Plasma Cell Neoplasms & Related Entities

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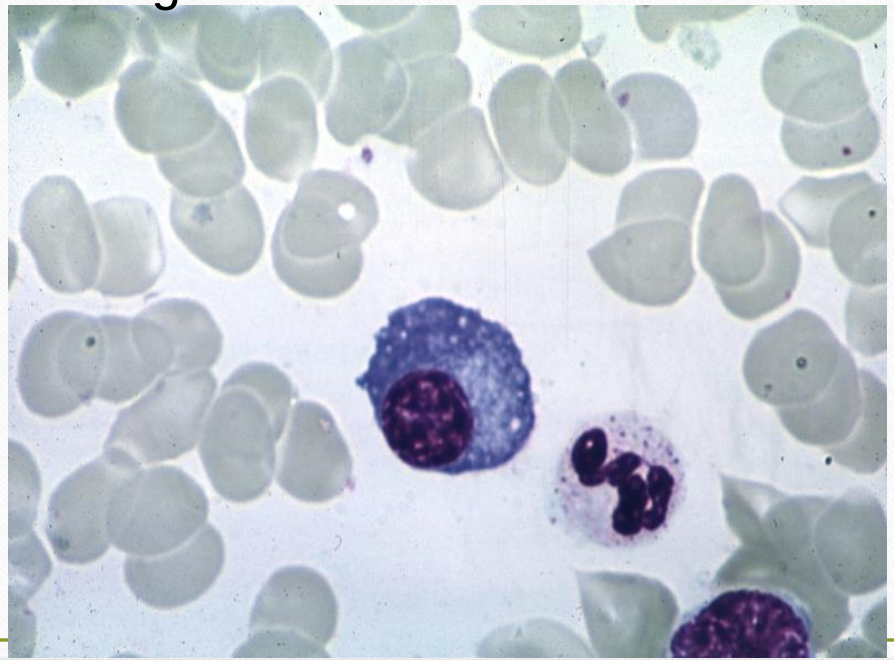
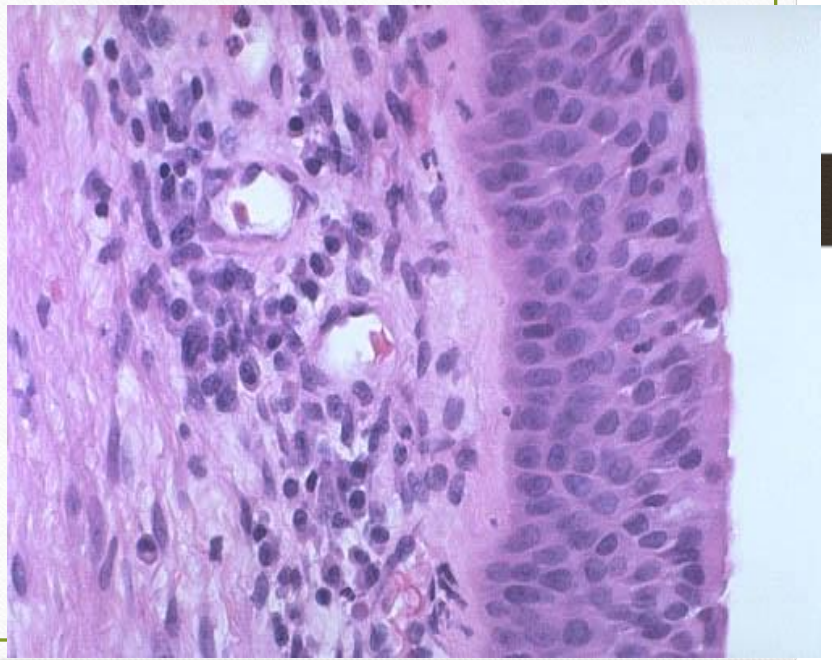
The last stage of B cell maturation, express CD38 but lose CD19:
+ cannot switch antibody classes.
+can only produce a single kind of antibody in a single class of immunoglobulin.





Plasma Cell Neoplasms and Related Entities

- B cell proliferations contain neoplastic plasma cells
- Always secrete a **monoclonal** immunoglobulin or their fragment.
- These serve as tumor markers and often have pathologic consequences.
- The most common & deadly of these neoplasms is multiple myeloma.

Plasma Cell Neoplasms and Related Entities

- **M protein:** A monoclonal immunoglobulin identified in the blood. They have high molecular weight, so they are restricted to plasma & extracellular fluid & excluded from urine.

- Neoplastic plasma cells also synthesize excess **immunoglobulin light chains** → smaller in size → excreted in the urine, where they are called → **Bence Jones proteins**.

- Monoclonal immunoglobulin can be detected by simple serum test → **Serum protein Electrophoresis**!

The abnormal Igs associated with plasma cell neoplasms include monoclonal gammopathy and paraproteinemia. These abnormal proteins are associated with the following clinicopathologic entities:

- Multiple myeloma (plasma cell myeloma)
- Waldenström macroglobulinemia . It occurs in older adults, most commonly in association with lymphoplasmacytic lymphoma
- Heavy-chain disease (Mediterranean lymphoma)
- Monoclonal gammopathy of undetermined significance (MGUS)

Multiple Myeloma

- One of the most common lymphoid malignancies.Median age 70 years, more common in males.
- Principally involves the bone marrow and ass with lytic lesions throughout the skeletal system.
- Most myelomas are associated with more than 3 g/dL of serum Ig and/or more than 6 mg/dL of urine Bence Jones protein
- The most frequent M protein produced by myeloma cells is **IgG** (60%), followed by IgA(20%), only rarely are IgM, IgD, or IgE M proteins obsereved.
- Plasma cells produce κ or λ light chains.

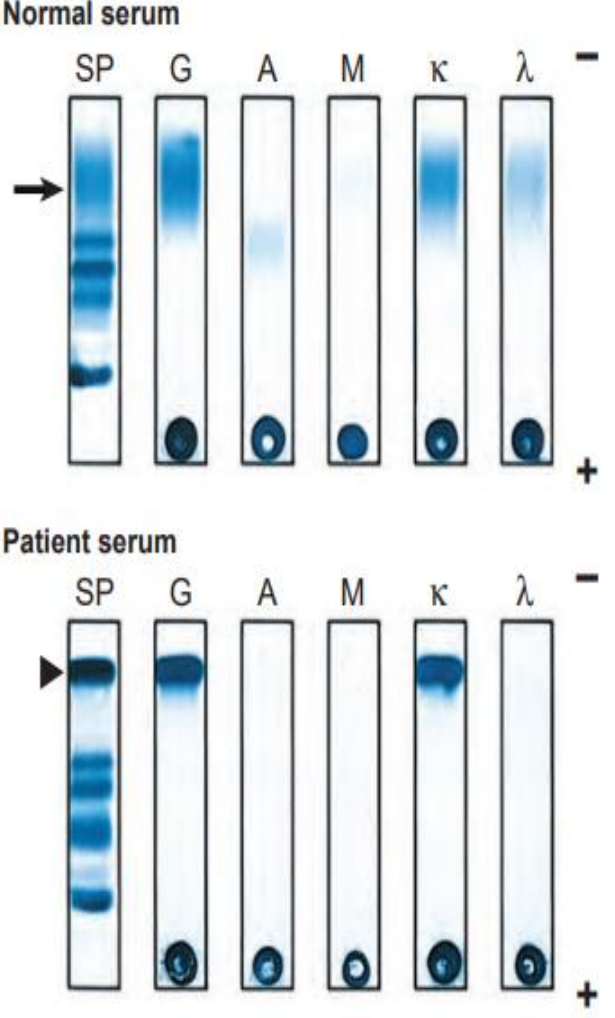


Figure 13.22 M protein detection in multiple myeloma. Serum protein electrophoresis *(SP)* is used to screen for a monoclonal immunoglobulin (Ig) (M protein). Polyclonal IgG in normal serum *(arrow)* appears as a broad band; in contrast, serum from a patient with multiple myeloma contains a single sharp protein band *(arrowhead)* in this region of the electropheretogram. The suspected monoclonal Ig is confirmed and characterized by immunofixation, in which proteins are trapped in the gel with antibodies specific for IgG *(G)*, IgA *(A)*, IgM *(M)*, or kappa *(κ)*, or lambda *(λ)* light chain and then visualized with a protein stain. Note the sharp band in the patient serum is cross-linked by antisera specific for IgG heavy chain and kappa light chain, indicating the presence of an IgGκ M protein. Levels of polyclonal IgG, IgA *(A)*, and lambda light chain *(λ)* are also decreased in the patient serum relative to normal, a finding typical of multiple myeloma. (Courtesy Dr. David Sacks, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

Multiple Myeloma - pathogenesis

- Myeloma often has chromosomal translocations that fuse the **IgH locus** on chromosome **14** to oncogenes such as the cyclin D1 and cyclin D3 genes.

- Multiple myeloma has a number of effects on the skeleton, the immune system, and the kidney, all of which contribute to morbidity and mortality of the disease.

- The clinicopathologic diagnosis of multiple myeloma

relies on :

identification of clonal plasma cells in the marrow and the presence of **CRAB** criteria (hypercalcemia, renal dysfunction, anemia, and bone lesions).

Multiple Myeloma - Bone

- Bone destruction → the major pathologic feature of multiple myeloma.
- MM release factors that :

+ upregulates the expression of the receptor activator of NF-κB ligand (RANKL) by bone marrow stromal cells → activate osteoclasts.
+ are potent inhibitors of osteoblast function.

- Net effect: increased bone resorption →hypercalcemia & pathologic fractures.

Multiple Myeloma - Humoral immunity

- MM Compromises the function of normal B cells → production of functional antibodies often is profoundly depressed → patients are at high risk for bacterial infections.

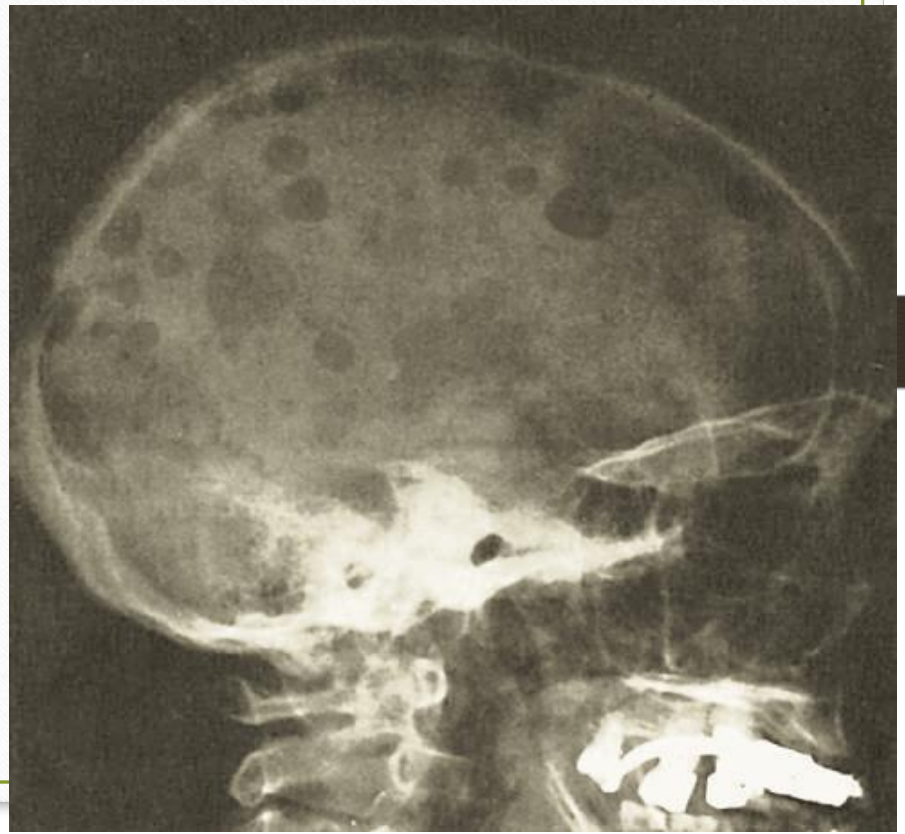
Multiple Myeloma - Renal dysfunction

Several pathologic effects of MM:

- obstructive proteinaceous casts; composed of Bence jones proteins in the distal tubules.
- Light chain deposition in the glomeruli or the interstitium, either as amyloid or linear deposits →may contribute to renal damage.
- Hypercalcemia, lead to dehydration and renal stones,
- Bacterial pyelonephritis,

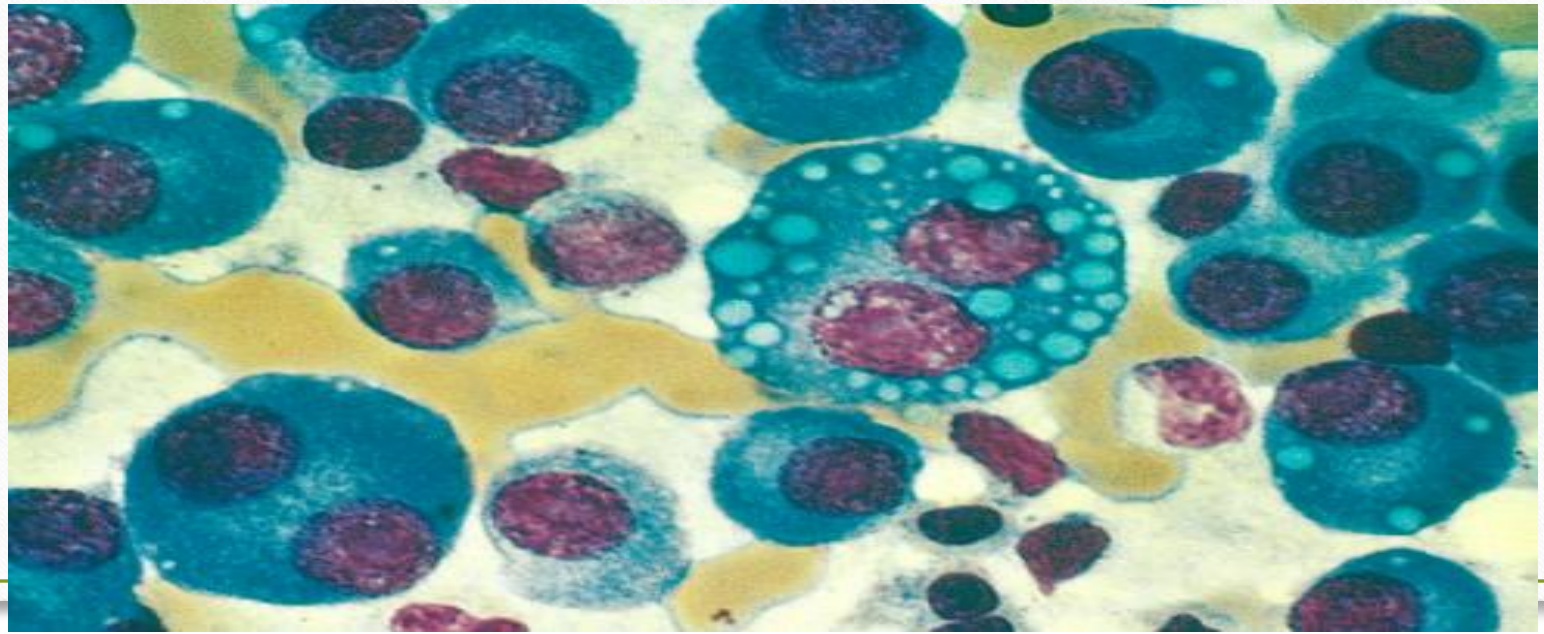
Multiple Myeloma - Morphology

- Multifocal destructive skeletal lesions mostly involve the vertebral column, ribs, skull, pelvis, femur.
- The lesions arise in the **medullary cavity**.
- Bone destruction leads to pathologic fractures.



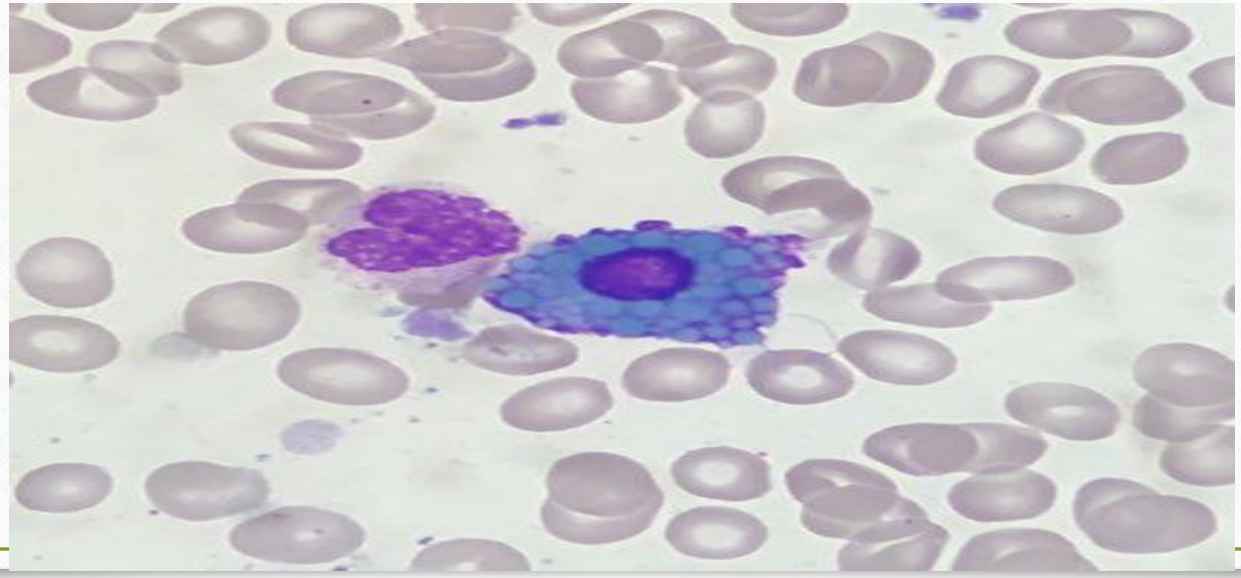
Multiple Myeloma - Morphology

Microscopically: the marrow shows increased numbers of plasma cells, usually > 30% of the cellularity.



Multiple Myeloma - Morphology

Mott cells are plasma cells that have spherical inclusions packed with Ig in their cytoplasm, Inclusions: **Russell bodies**



Multiple Myeloma - Clinical Features.

- Bone resorption: Bone pain & pathologic fractures
- Hypercalcemia: neurological manifestations;
  + Confusion, lethargy and weakness.
- Recurrent bacterial infections:
  +The most common of death.
- Renal dysfunction:
  +Second most common cause of death.
- Median survival is 4-7 years
- No cure yet.

Multiple Myeloma - Laboratory analyses

- Increased levels of:

1) Immunoglobulins in the blood.
2) and/or Bence Jones proteins in the urine.

- Patients have Both in ~ 70% of cases, 20% have only free light chains, & 1% of myelomas are nonsecretory.
- Anemia, thrombocytopenia and leukopenia.
- Elevated creatinine or urea (Renal dysfunction).

+Monoclonal gammopathy of undetermined significance (MGUS) : By definition, patients are asymptomatic and the serum M protein level is less than 3 g/dL.

+ MGUS is very common in older adult.
+ Has a low but constant rate of transformation to MM

+Smoldering myeloma: This entity defines a middle ground between multiple myeloma and MGUS. Plasma cells make up 10% to 30% of the marrow cellularity, and the serum M protein level is greater than 3 g/dL, but patients are asymptomatic.

+Solitary plasmacytoma: An infrequent variant that presents as a single mass in bone or soft tissue.

+ Waldenström macroglobulinemia: A syndrome in which high levels of IgM lead to symptoms related to hyperviscosity of the blood. (ass with lymphoplasmacytic lymphoma).

Lymphoplasmacytic Lymphoma

- A B-cell neoplasm that usually presents in old age.
- Most commonly, the plasma cell component secretes monoclonal IgM.

- Amounts sufficient to cause a hyperviscosity syndrome → Waldenström macroglobulinemia.

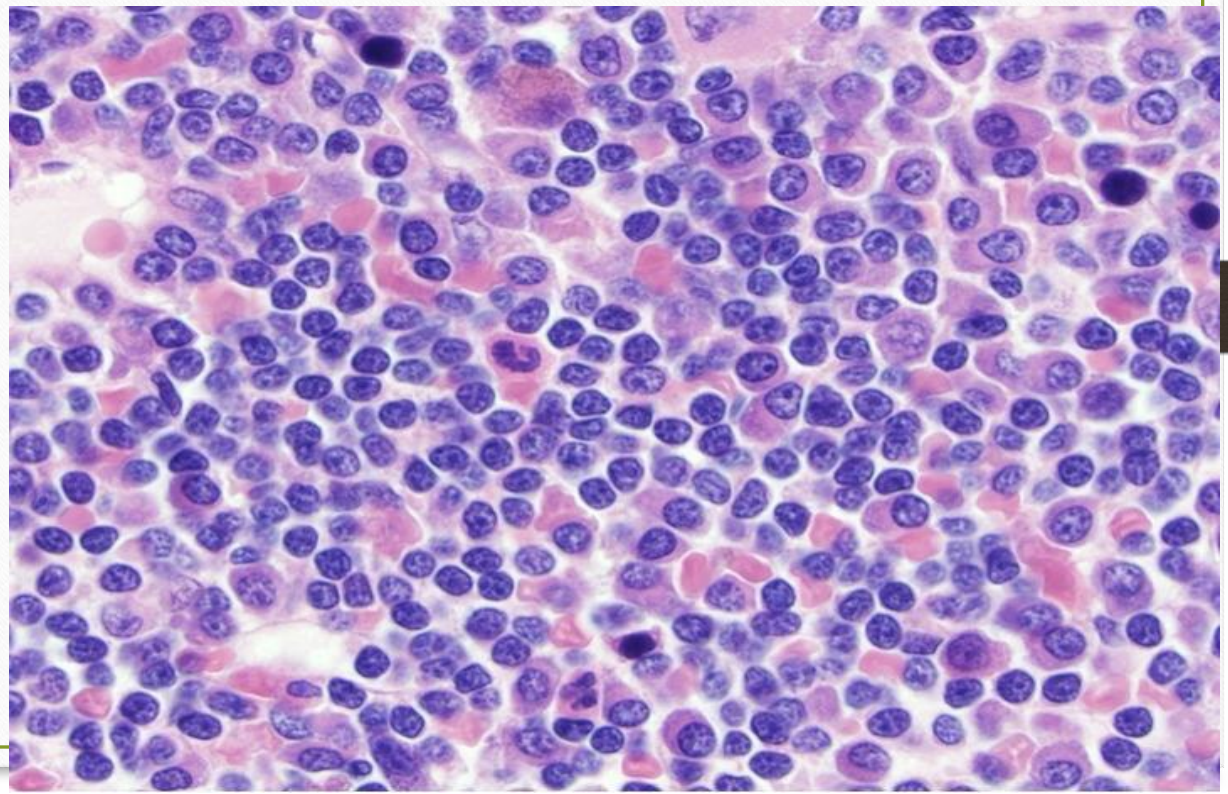
- Complications from the secretion of free light chains (e.g.; renal failure) are relatively rare & no bone destruction.

Lymphoplasmacytic Lymphoma - Pathogenesis

- All cases of lymphoplasmacytic lymphoma are associated with acquired mutations in **MYD88**.

Lymphoplasmacytic Lymphoma - Morphology

The marrow is infiltrated by lymphocytes, plasma cells, & plasmacytoid lymphocytes in varying proportions.



Waldenström macroglobulinemia

- Patients with IgM-secreting tumors have signs & symptoms stemming from the physicochemical properties of IgM. (large size → at high concentrations IgM greatly increases the blood viscosity → hyperviscosity syndrome.

Waldenström macroglobulinemia

Characterized by the following:

- Visual impairment: due to venous congestion & retinal hemorrhages.
- Neurologic problems such as headaches, dizziness, deafness, due to sluggish venous blood flow.
- Bleeding due to formation of complexes between macroglobulins & clotting factors as well as interference with platelet function.
- Cryoglobulinemia the precipitation of macroglobulins at low temperatures →Raynaud phenomenon.

Lymphoplasmacytic Lymphoma – Clinical features

- An incurable progressive disease.
- Median survival 4 year