2.
Neoplastic Proliferations of White Cells

~ Plasma Cell Neoplasms & Related Entities

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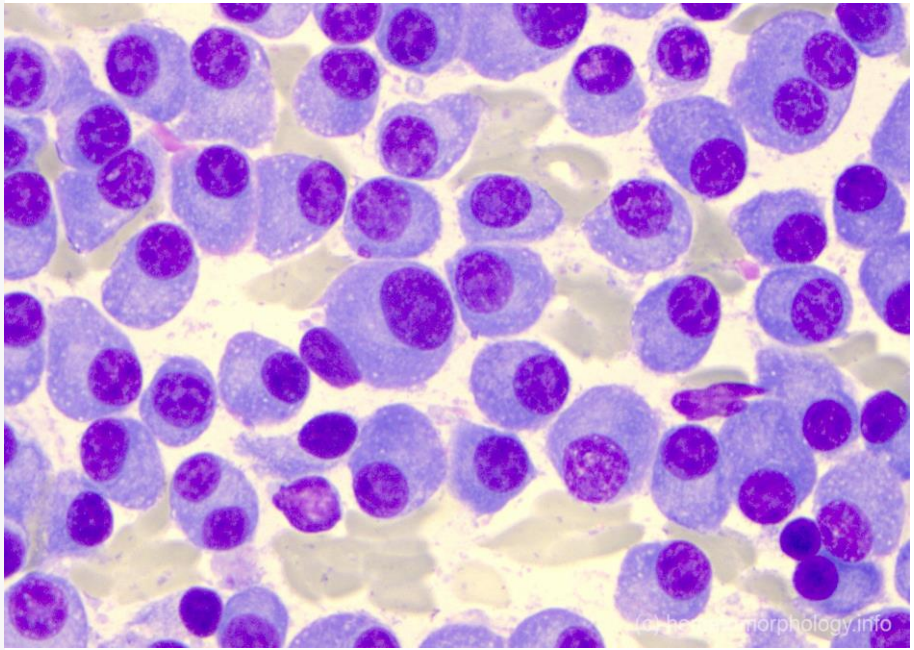
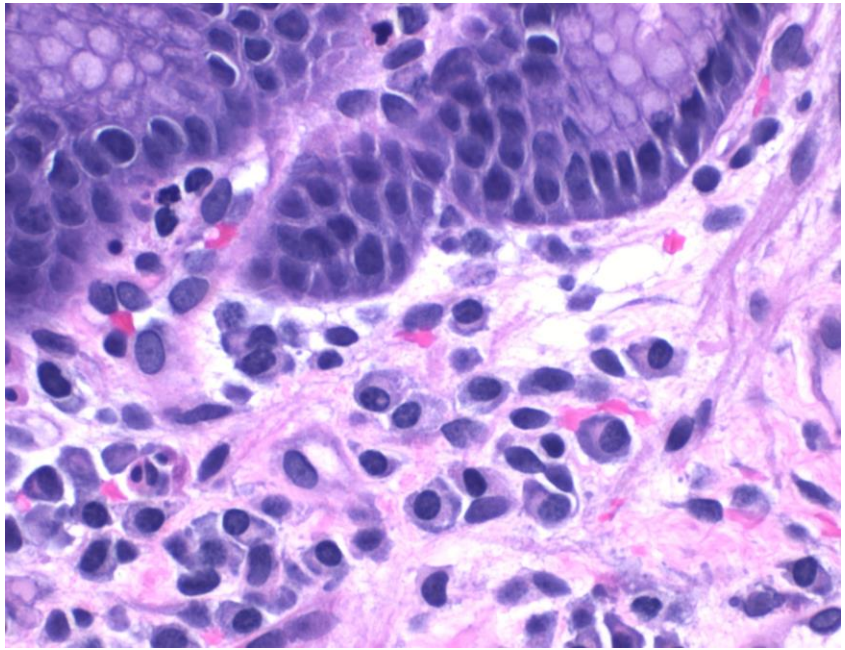
The last stage of B cell maturation, express CD138 but lose CD19:
+cannot switch antibody classes.
+can only produce a single kind of antibody in a single class of immunoglobulin.





Plasma cell: eccentric nuclei and perinuclear halo of clearer cytoplasm (Golgi apparatus)

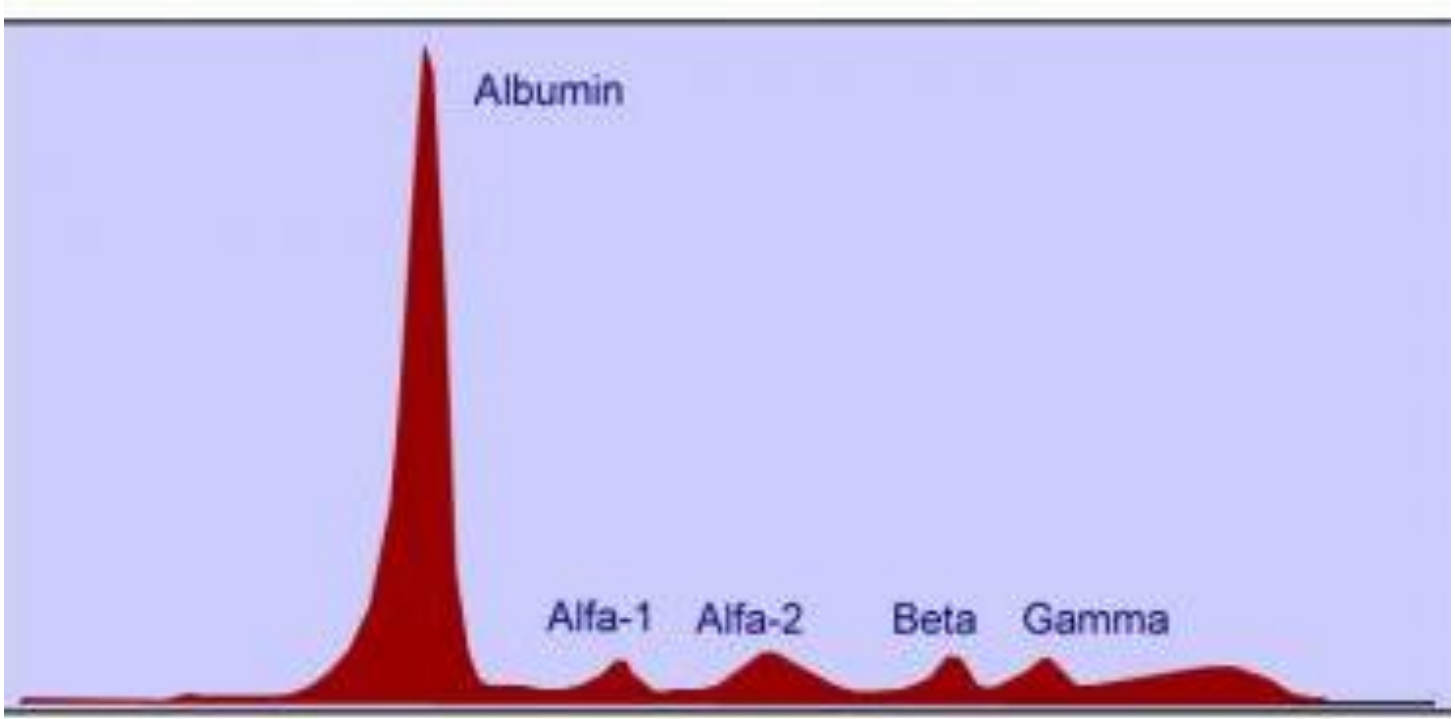
Plasma Cell Neoplasms and Related Entities

- 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.

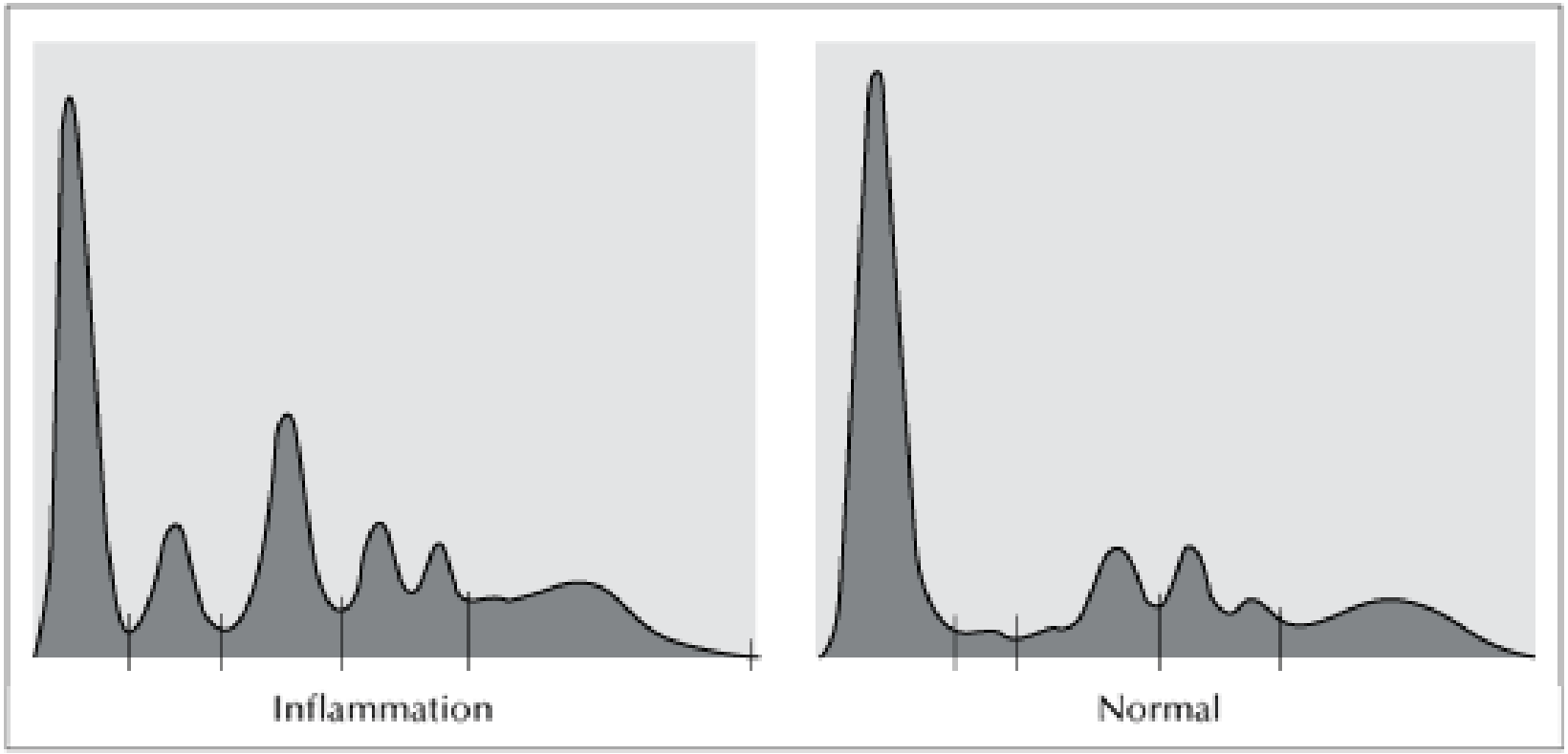
Plasma Cell Neoplasms and Related Entities

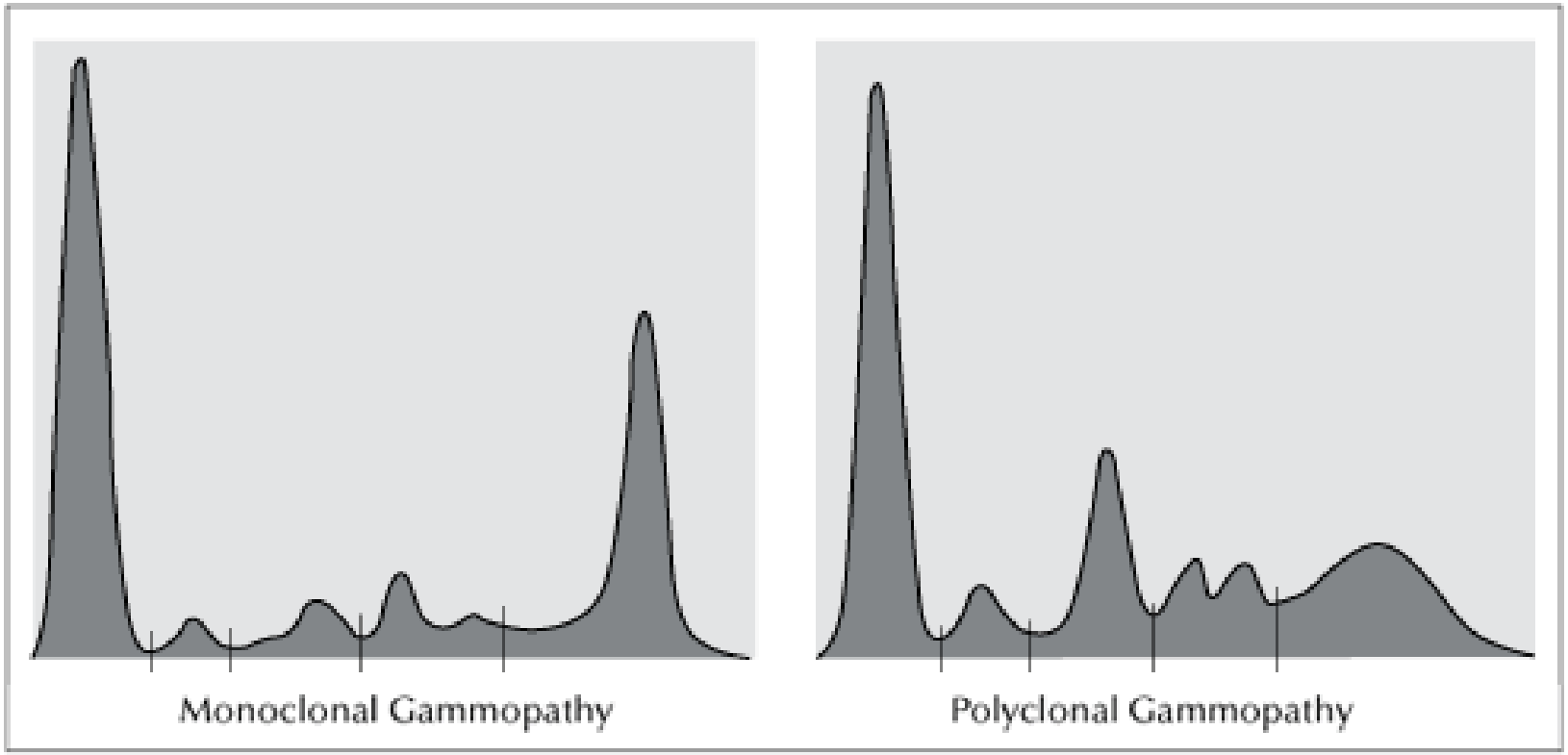
- **M protein**: A monoclonal immunoglobulin identified in the blood. They have high molecular weight, so they are restricted to plasma & extracellular fluid & excluded from urine.
- Neoplastic plasma cells also synthesize excess immunoglobulin light chains → smaller in size → excreted in the urine, where they are called → **Bence Jones proteins.**
- Monoclonal immunoglobulin can be detected by simple serum test → Serum protein Electrophoresis!

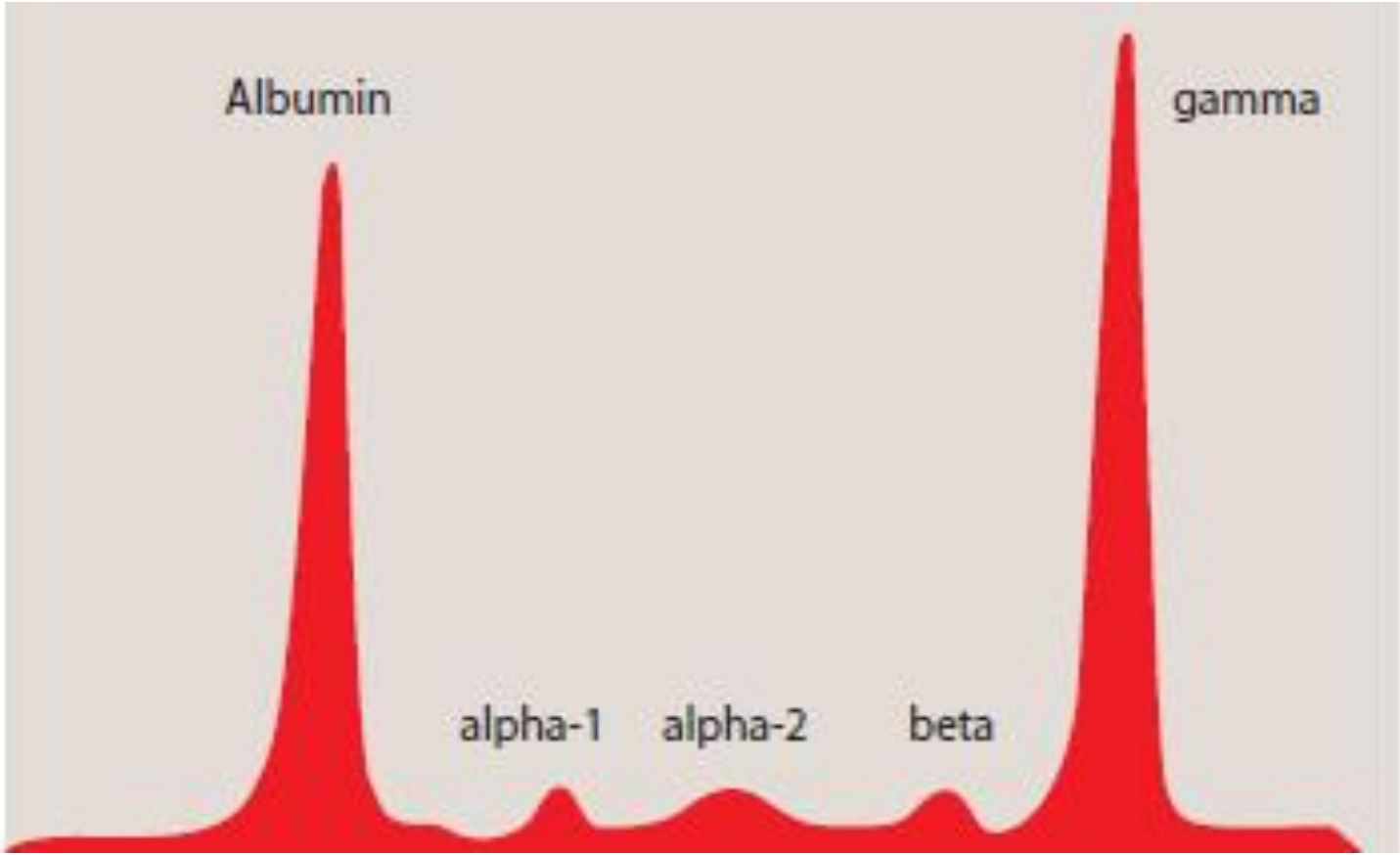
Serum protein Electrophoresis:



Normal serum protein electrophoresis diagram with legend of different zones


Inflammation
Normal


Monoclonal Gammopathy
Polyclonal Gammopathy


Albumin
gamma
alpha-1
alpha-2
beta

Plasma Cell Neoplasms and Related Entities

Abnormal immunoglobulins are associated with several clinicopathologic entities:

- **Multiple myeloma (MM)(plasma cell myeloma):** The most important plasma cell neoplasm.

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

+Smoldering myeloma: another uncommon variant defined by a lack of symptoms and a high plasma M component.

Plasma Cell Neoplasms and Related Entities

- **Monoclonal gammopathy of undetermined significance (MGUS)** : Applied to patients without signs or symptoms, & small to moderately large M components in blood.
  +MGUS is very common in older adult.
  + Has a low but constant rate of transformation to MM.
- **Waldenström macroglobulinemia:** A syndrome in which high levels of **IgM** lead to symptoms related to hyperviscosity of the blood. (ass/w lymphoplasmacytic lymphoma).

Multiple Myeloma

- One of the most common lymphoid malignancies.
- Median age 70 years, more common in males.
- Principally involves the bone marrow and ass/w lytic lesions throughout the skeletal system.
- The most frequent M protein produced by myeloma cells is **IgG** (60%), followed by **IgA**.
- Plasma cells produce κ or λ light chains.

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.

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, bone pain & 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.

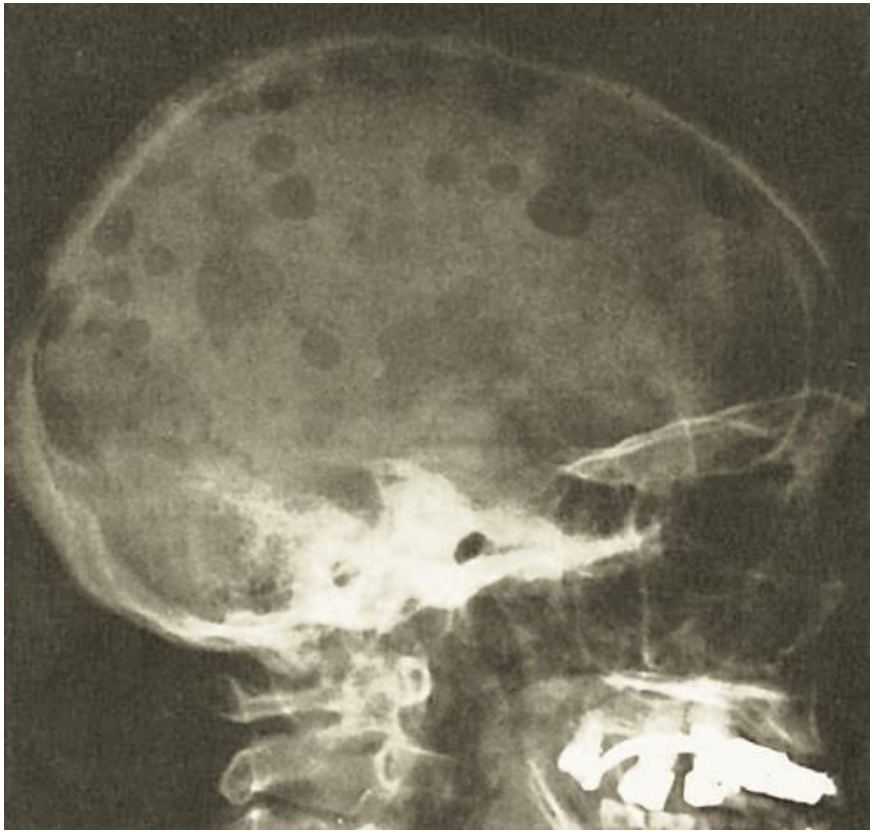
Multiple Myeloma – Renal dysfunction

- Several pathologic effects of MM:

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

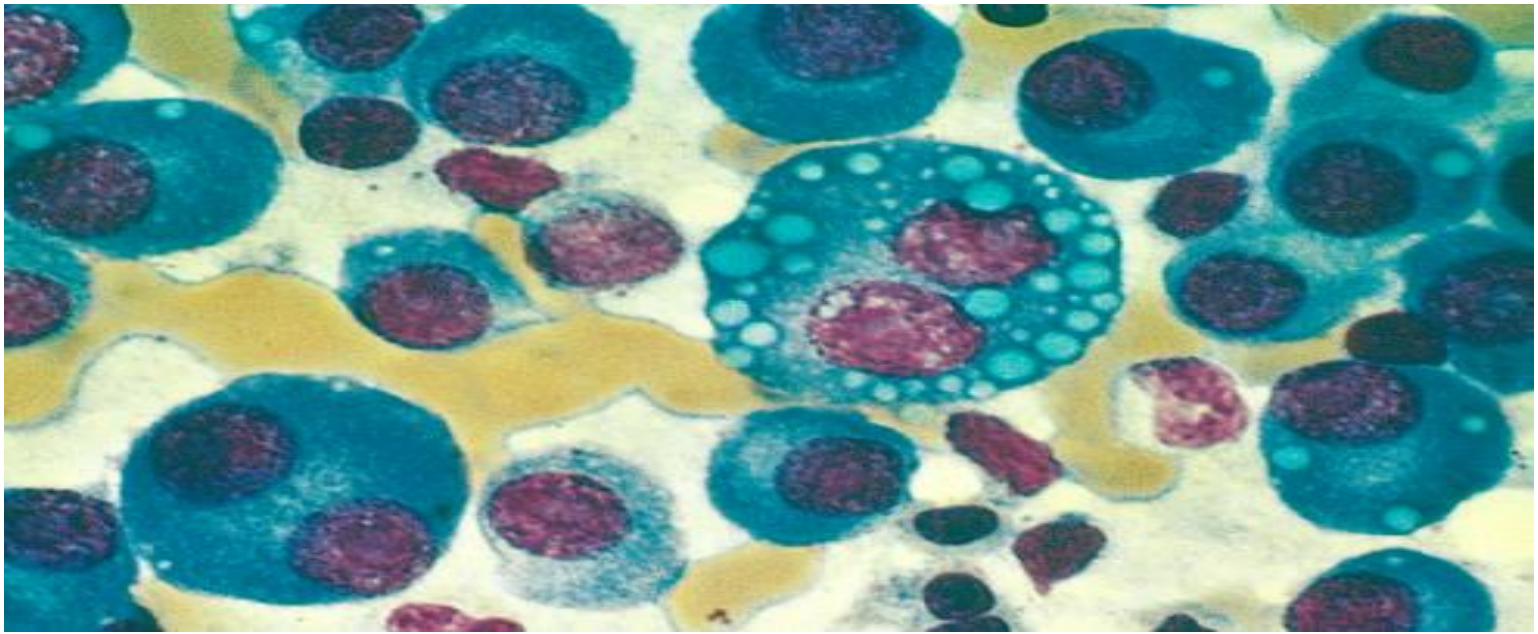
Multiple Myeloma – Morphology

- Multifocal destructive skeletal lesions (mostly; vertebral column, ribs, skull, pelvis, & femur.)
- The lesions arise in the medullary cavity. (punched-out defects)
- Bone destruction leads to pathologic fractures. (Common 1st presentation)



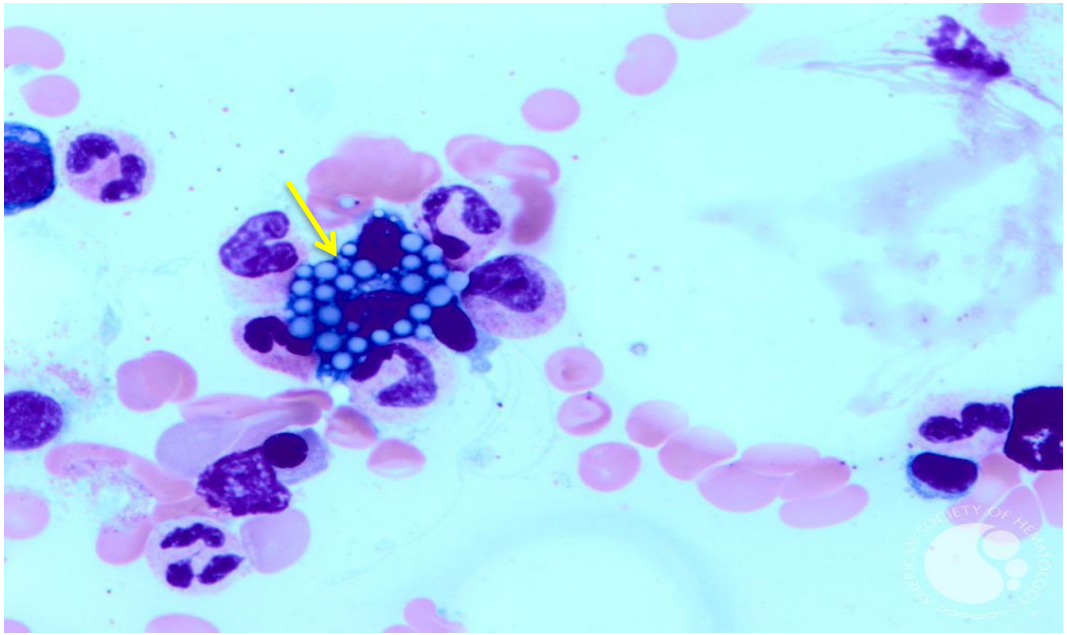
Multiple Myeloma – Morphology

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
- Variable prognosis. 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).

Lymphoplasmacytic Lymphoma

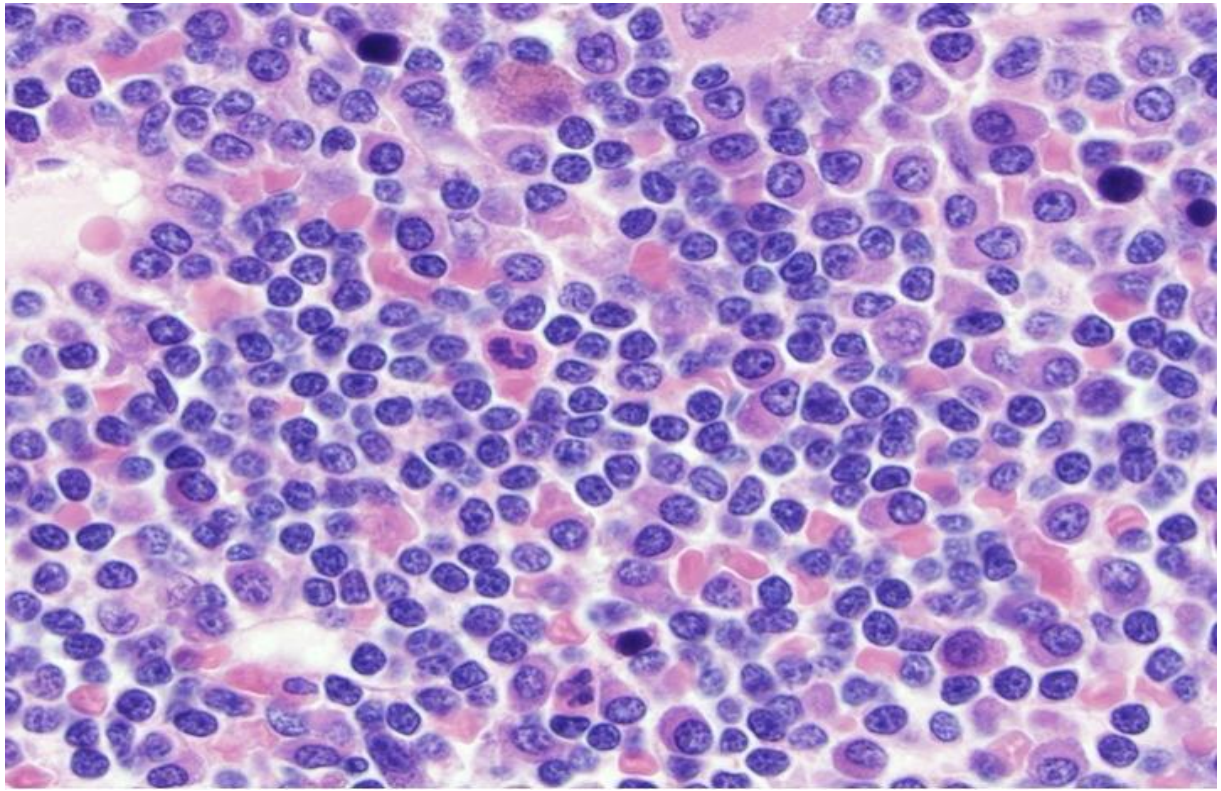
- A B-cell neoplasm that usually presents in old age.
- Most commonly, the plasma cell component secretes monoclonal **IgM**.
- Amounts sufficient to cause a hyperviscosity syndrome → **Waldenström macroglobulinemia.**
- Complications from the secretion of free light chains (e.g.; renal failure) are 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

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Thank you!!