Although the plasma usually contains increased immunoglobulin owing to the presence of an M protein, the levels of functional antibodies often are profoundly depressed, leaving patients at high risk for bacterial infections
MM, renal dysfunction is a common, serious problem in myeloma

- Mostly due to obstructive proteinaceous casts, which often form in the distal convoluted tubules and the collecting ducts... The casts consist mostly of Bence Jones proteins along with variable amounts of complete immunoglobulins, Tamm-Horsfall protein, and albumin

- Light chain deposition in the glomeruli or the interstitium... either as amyloid or linear deposits... also may contribute to renal dysfunction
MM, renal dysfunction, cont’d

• Hypercalcemia, which may lead to dehydration and renal stones

• Frequent bouts of bacterial pyelonephritis, which stem in part from the hypogammaglobulinemia
• **Bone pain**, due to pathologic fractures. Pathologic fractures of vertebrae may lead to spinal cord impingement, an oncologic emergency.

• **Hypercalcemia** stemming from bone resorption leads to neurologic manifestations such as confusion and lethargy and contributes to renal dysfunction.

• **Anemia**, due to marrow replacement by tumor cells as well as suppression of hematopoiesis through uncertain mechanisms.

• **Recurrent infections** with bacteria such as *S. aureus, S. pneumoniae, and E. coli*, resulting from the marked suppression of normal humoral immunity.

• **Renal insufficiency** (in up to 50% of patients), resulting from the deleterious effect of Bence Jones proteins on renal tubular cells, as well as bacterial infections, hypercalcemia, and amyloidosis.

• **AL-type amyloidosis** (5% to 10% of patients)

• Symptoms related to hyperviscosity may occur owing to excessive production and aggregation of M proteins but this clinical presentation is much more characteristic of lymphoplasmacytic lymphoma.

**MM, clinical manifestations**
MM, diagnostic tests

- Serum and urine electrophoresis
  ...in 99% of cases, either a monoclonal complete immunoglobulin or a monoclonal free immunoglobulin light chain is present in the serum, the urine, or both
  ...sometimes: nonsecretory and only detected in plasma cells

- Bone marrow: increased plasma cells
MGUS

• M proteins are found in the serum of 1% to 3% of otherwise healthy persons older than age 50 years
  ...the most common plasma cell proliferation

• A precursor of MM...1% per year

• Similar chromosomal translocations

• Patients with MGUS have less than 3 g/dL of monoclonal protein in the serum and no Bence Jones proteinuria
## Diagnostic Criteria

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<th>Disorder</th>
<th>Disease Definition</th>
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| **MGUS** - All 3 criteria must be met          | Serum monoclonal protein < 3 g/dL  
Clonal bone marrow plasma cells < 10%  
Absence of end-organ damage by the CRAB criteria |
| Smoldering myeloma or asymptomatic myeloma – Both criteria must be met | Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL and/or clonal bone marrow plasma cells ≥ 10%  
Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure* |
| **Multiple myeloma** – All 3 criteria must be met | Clonal bone marrow plasma cells ≥ 10%  
Presence of serum and/or urinary monoclonal protein  
Evidence of end-organ damage*  
  - Serum calcium ≥ 11.5 mg/dL or  
  - Serum creatinine > 1.73 mmol/L (renal insufficiency)  
  - Anemia (hemoglobin > 2 g/dL below LLN or value < 10 g/dL)  
  - Bone lesions (lytic lesions, severe ostopenia, or pathologic fractures) |

Lymphoplasmacytic lymphoma

• Peak incidence is between 6th and 7th decade

• Secrete M proteins...mostly IgM (macroglobulin)

• The tumor is a mixture of small B lymphocytes, plasmacytic lymphocytes and plasma cells

• An indolent lymphoma with common involvement of L.N.s, spleen & bone marrow
Lymphoplasmacytic lymphoma, cont’d

• The high levels of IgM cause the blood to become viscous
  …producing a syndrome called Waldenstrom macroglobulinemia

• Unlike multiple myeloma:
  -no free light chains or Bence Jones proteinuria
  -no lytic bone lesions
  -only rarely associated with amyloidosis
Lymphoplasmacytic lymphoma, Waldenstrom macroglobulinemia

• Visual impairment
due to: retinal vascular changes

• Neurologic problems...due to sluggish blood flow

• Bleeding...interfering with clotting factors & platelets

• Cryoglobulinemia...precipitation of IgM at low temperature...will cause Raynaud phenomenon & cold urticaria