

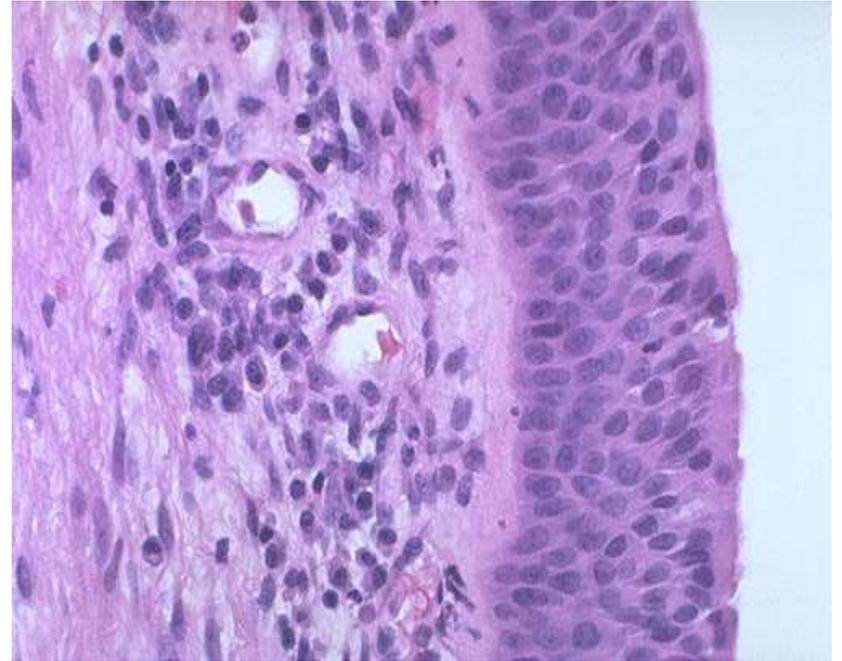
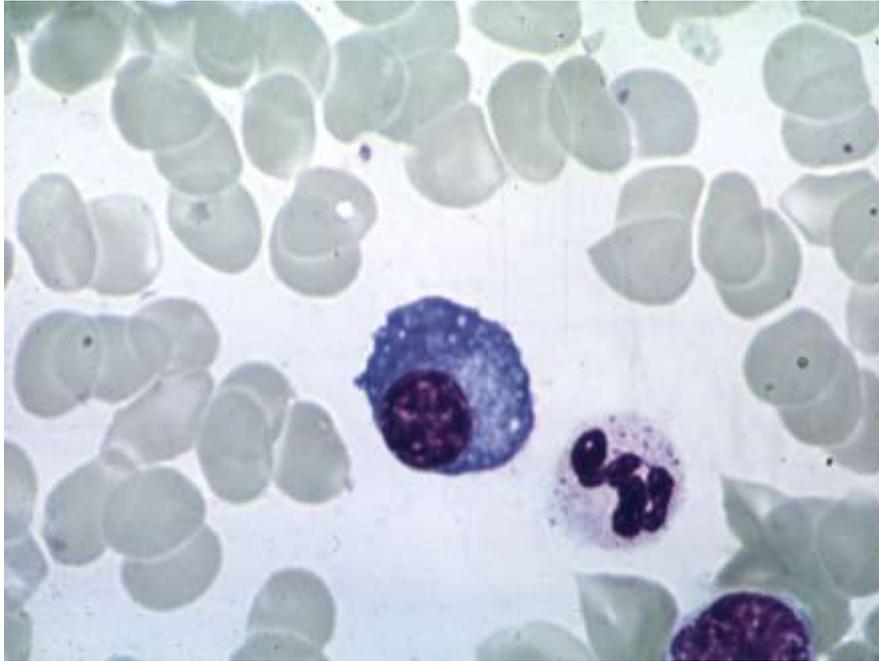
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Neoplastic Proliferations of White Cells

~ 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.

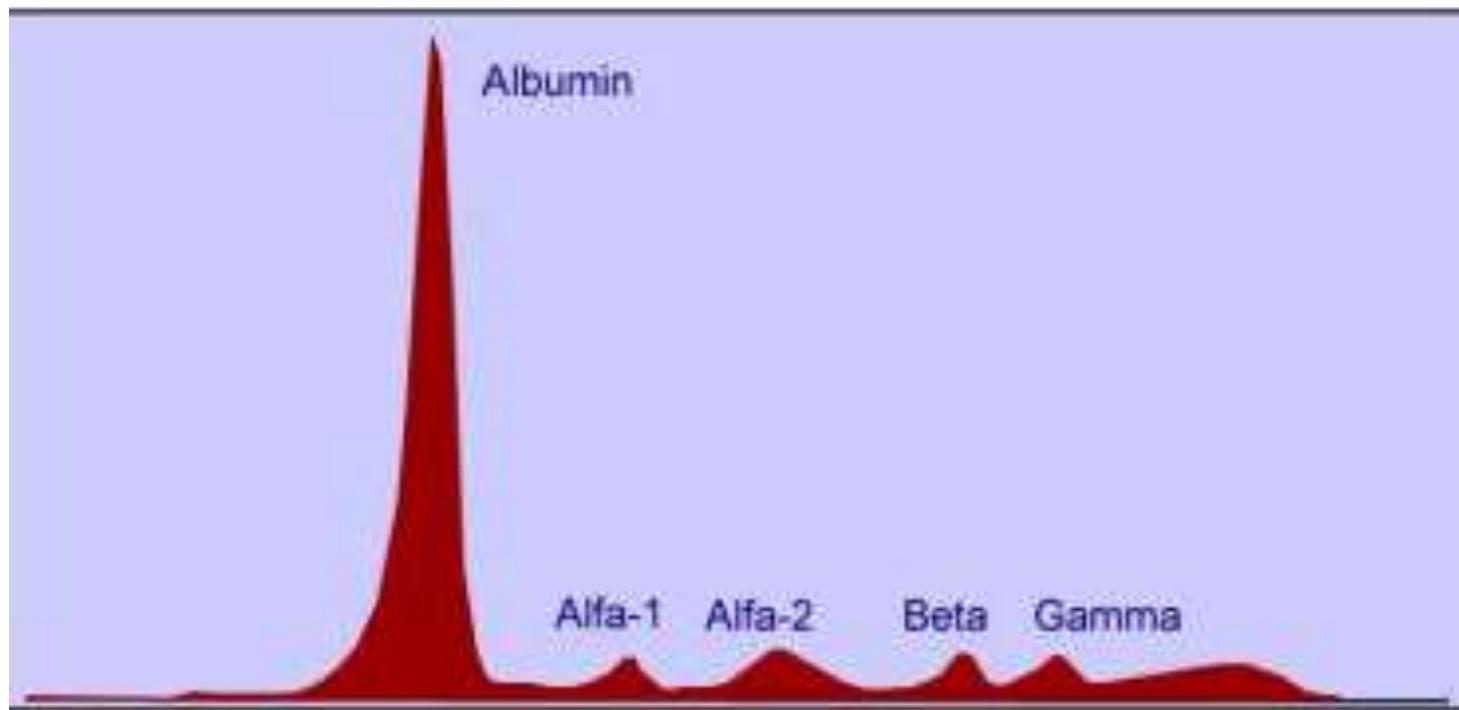


Plasma Cell Neoplasms and Related Entities

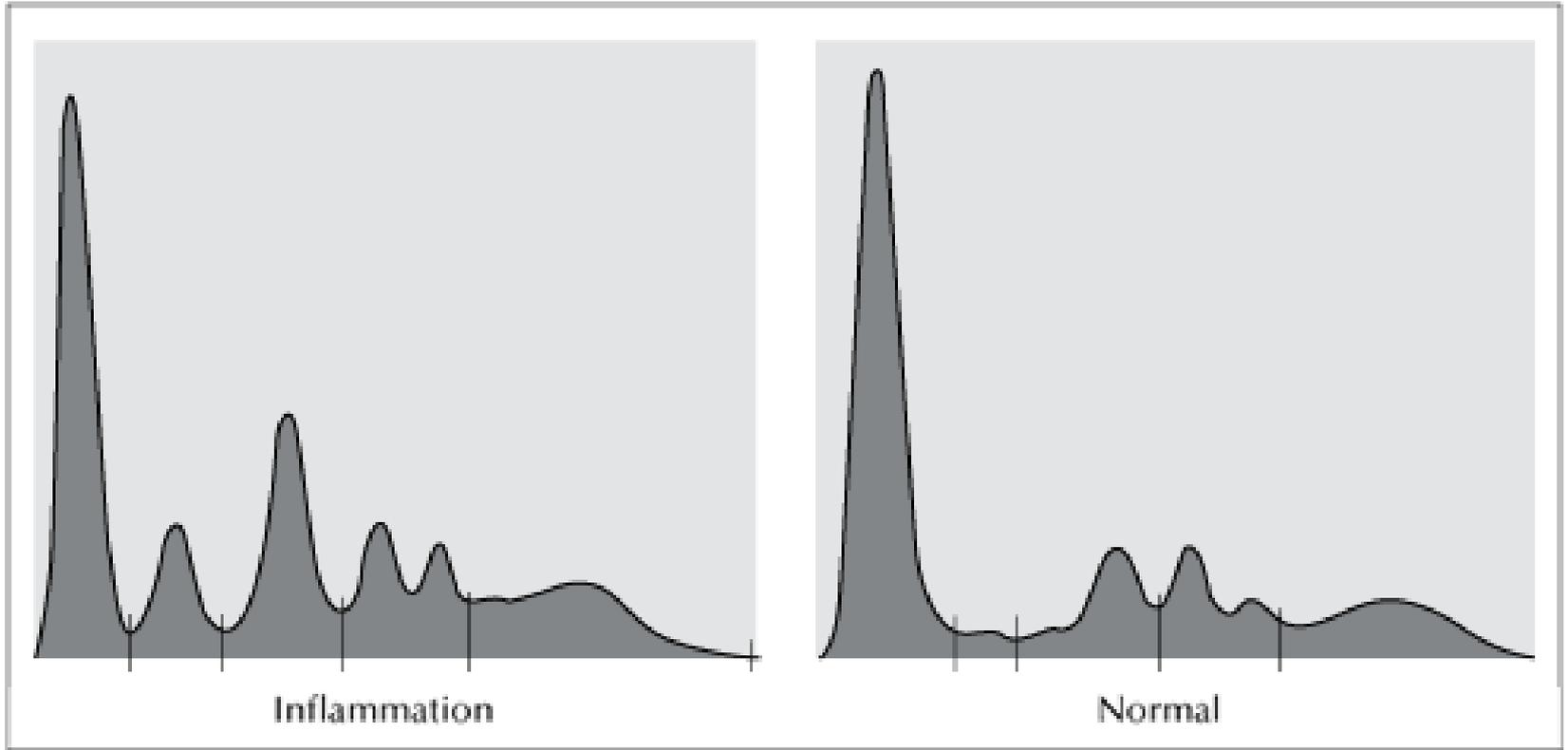
- ▶ B cell proliferations contain neoplastic plasma cells
- ▶ Always secrete a **monoclonal** immunoglobulin or their fragment.
- ▶ These serve as tumor markers and often have pathologic consequences.
- ▶ The most common & deadly of these neoplasms is multiple myeloma.

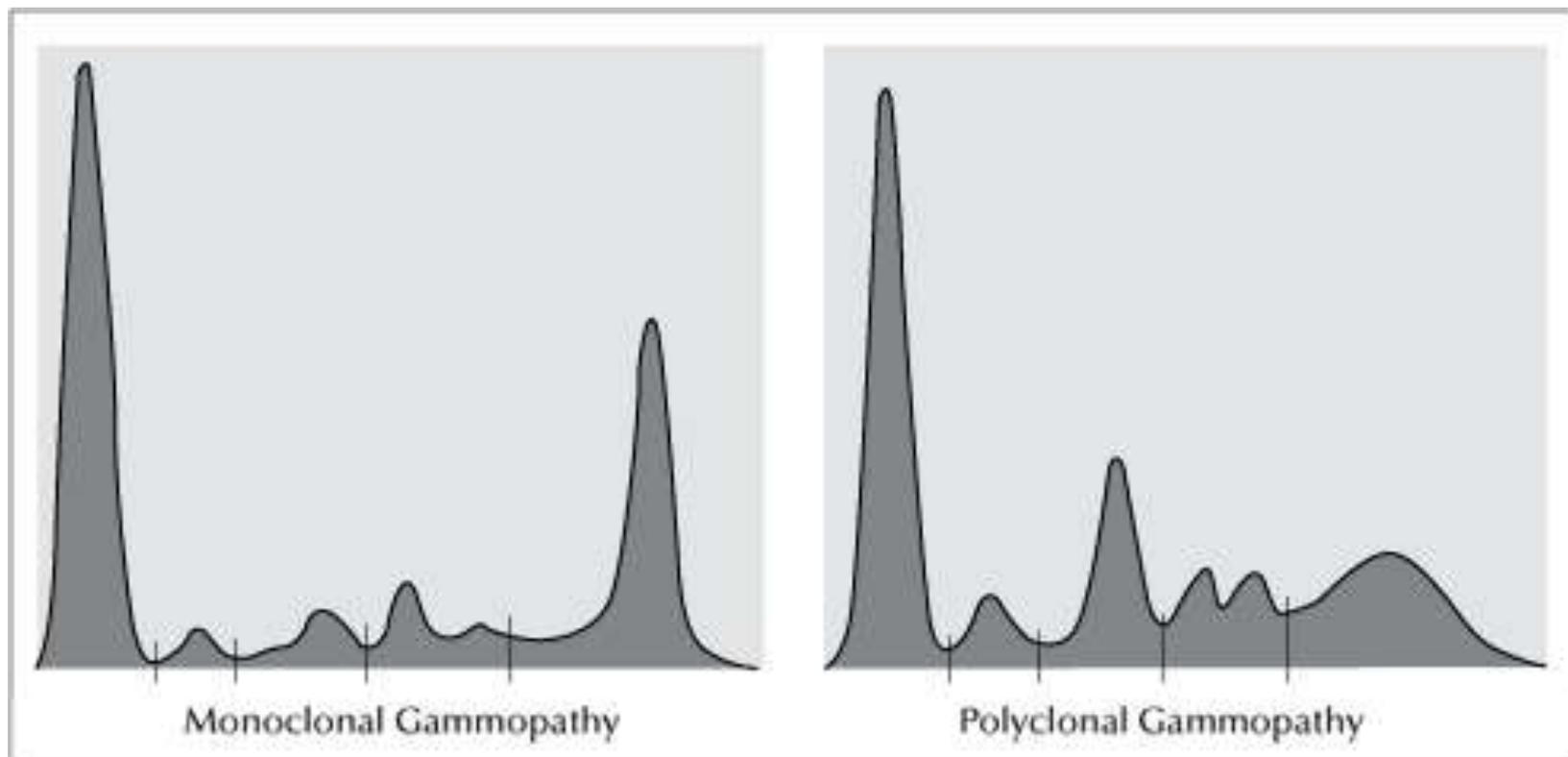
Plasma Cell Neoplasms and Related Entities

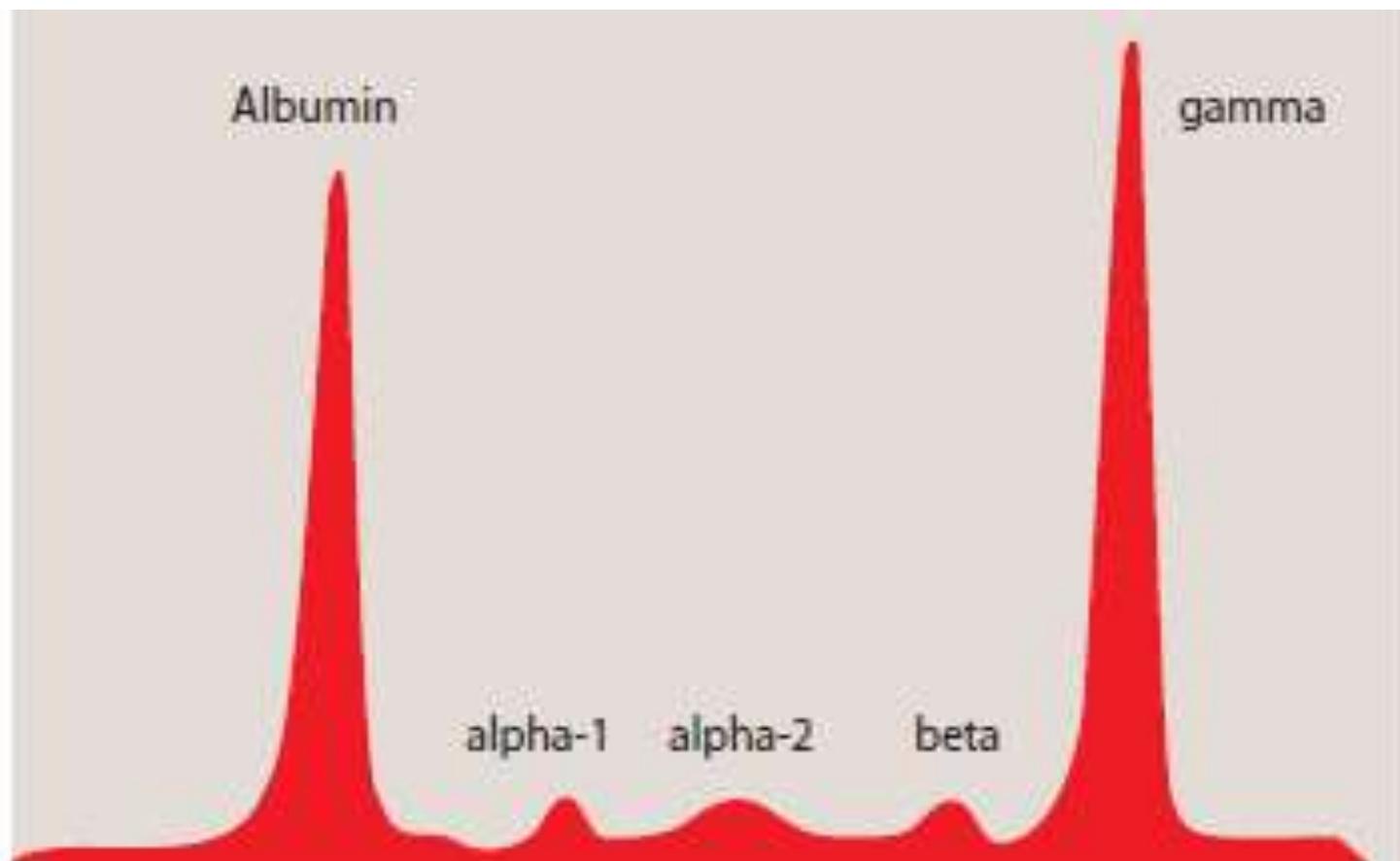
- ▶ **M protein**: A monoclonal immunoglobulin identified in the blood. They have high molecular weight, so they are restricted to plasma & extracellular fluid & excluded from urine.
- ▶ Neoplastic plasma cells also synthesize excess **immunoglobulin light chains** → smaller in size → excreted in the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



Normal serum protein electrophoresis diagram with legend of different zones







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 with 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 associated with 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- κ B 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

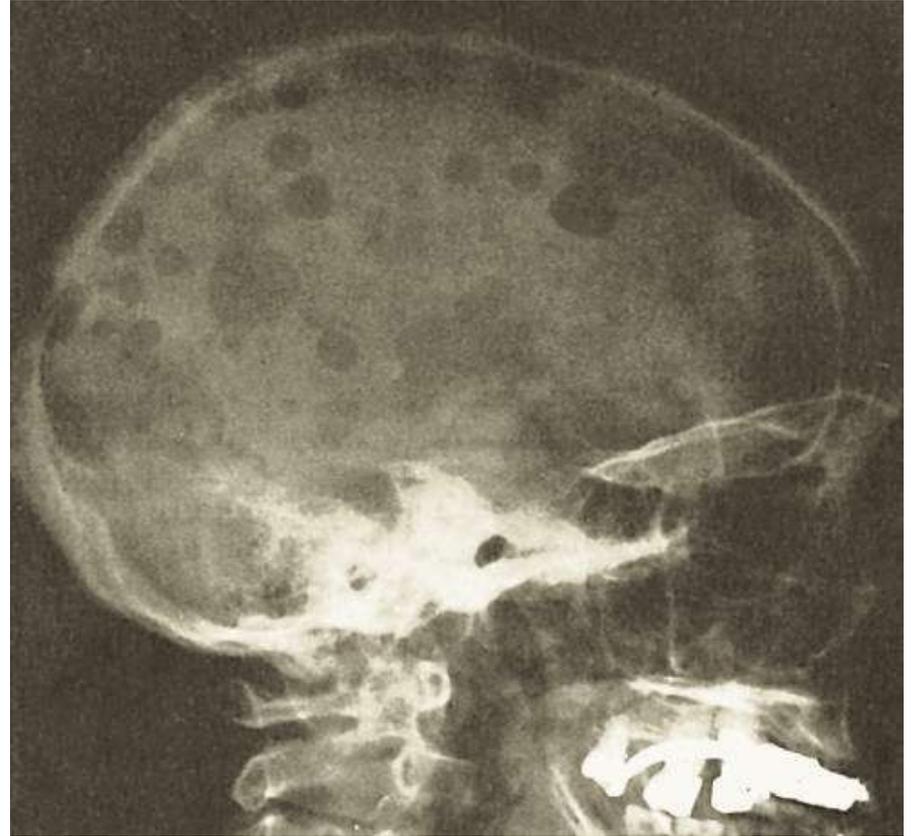
- ▶ MM Compromises the function of normal B cells → production of functional antibodies often is profoundly depressed → patients are at high risk for bacterial infections.

Multiple Myeloma - Renal dysfunction

- ▶ Several pathologic effects of MM:
 - 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,

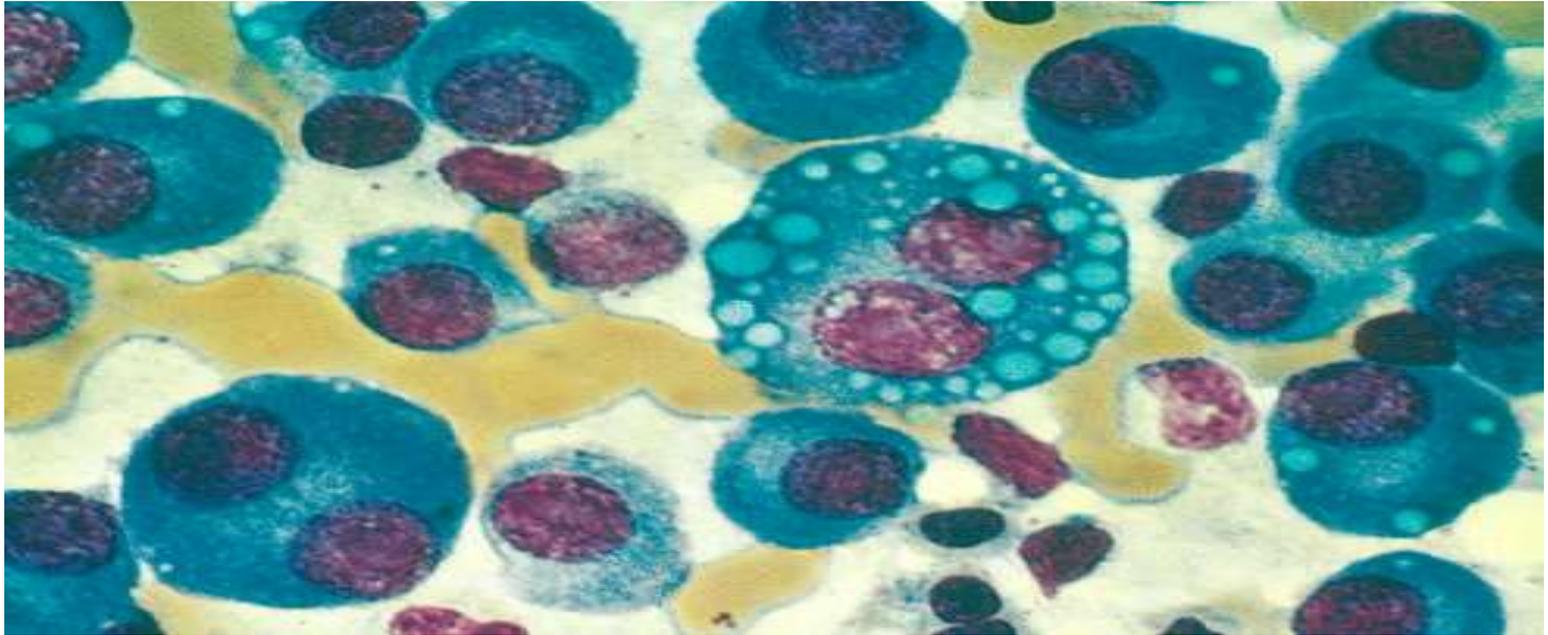
Multiple Myeloma - Morphology

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



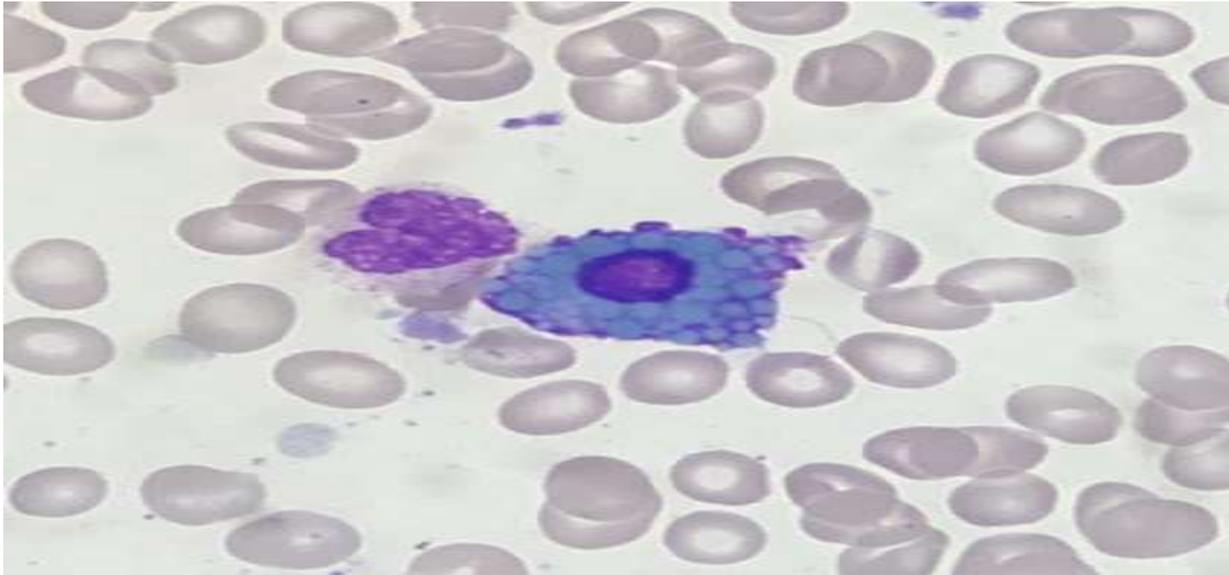
Multiple Myeloma - Morphology

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).

Lymphoplasmacytic Lymphoma

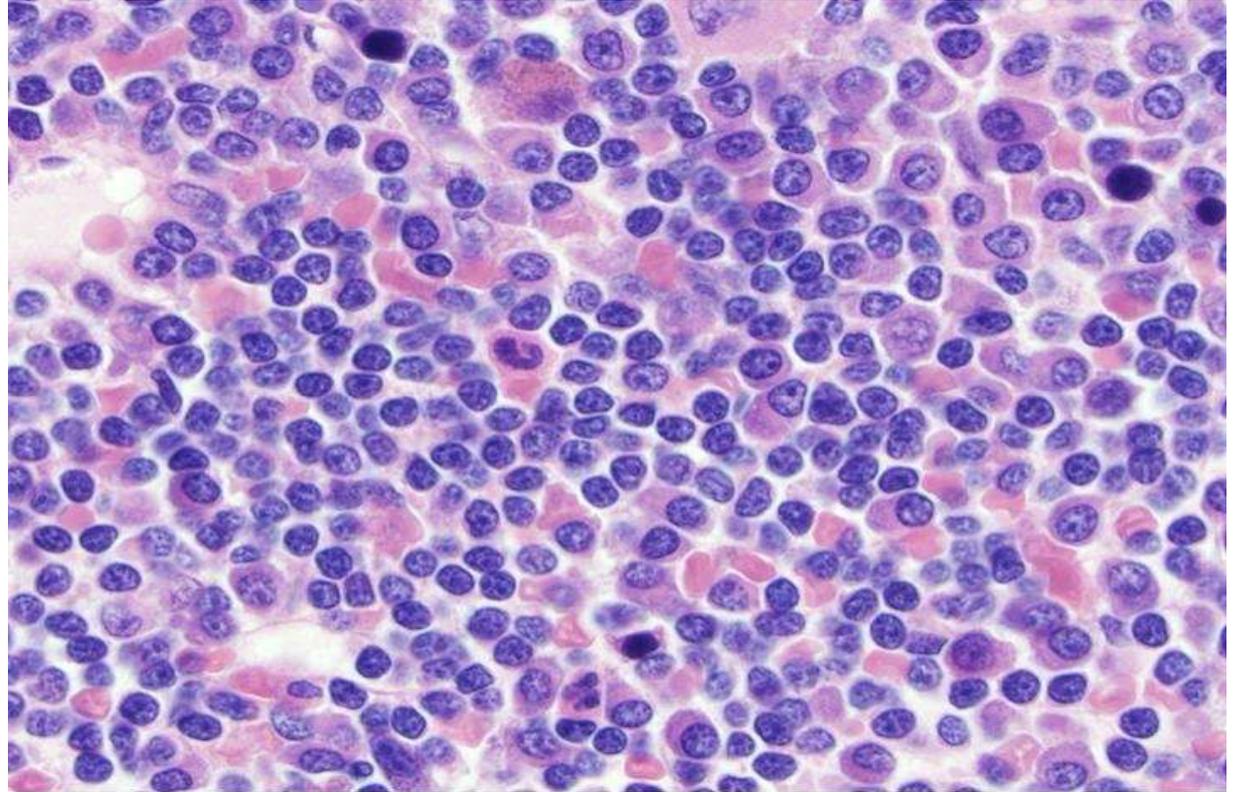
- ▶ A B-cell neoplasm that usually presents in old age.
- ▶ Most commonly, the plasma cell component secretes monoclonal **IgM**.
- ▶ Amounts sufficient to cause a hyperviscosity syndrome
→ **Waldenström macroglobulinemia**.
- ▶ Complications from the secretion of free light chains (e.g.; renal failure)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

قال الفضيل بن عياض: "من عرف الناس
استراح فلا يطرب لمدحهم ولا يجزع
لذمهم فإنهم سريعوا الرضا سريعوا
السخط والهوى يحركهم"

Thank you!!