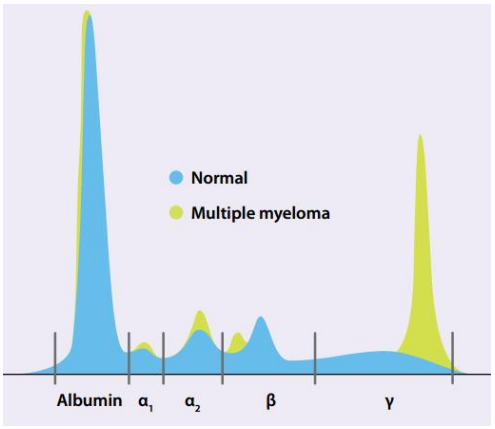
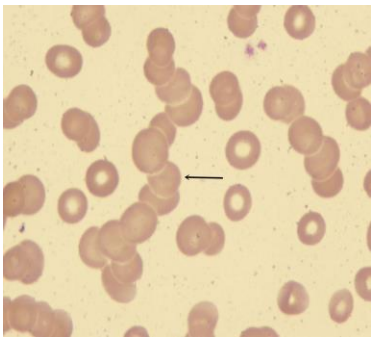
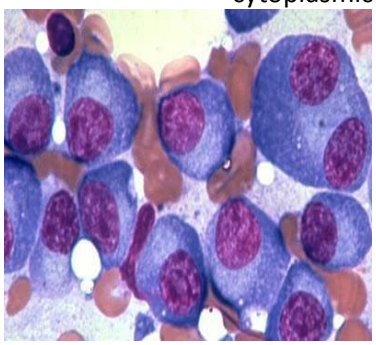
Problem 10 – Unit 6 – Pathology: Multiple myeloma (MM) & MGUS



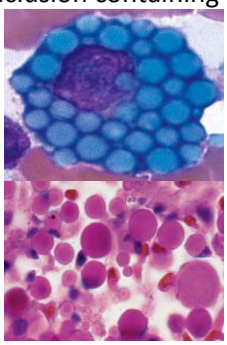
- **Plasma cell neoplasms**: clonal proliferations of immunoglobulin-producing plasma cells or lymphocytes which make and secrete a single complete or partial immunoglobulin.
- The secreted immunoglobulin is detected as a monoclonal protein (M protein) on serum or urine protein electrophoresis **(figure).**
- **Multiple myeloma (MM):**
  - **Definition**: it is a bone marrow based (lytic lesion are found throughout the skeletal system: **figure**), multifocal (متعدد البُؤر), plasma cell neoplasm associated with M protein (igG is 60% of cases followed by IgA in 20% of cases).
  - **People at risk**: elderly (median age is 70 years) – males more than females.
  - **Pathogenesis**:
    - ✓ Chromosomal translocation involving IgH and other genes (cyclin D1, cyclin D3, FGFR-3).
    - ✓ Fibroblasts and macrophages in the bone marrow → producing IL-6 → supporting the proliferation of myeloma cells.
    - ✓ Myeloma cells will secrete cytokines (IL-1β, IL-6 and TNF) →stimulating production of RANK-ligand → which in turn stimulates the differentiation and absorptive capacity of osteoclasts → bone marrow lytic lesions (involving the vertebral column, ribs, skull, pelvis, femur, clavicle and scapula).
    - ✓ Myeloma cells will also interfere with the function of normal plasma cells resulting in defects in antibody production. Low levels of functional antibodies will predispose the patient to bacterial infections.
    - ✓ There will be renal dysfunction (WHY?)
      * Hypercalcemia → dehydration and renal stones.
      * Obstructive proteinaceous casts in distal convoluted tubules and collecting ducts. Multinucleate giant cells usually surround the casts.
      * Light chain deposition in the glomeruli or interstitium (either as amyloid or linear deposits).
      * Frequent bacterial pyelonephritis.
  - **Morphology:**
    - ✓ the bone marrow will show increased number of plasma cells (usually > 30%). Plasma cells may infiltrate other organs.
    - ✓ Myeloma cells resemble plasma cells but they might have prominent nucleoli or cytoplasmic inclusion containing immunoglobulin.



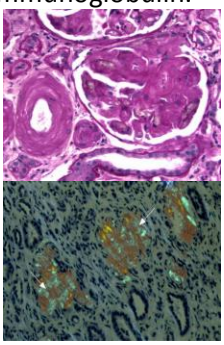
Rouleaux formation in a blood smear (aggregation of RBCs) seen in a patient with myltiple myeloma



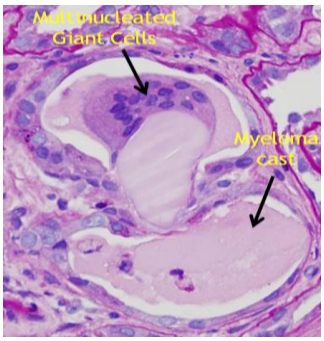
The bone marrow in multiple myeloma showing large numbers of plasma cells with many abnormal forms



Mott cells (pasma cells with spherical inclusion packed in their cytoplasm) and Russell bodies are seen in plasma cell neoplasm



Amyloid deposition in the kidney (above: H&E staining – Below: Congo red staining)



Myeloma cast nephropathy with myeloma casts surrounded by multinucleated giant cell

- **Clinical features:**
  - ✓ Bone pain because those lytic lesions will lead to pathologic fractures.
  - ✓ Hypercalcemia due to increased activity of osteoclasts leading to neurologic manifestations (confusion & lethargy) and renal dysfunction.
  - ✓ Anemia.
  - ✓ Recurrent infection with bacteria (because of decreased antibody production by plasma cells).
  - ✓ AL-type amyloidosis.
  - ✓ Symptoms related to hyperviscosity.

- **Monoclonal gammopathy of undetermined significance (MGUS):**
  - It is an asymptomatic plasma cell neoplasm. It is considered as a precursor lesion that will evolve to multiple myeloma (MM).
  - **People at risk**: 1-3% of healthy people are above 50 years.
  - **Pathogenesis**: same chromosomal translocations as multiple myeloma.
  - **Diagnostic criteria:**
    - ✓ M component < myeloma levels.
    - ✓ Marrow plasmacytosis is < 10% (presence of plasma cells in the bone marrow).
    - ✓ No lytic bone lesions.
    - ✓ No myeloma-related symptoms.