Plasma Cell Disorders

- One clone of plasma cells multiplies excessively. As a result, this clone produces vast amounts of a single antibody (monoclonal antibody) known as the M-protein.

- Multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis, and the heavy chain diseases comprise this group

Multiple Myeloma

- Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone.
- Result in a number of organ dysfunctions and symptoms of bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, and occasionally clotting abnormalities, neurologic symptoms, and manifestations of hyperviscosity.

Etiology

- Exposed to the radiation.
- A variety of chromosomal alterations have been found in patients with myeloma; 13q14 deletions, 17p13 deletions, and 11q abnormalities predominate. The most common translocations are t(11;14)(q13;q32) and t(4;14)(p16;q32),
- Seen more commonly than expected among farmers, wood workers, leather workers, and those exposed to petroleum products

Incidence and Prevalence

- 4 per 100,000/Y and remarkably similar throughout the world.
- Males are more commonly affected than females, and blacks have nearly twice the incidence of whites.
- The median age at diagnosis is 70 years; it is uncommon under age 40.
- The incidence of myeloma is highest in African-American and Pacific islanders; intermediate in Europeans and North American Caucasians; and lowest in developing countries including Asia.

Clinical Manifestations

- **Bone pain** is the most common symptom, affecting nearly 70% of patients.
- The pain usually involves the back and ribs, the pain of myeloma is precipitated by movement. Persistent localized pain in a patient with myeloma usually signifies a pathologic fracture.
- The bone lesions of myeloma are caused by the proliferation of tumor cells, activation of osteoclasts that destroy bone, and suppression of osteoblasts that form new bone.
- The bone lesions are lytic in nature

Clinical Manifestations

- **Susceptibility to bacterial infections -** next most common clinical problem.
- The most common infections are pneumonias and pyelonephritis, and the most frequent pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* in the lungs and *Escherichia coli* and other gram-negative organisms in the urinary tract.

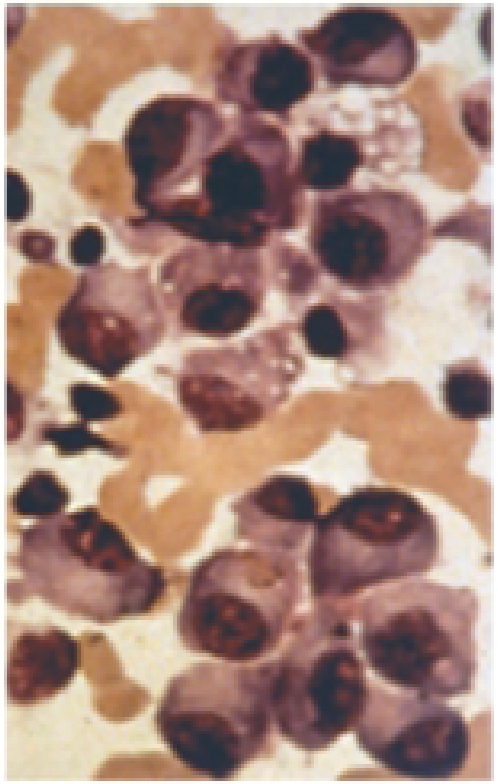
Clinical Finding	Underlying Cause
Hypercalcemia, osteoporosis, pathologic fractures, lytic bone lesions, bone pain	Tumor expansion, production of osteoclast activating factor by tumor cells, osteoblast inhibitory factors
Renal failure	Hypercalcemia, light chain deposition, amyloidosis, urate nephropathy, drug toxicity (nonsteroidal anti-inflammatory agents, bisphosphonates), contrast dye
Easy fatigue—anemia	Bone marrow infiltration, production of inhibitory factors, hemolysis, decreased red cell production, decreased erythropoietin levels
Recurrent infections	Hypogammaglobulinemia, low CD4 count, decreased neutrophil migration
Neurologic symptoms	Hyperviscosity, cryoglobulinemia, amyloid deposits, hypercalcemia, nerve compression, anti-neuronal antibody, POEMS syndrome, therapy-related toxicity
Nausea and vomiting	Renal failure, hypercalcemia
Bleeding/clotting disorder	Interference with clotting factors, antibody to clotting factors, amyloid damage of endothelium, platelet dysfunction, antibody coating of platelet, therapy-related hypercoagulable defects

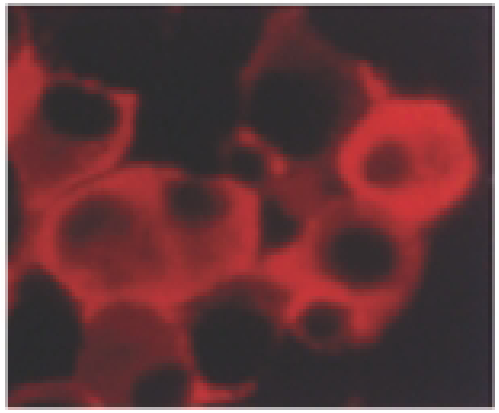
Diagnosis

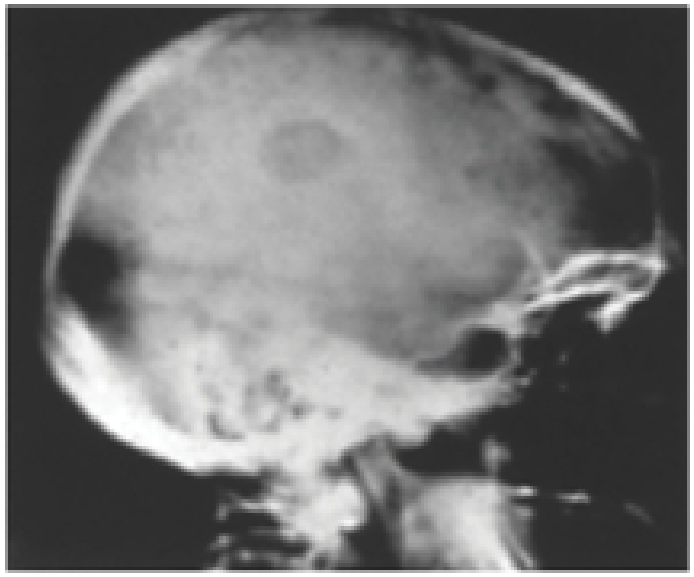
- The classic triad of myeloma is marrow plasmacytosis (>10%), lytic bone lesions, and a serum and/or urine M component.
- ESR > 100
- anaemia, thrombocytopenia
- rouleaux in peripheral blood smears
- marrow plasmacytosis > 10 -15%
- Chest and bone radiographs may reveal lytic lesions or diffuse osteopenia.
- Hypercalcemia, Serum alkaline phosphatase is usually normal
- Proteinuria, Bence Jones protein
- azotemia

Diagnosis

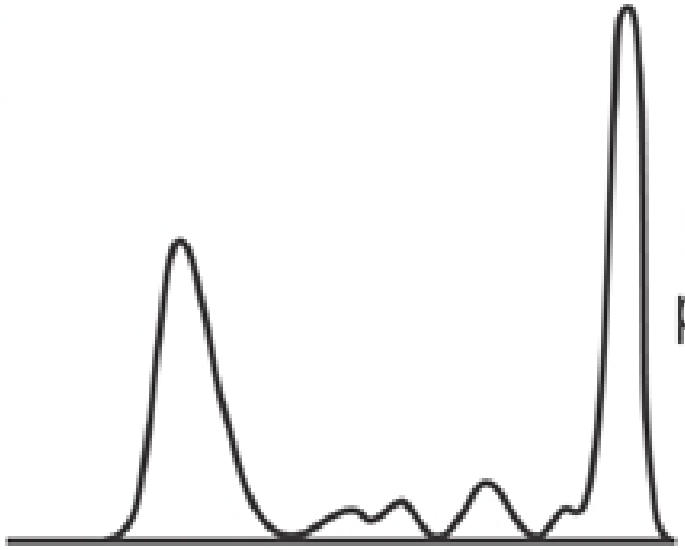
Bone marrow







X-ray



Electro-pheresis

Criteria for Diagnosis of Myeloma

MGUS	Smoldering MM	Symptomatic MM
<3 g M spike <10% PC	≥3 g M spike OR ≥10% PC	≥10% PC M spike +
No anemia or bone lesions Normal calcium and kidney function		Anemia, bone lesions, high calcium or abnormal kidney function

variants of myeloma

Solitary bone plasmacytoma and **extramedullary plasmacytoma**.

- These lesions are associated with an M component in <30% of the cases, they may affect younger individuals, and both are associated with median survivals of 10 years.

- Solitary bone plasmacytoma is a single lytic bone lesion without marrow plasmacytosis, may recur in other bony sites or evolve into myeloma.
- Extramedullary plasmacytomas usually involve the submucosal lymphoid tissue of the nasopharynx or paranasal sinuses without marrow plasmacytosis. rarely recur or progress

- Both tumors are highly responsive to local radiation therapy. If an M component is present, it should disappear after treatment.

Myeloma Staging Systems
Durie-Salmon Staging

Stage	Criteria	Estimated Tumor Burden, x 10^{12} cells/m^2
I	All of the following	
	1. Hemoglobin >10 g/dL 2. Serum calcium <12 mg/dL 3. Normal bone x-ray or solitary lesion 4. Low M-component production a. IgG level <5 g/dL b. IgA level <3 g/dL c. Urine light chain <4 g/24 h	<0.6 (low)
II	Fitting neither I nor III	0.6–1.20 (intermediate)
III	One or more of the following	
	1. Hemoglobin <8.5 g/dL 2. Serum calcium >12 mg/dL 3. Advanced lytic bone lesions 4. High M-component production a. IgG level >7 g/dL b. IgA level >5 g/dL c. Urine light chains >12 g/24 h	>1.20 (high)

International Staging System

Level	Stage	Median Survival, Months
β_2M < 3.5, alb ≥3.5	I (28%)	62
β_2M < 3.5, alb < 3.5 *or* β_2M = 3.5–5.5	II (39%)	44
β_2M > 5.5	III (33%)	29

Poor prognostic factors

- cytogenetic abnormalities of 11 and 13 chromosomes
- beta-2 microglobulines > 2.5 ug/ml
- High labelling index and high levels of lactate dehydrogenase
- % plasma cells in the marrow; circulating plasma cells; performance status; as well as serum levels of soluble IL-6 receptor, C-reactive protein.

Treatment

- Symptomatic supportive care to prevent serious morbidity from the complications of the disease
  - **biphosphonates, calcitonin**
  - **recombinant erythropoietin**
  - **immunoglobulins**
  - **plasma exchange**
  - **radiation therapy**

Treatment-Chemotherapy

- Systemic therapy to control the progression of myeloma
- The initial standard treatment for newly diagnosed myeloma is dependent on whether or not the patient is a candidate for high-dose chemotherapy with autologous stem cell transplant.
- In patients who are transplant candidates, alkylating agents such as melphalan should be avoided since they damage stem cells, leading to decreased ability to collect stem cells for autologous transplant.

In patients who are transplant candidates

Induction

- High-dose pulsed glucocorticoids (dexamethasone 40 mg for 4 days every 2 weeks)
- VAD chemotherapy (vincristine, 0.4 mg/d in a 4-day continuous infusion; doxorubicin, 9 mg/m^2 per day in a 4-day continuous infusion; dexamethasone, 40 mg/d for 4 days per week for 3 weeks)
- Thalidomide (200 mg PO qhs) plus dexamethasone (40 mg for 4 days every 2 weeks)
- dexamethasone+ bortezomib/ lenalidomide

Successful harvesting of peripheral blood stem cells for transplantation

In patients who are not transplant candidates

- Intermittent pulses melphalan(8 mg/m^2 per day) and prednisone(25–60 mg/m^2 per) administered for 4–7 days every 4–6 weeks.

- Melphalan+ thalidomide

Treatment

Maintenance therapy- IFN, prednisone

Relapsed myeloma can be treated with novel agents including lenalidomide and/or bortezomib+ dexamethasone

- The median overall survival of patients with myeloma is 5–6 years
- The major causes of death are progressive myeloma, renal failure, sepsis, or therapy-related acute leukemia or myelodysplasia.