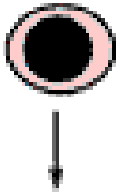
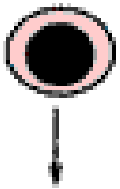
Plasma Cell Neoplasms

Multiple Myeloma and Related Disorders

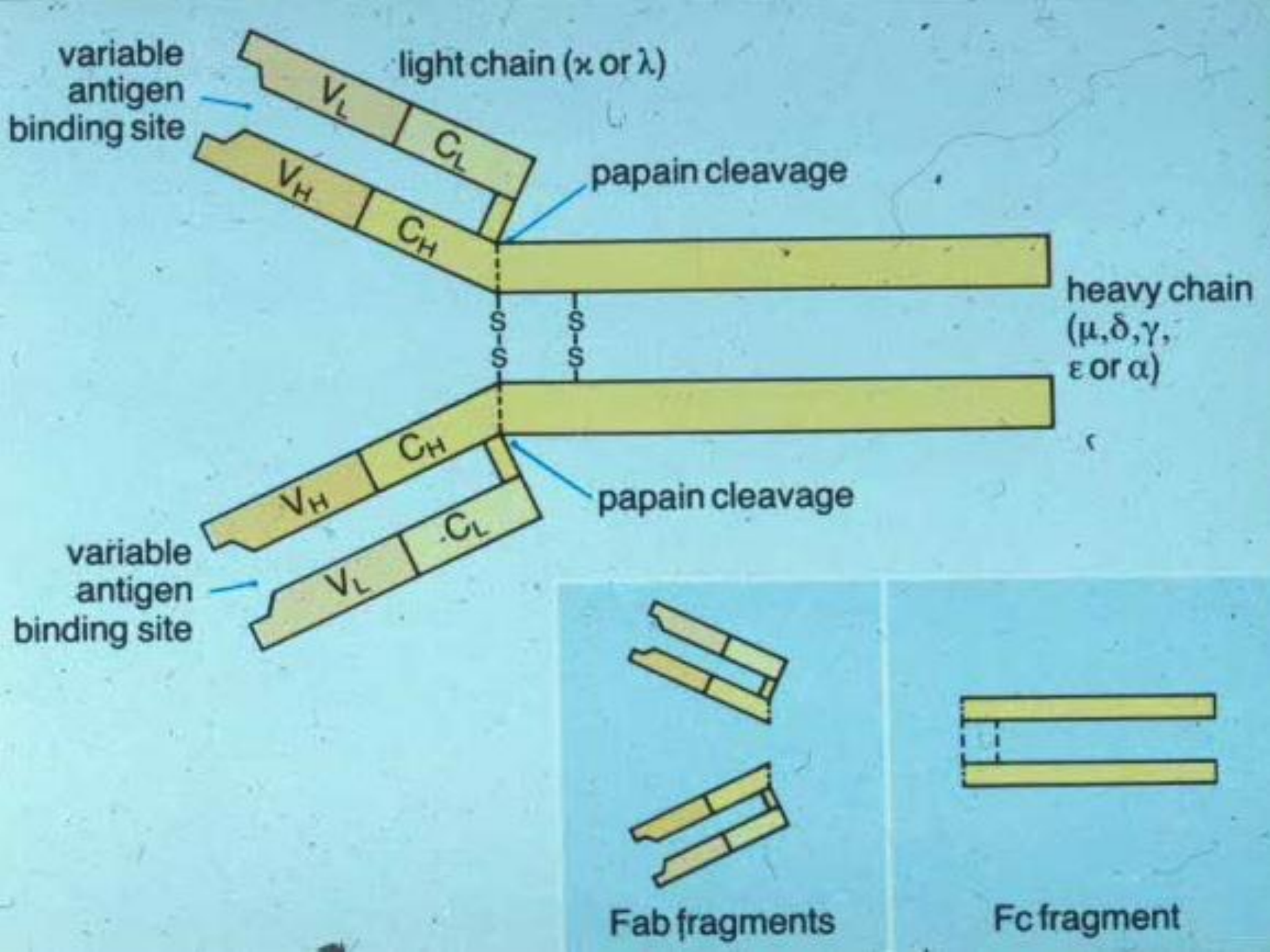
A group of diseases that involve malignant proliferation of Ig-secreting cells of B-cell lineage that are usually associated with paraproteinemia or paraproteinuria.

- Plasma Cell Dyscrasia
  - MGUS
  - Plasmacytoma
- Multiple myeloma
  - Smoldering
  - POEMS
- Waldenstrom's Macroglobulinemia
- Amyloidosis

Stage B of cell maturation		Corresponding Malignancy
stem cell		acute lymphocytic leukemia lymphoblastic lymphoma
pre-B cell		
immature B cell		small non-cleaved cell lymphoma (Burkitt's)
B cell pre-antigen exposure		chronic lymphocytic leukemia small lymphocytic lymphoma
B cell post-antigen exposure		follicular lymphomas large cell lymphoma immunoblastic lymphoma
antibody-producing B cell		myeloma

The Continuum of Plasma Cell Disorders

Normal MGUS Indolent Myeloma Multiple Myeloma


variable
antigen
binding site
light chain (κ or λ)
V_L
C_L
V_H
C_H
papain cleavage
heavy chain
(μ,δ,γ,
ε or α)
S-S
S-S
C_H
V_H
papain cleavage
C_L
V_L
variable
antigen
binding site
Fab fragments
Fc fragment

The hallmark of plasma cell disorders is the presence of a paraprotein in the serum and/or urine.

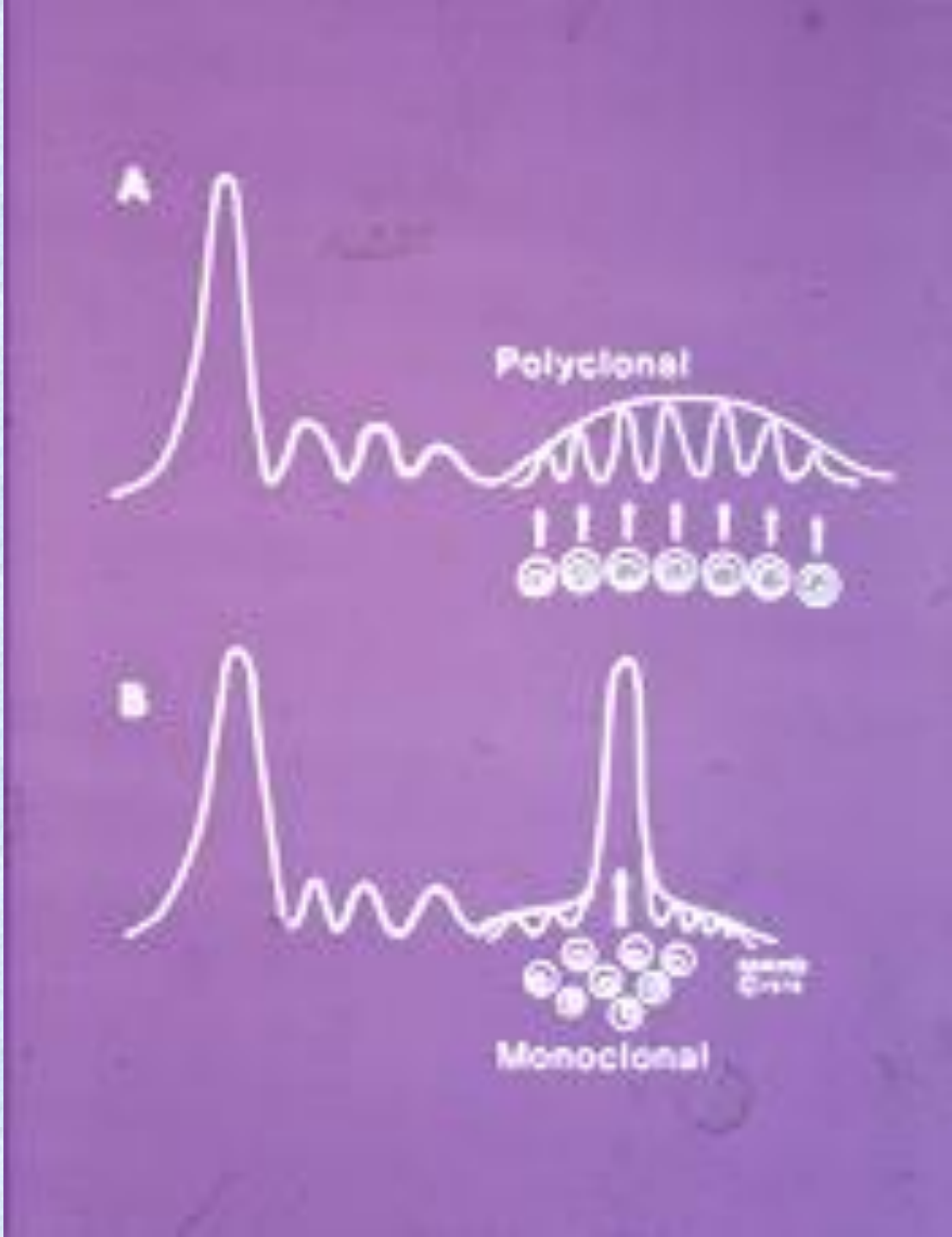
Paraproteinemias

- **Normal immunoglobulin pattern**
  - **Polyclonal reflects progeny of different plasma cells**
- **Paraproteinemia**
  - **Monoclonal immunoglobulin band in sera reflects synthesis from single plasma cell clone**

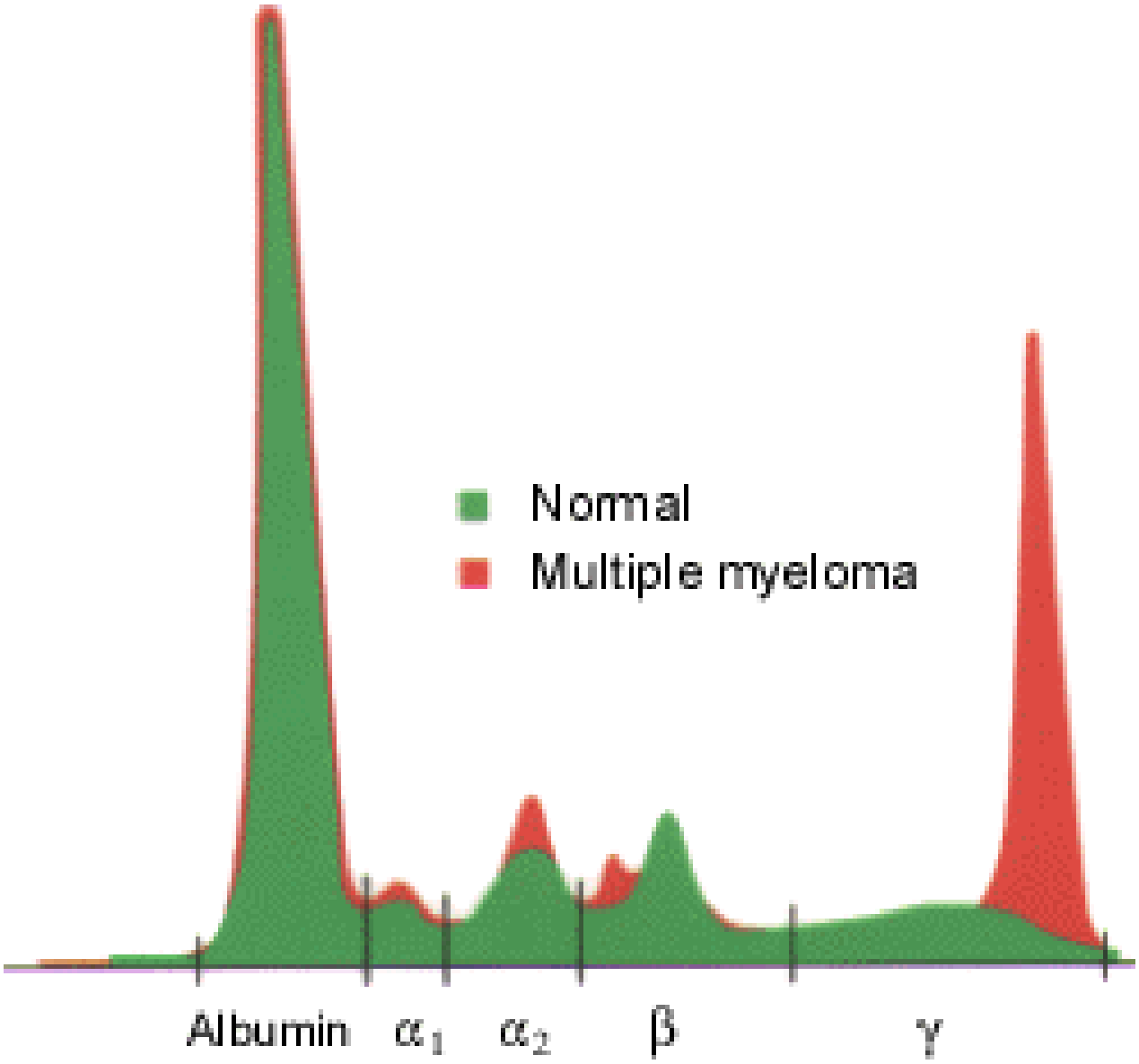
SPEP

Polyclonal Gammopathy

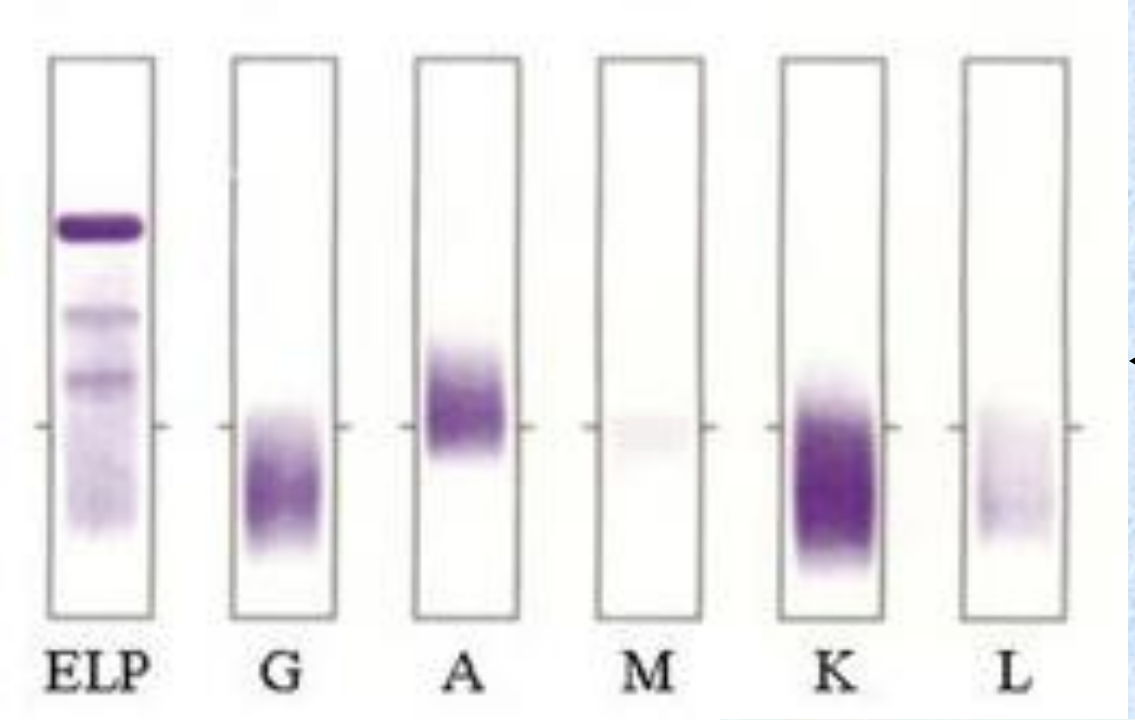
Monoclonal Gammopathy



Serum Protein Electrophoresis

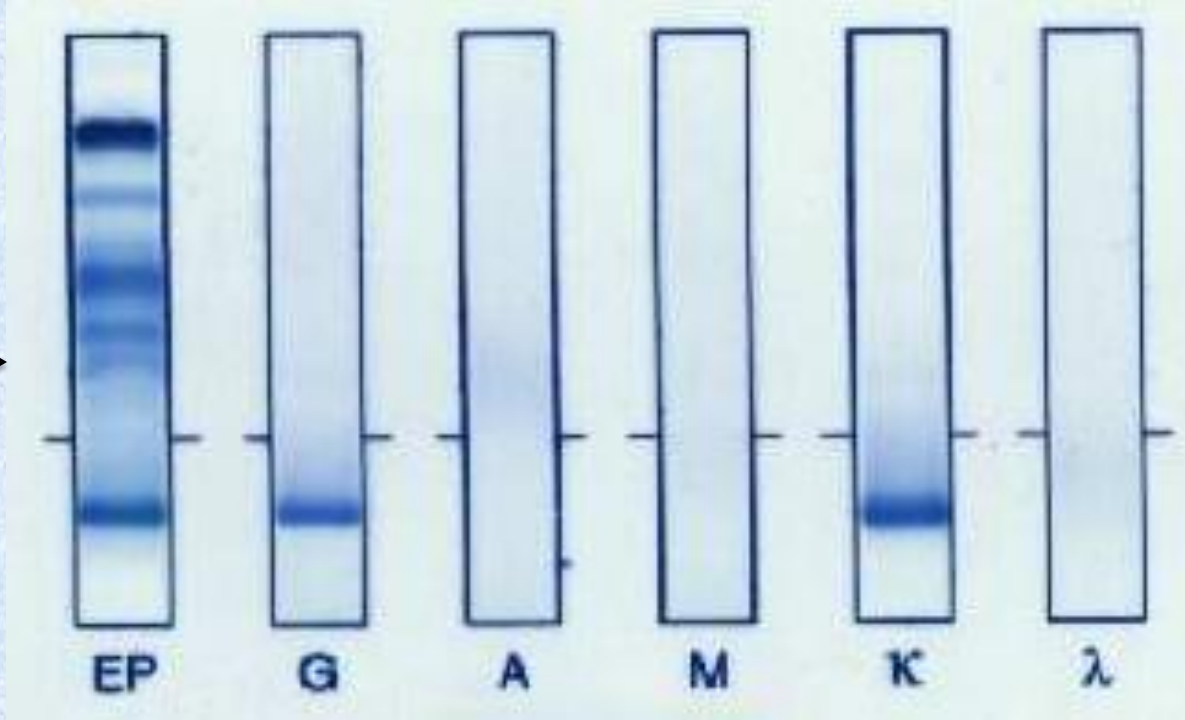


Immunofixation



Normal

Abnormal



Etiology

- Etiology is not known.
- Risk factors: Race, sex.
- Increased risk with ionizing radiation and exposure to pesticides like Dioxin.
- Recently viruses like HHV-8 and SV-40, have been linked to myeloma development.

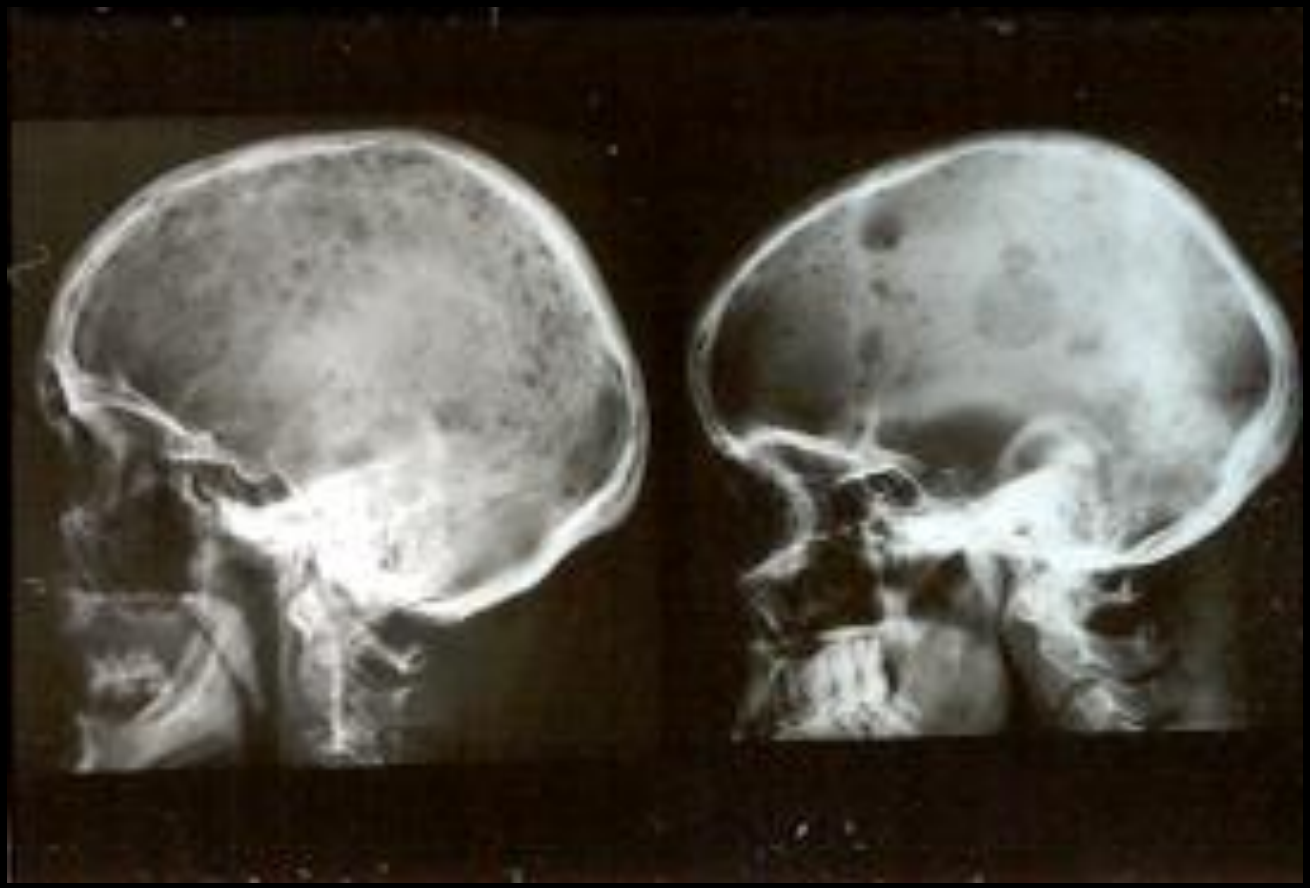
Pathogenesis

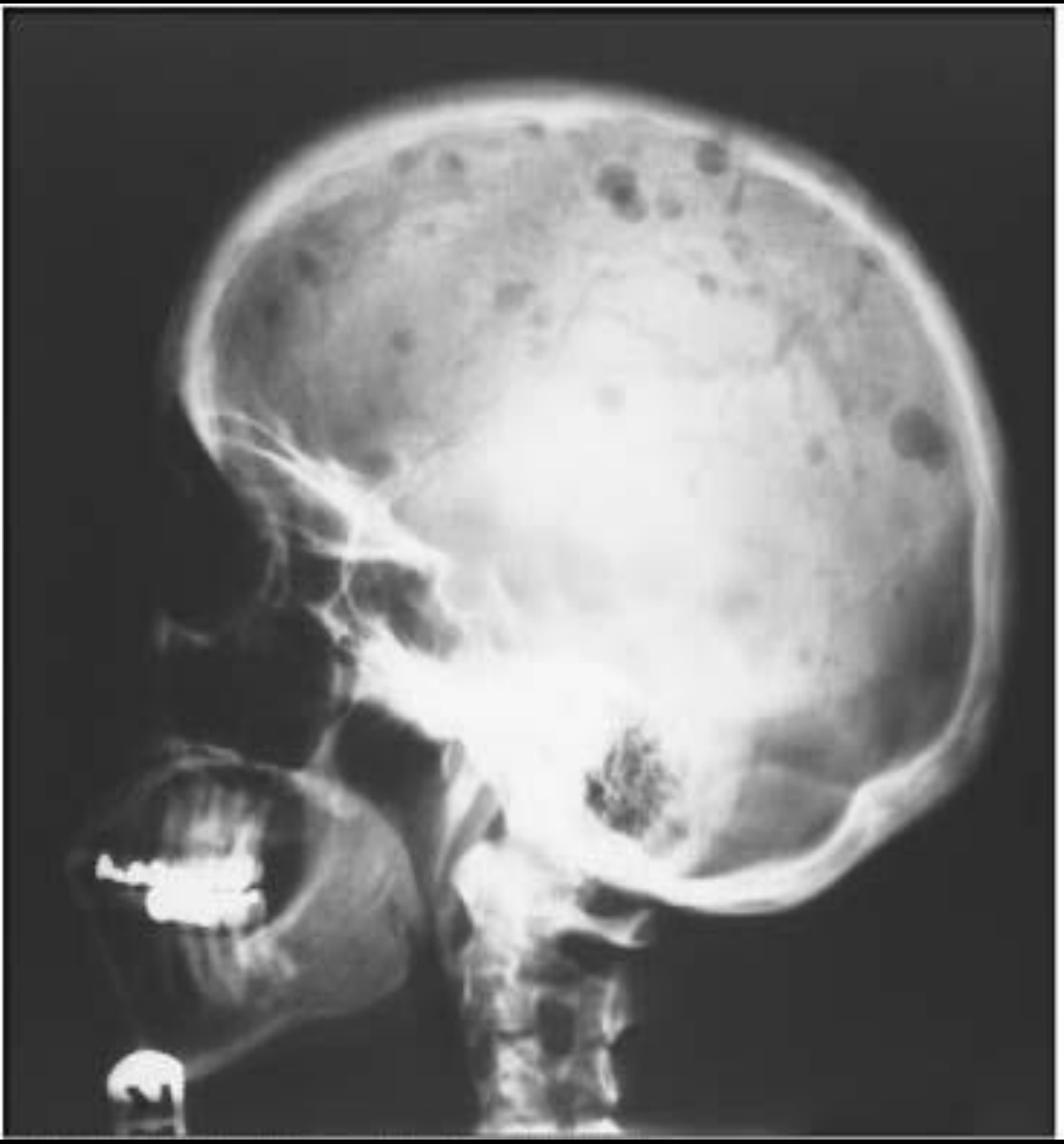
- Bone marrow microenvironment very important for proliferation and chemotherapy resistance.
- BM stromal cells produce IL-6, responsible for pathogenesis and progression.
- IL-6 inhibits apoptosis of plasma cells.
- IL-6 contributes to bone loss by stimulating osteoclasts and inhibiting bone formation.
- Interaction with extracellular matrix proteins protect cells from chemo and radiation.

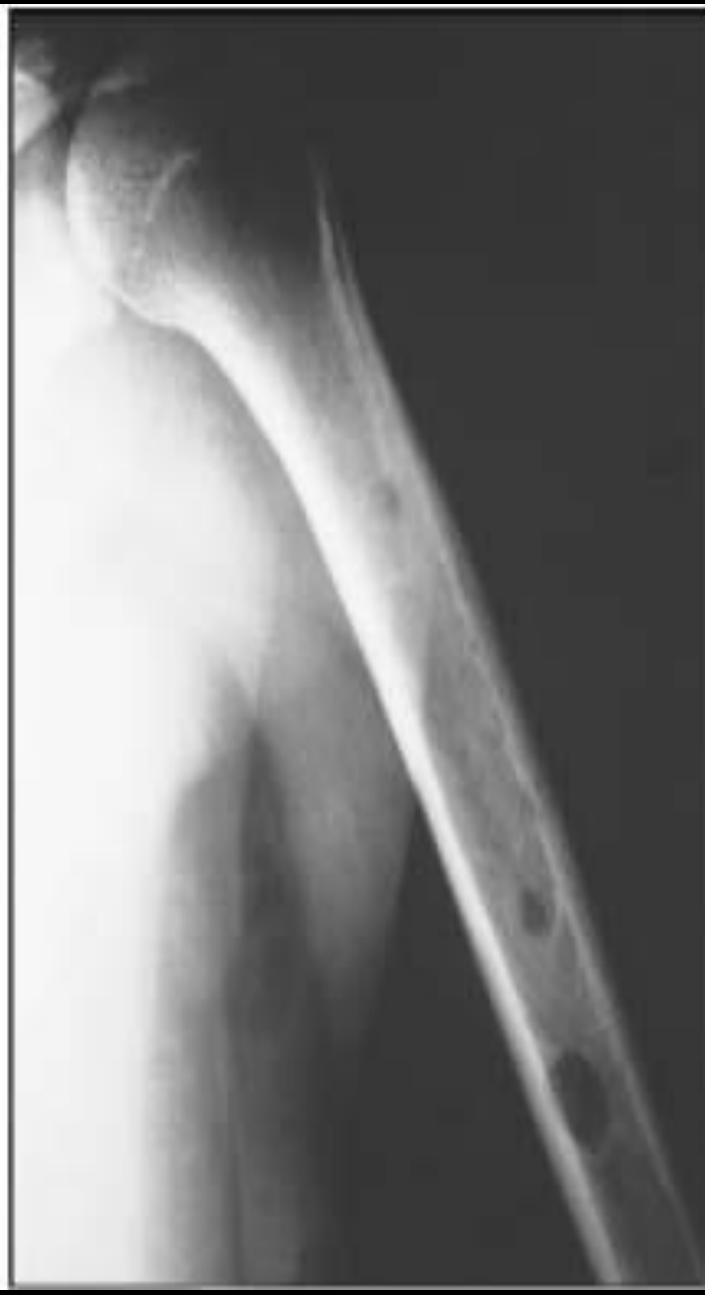
MM: Clinical Features

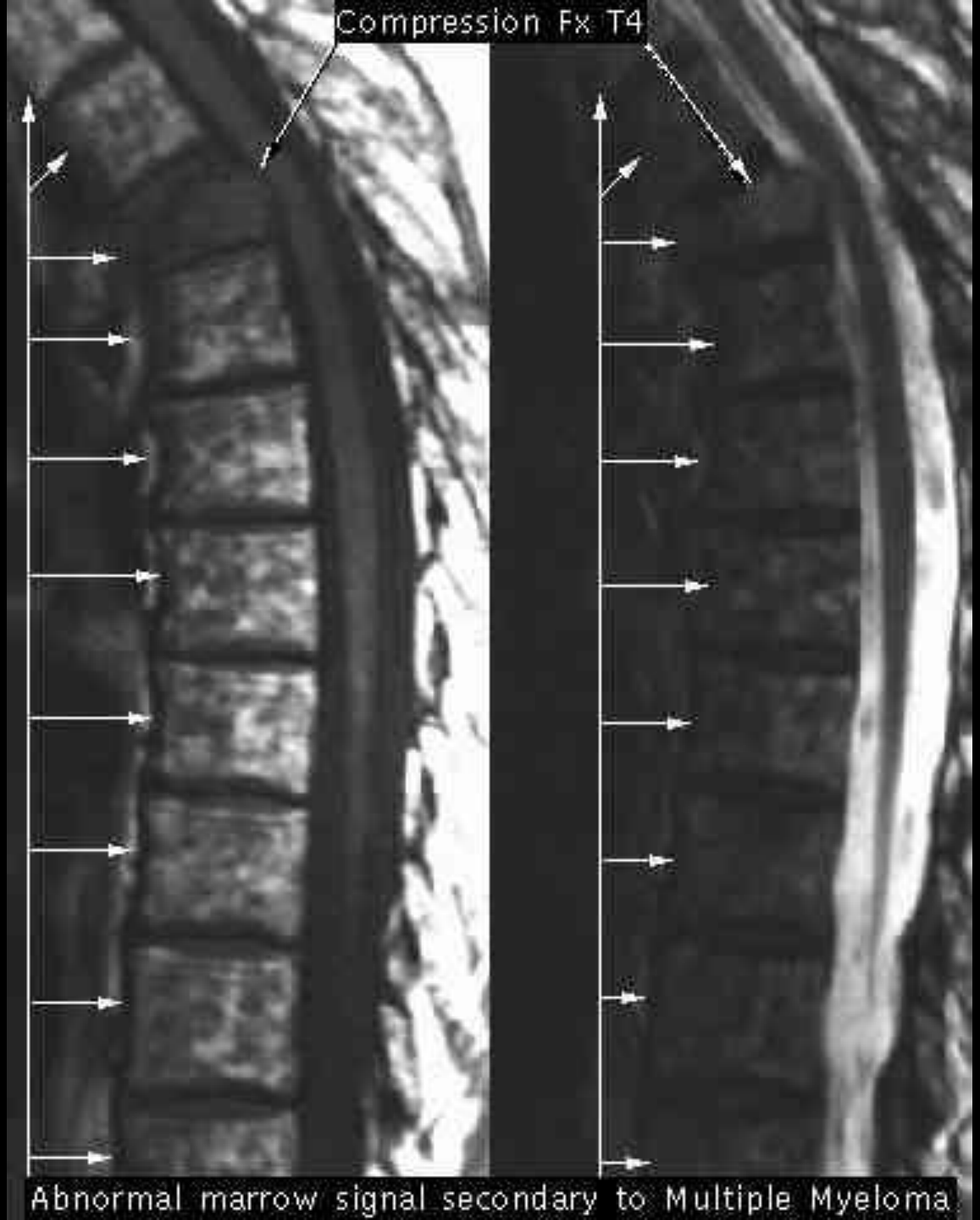
- Disease of the elderly (7th decade)
- Bone pain
  - most commonly vertebra and long bones
    - Vertebral column – 66%
    - Ribs – 44%
    - Skull – 41%
  - Lytic lesions – 1 to 4 cm in diameter
  - fractures

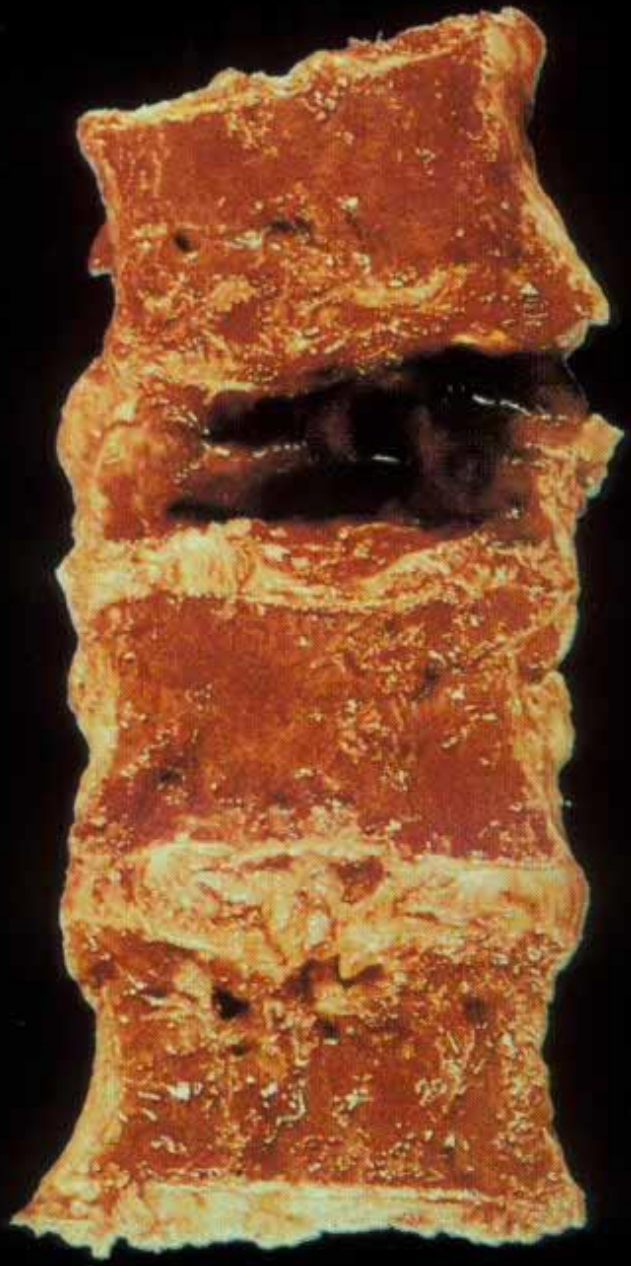
Multiple Myeloma
Typical "Punched Out" Lesions



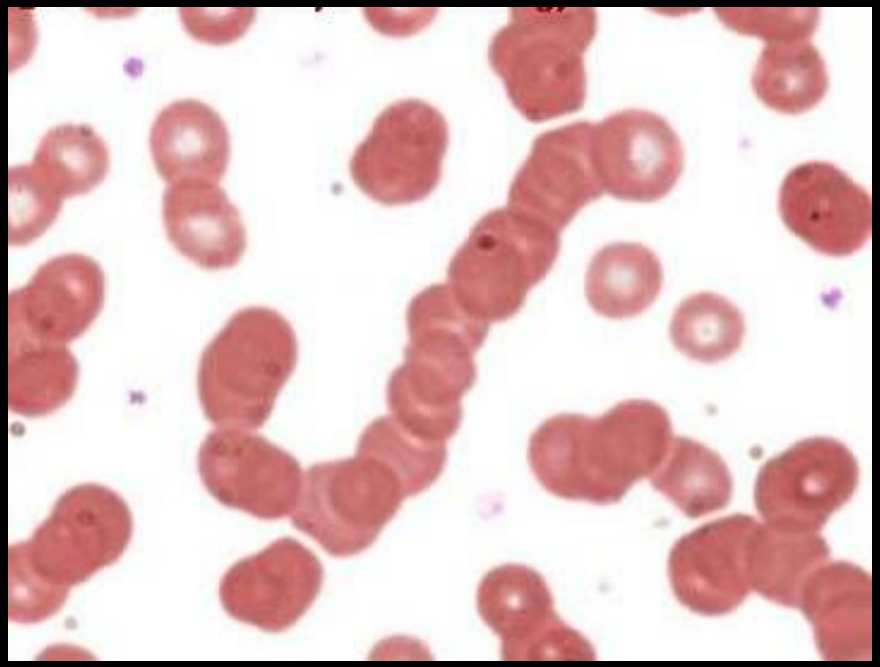


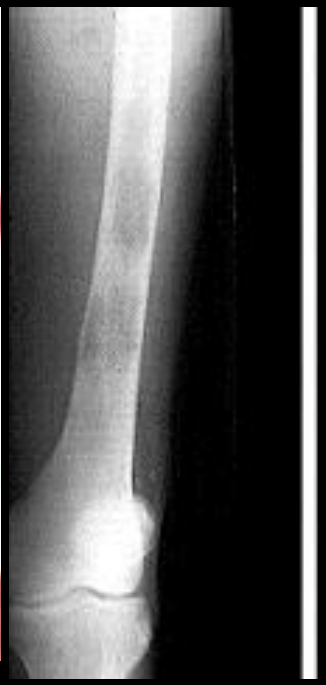


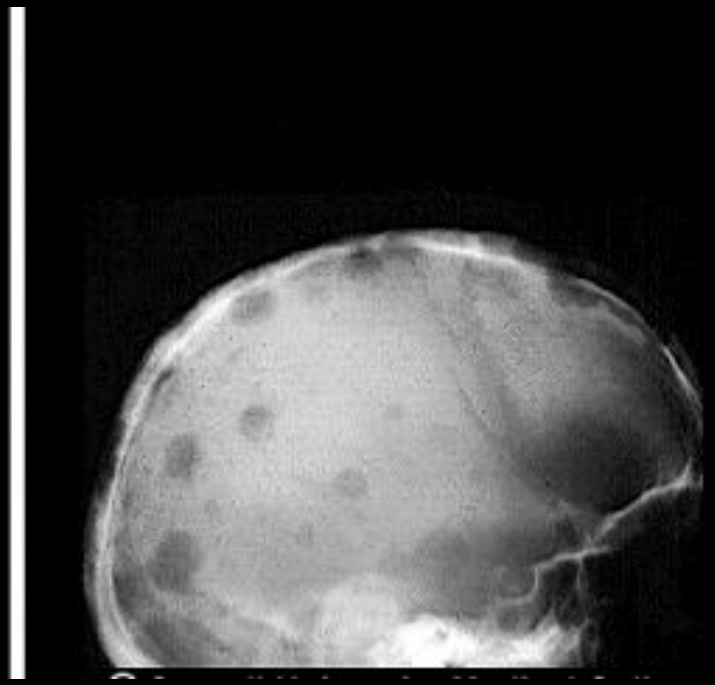

Compression Fx T4
Abnormal marrow signal secondary to Multiple Myeloma



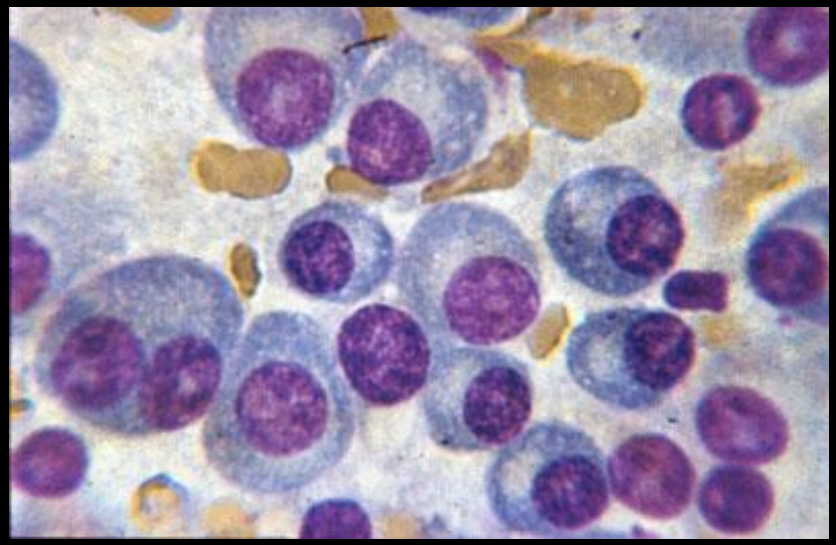
Multiple Myeloma

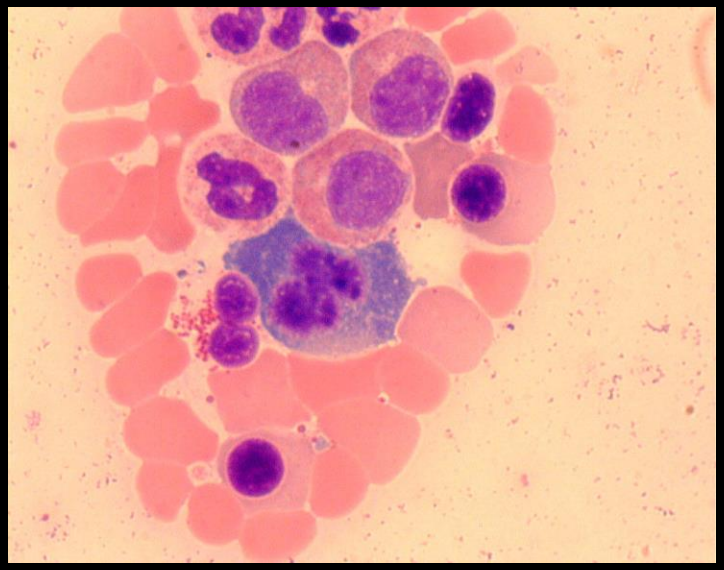


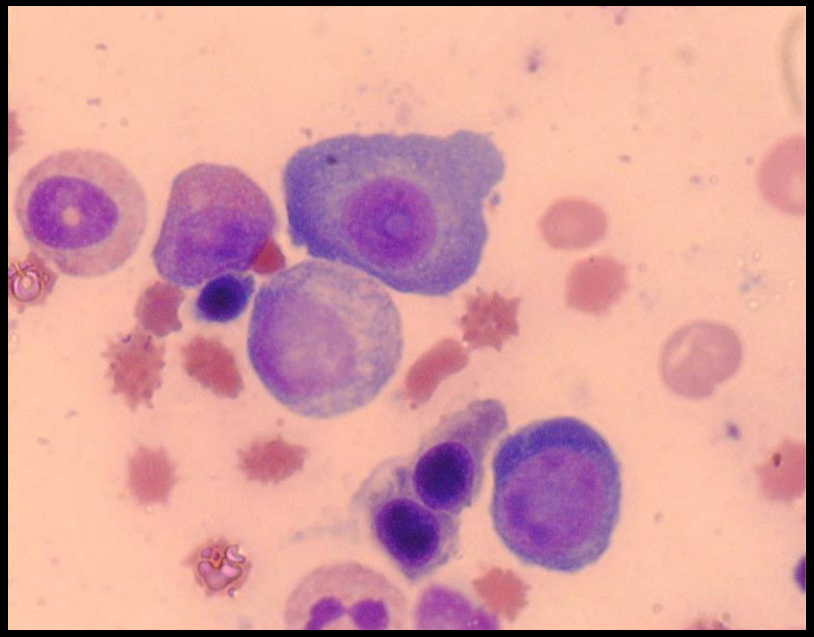


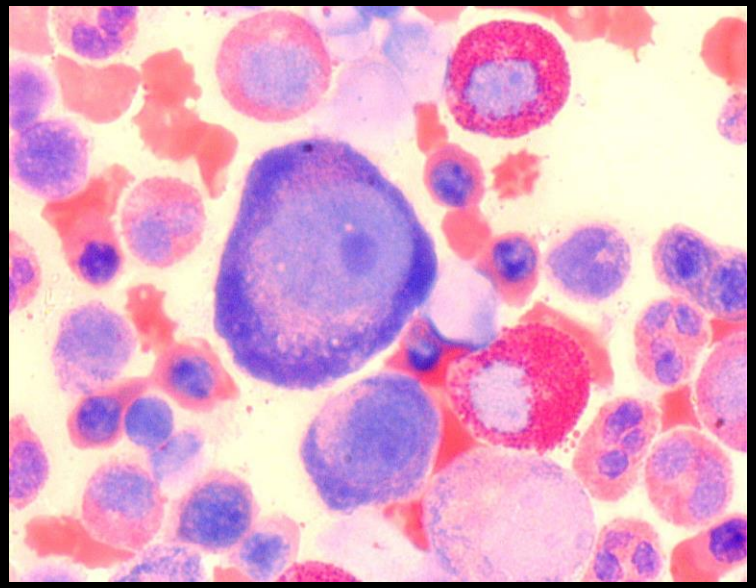


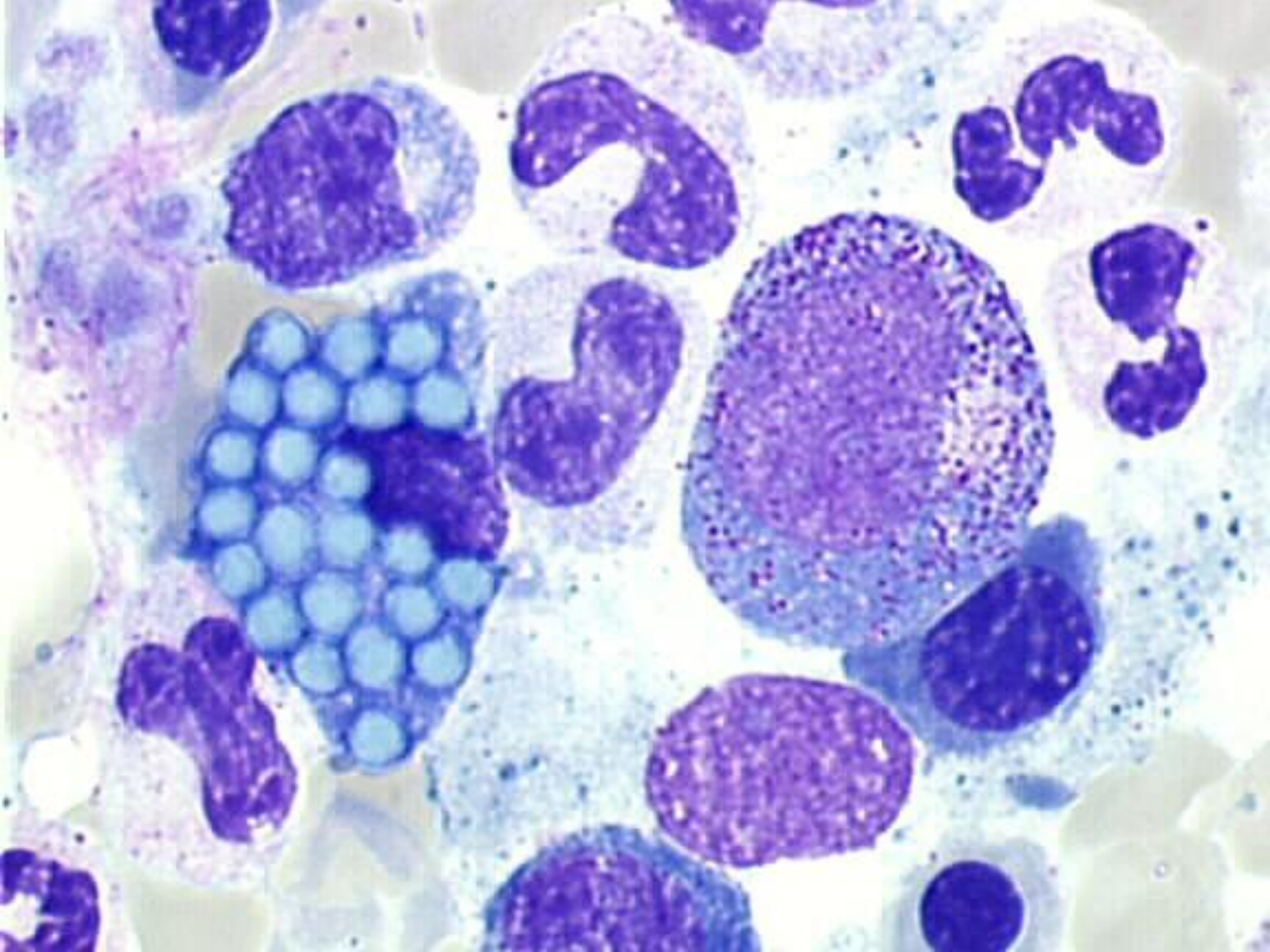
Morphology

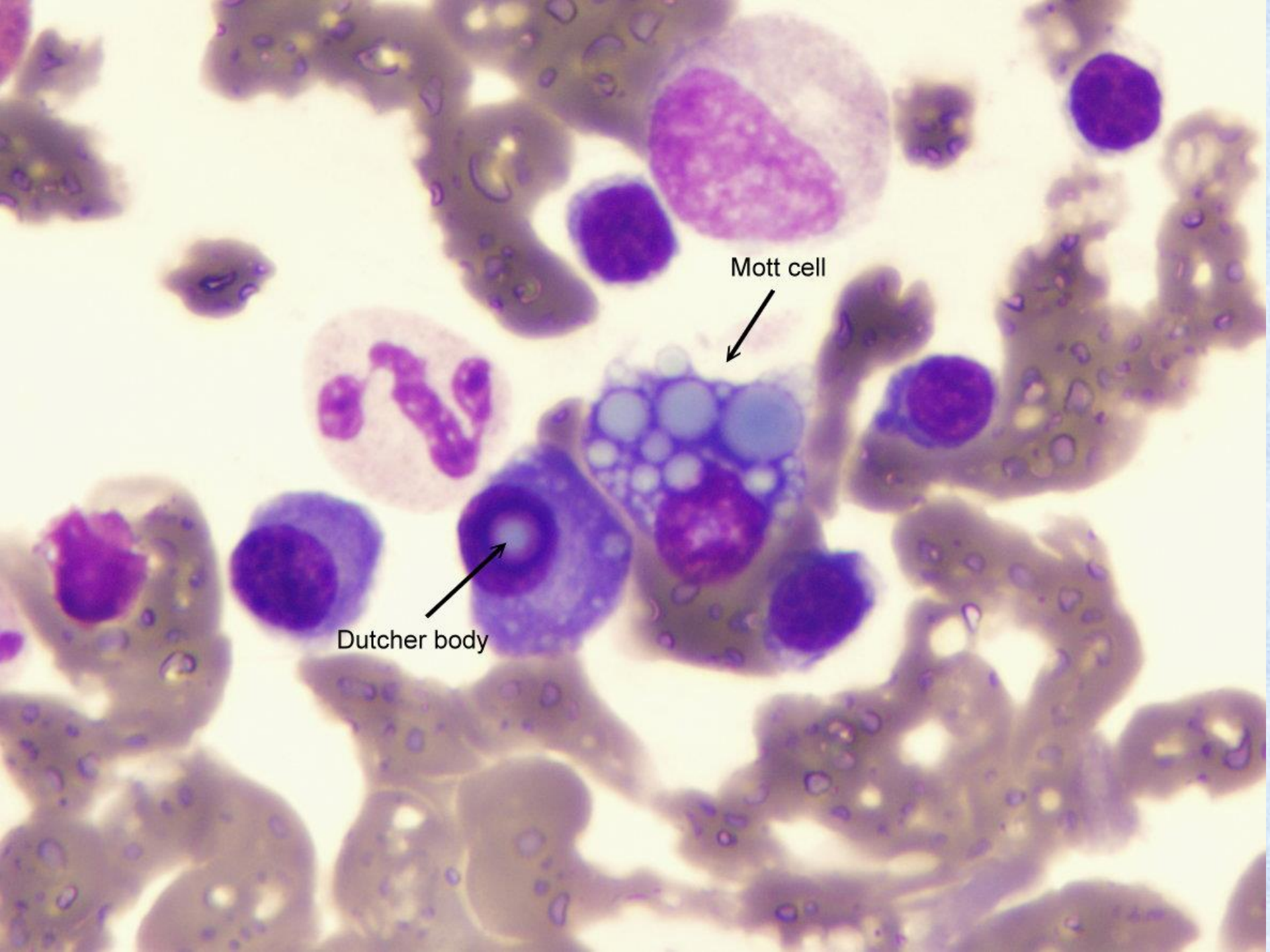


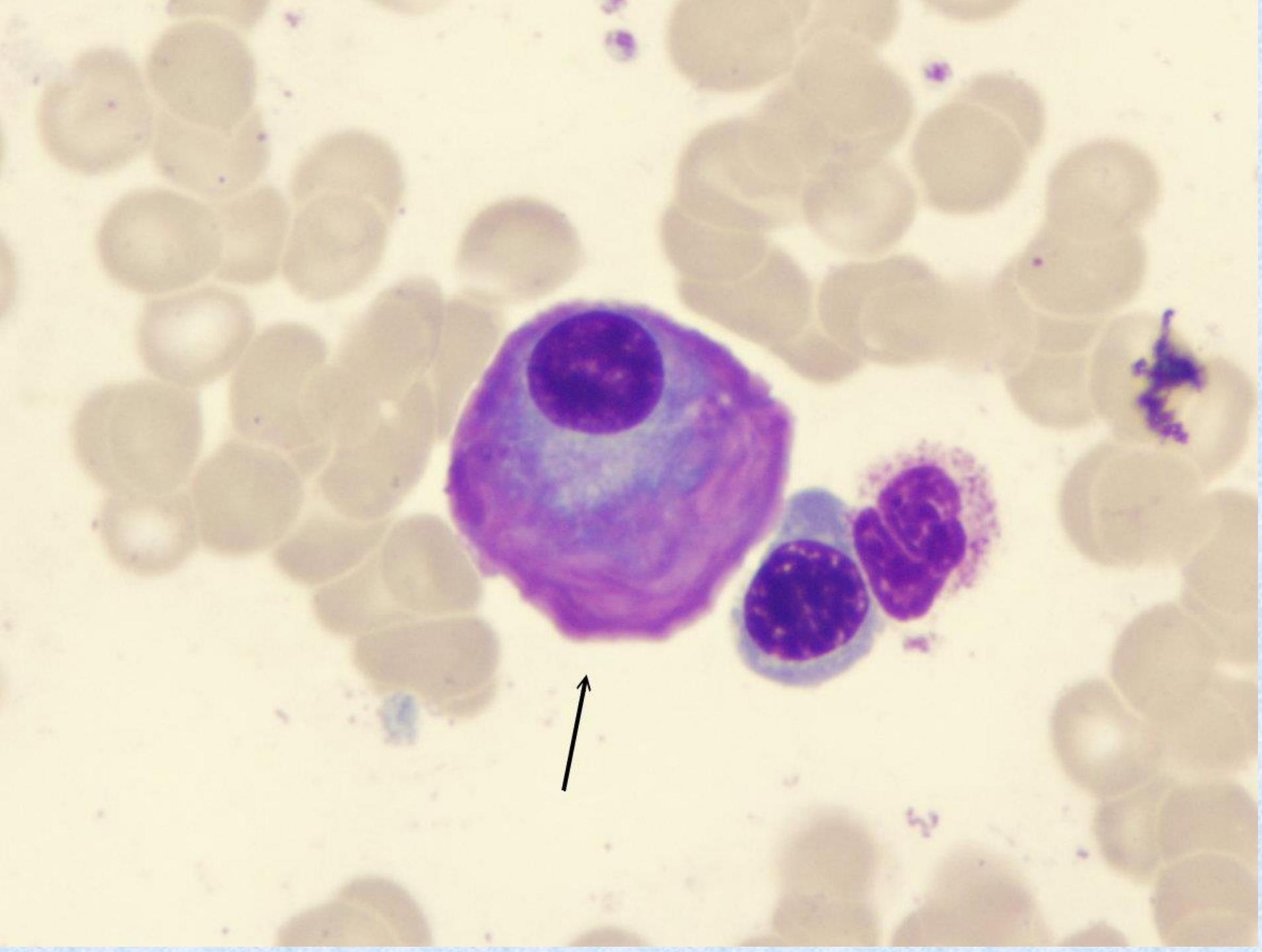









Mott cell
Dutcher body



Clinical Course

- Infiltration of organs esp bones
  - Hypercalcemia
  - Anemia
- Excess immunoglobulins
  - hyperviscocity
- Suppression of normal humoral immunity
  - Recurrent infections

- Renal Damage
  - Bence Jones Proteinuria – tubular toxicity (cast nephropathy)
  - Amyloidosis
  - Hypercalcemia
  - Infections

Diagnostic Criteria

- M component (any quantity)
- Bone marrow plasmacytosis (any %)
- Myeloma related organ or tissue impairment [ROTI]
  - C – hypercalcemia
  - R – renal failure
  - A – anemia
  - B – bone lesions

M component

- IgG – 55%
- IgA – 25%
- Hyperviscosity syndromes

Myeloma Diagnostic Work-Up

- SPEP and UPEP (24 collection) with immunofixation
  - 3% nonsecretory: check serum free light chains
- Skeletal survey
- Quantitative serum immunoglobulins (IgA, IgG, IgM)
- Bone Marrow Aspirate and Biopsy

- *Other tests (calcium, creatinine, beta-2 microglobulin, CRP, albumin, plasma cell labeling index, etc, etc) are only for staging/prognosis*

Prognosis

- Poor
- Survival – 6 to 12 months if untreated
- Bad Prognosis
  - Hemoglobin <8.5
  - Calcium >12
  - >3 lytic bone lesions
  - High M-protein
    - IgG >7 g/dL
    - IgA >5 g/dL
    - Bence Jones >12 g/24h

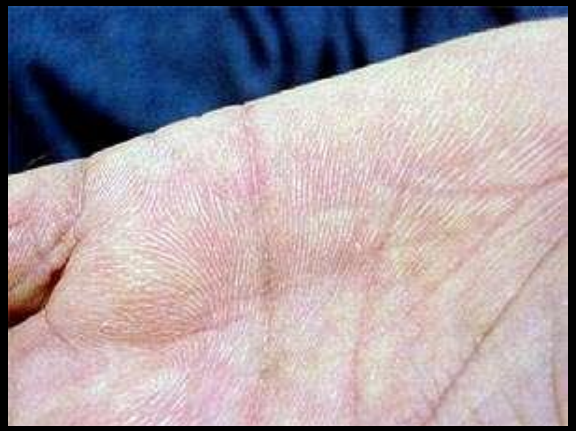
Solitary Plasmacytoma

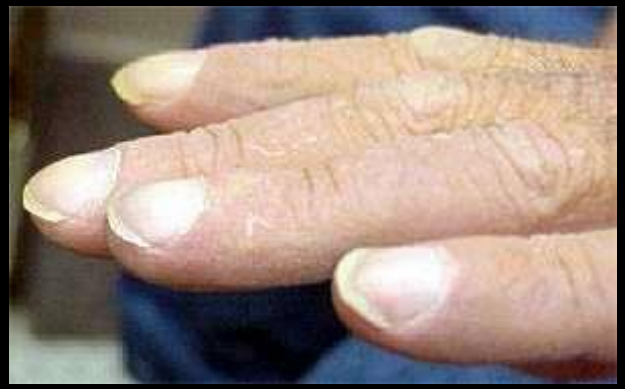
- 3 to 5 % of plasma cell neoplasms present as solitary lesion of bone or soft tissue
- Osseous – same sites as myeloma
- Extra osseous – lung, oro/nasophraynx, nasal sinuses
- Progression to myeloma common in solitary osseous.

Osteosclerotic Myeloma (POEMS)

- Polyneuropathy
  - Sensorimotor peripheral neuropathy in 75%
- Organomegaly
  - Lymphadenopathy, hepatomegaly, splenomegaly
- Endocrinopathy
  - Adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic
- M-Protein
- Skin changes
  - Hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails

Osteosclerotic Myeloma





MGUS

- Dysproteinemia without associated disease
- Most common cause of monoclonal gammopathy.
- 1% progress to myeloma every year
- M protein < 3g/dL
- No BJP

Smoldering Myeloma

- Serum M-protein >3 g/dL
- Marrow plasma cells >10%
- No lytic bone lesions, unexplained anemia, hypercalcemia, or renal insufficiency
- Evolve to overt multiple myeloma
  - 3.3% per year
  - Greatest for IgA

JCO 2002;20:1625.

Lymphoplasmacytic Lymphoma (Waldenstrom's Macroglobulinemia)

- Malignant proliferation of plasmacytoid lymphocytes secreting IgM M-protein
- Organomegaly/Peripheral neuropathies
- Cryoglobulinemia
  - Type I: Raynaud's phenomenon, cold urticaria, etc.
  - Type II: Purpura, arthralgias, renal failure, mononeuritis
- IgM tissue infiltration/AL amyloidosis
- Coagulation abnormalities

Hyperviscosity

- Usually IgM >5 g/dL, viscosity >4.0
- Eyes
  - "Sausage link" conjunctival and retinal veins
  - Retinal hemorrhages, Papilledema
- CNS
  - Ataxia, nystagmus, vertigo, confusion, altered consciousness
- Increased intravascular volume
  - Dilutional anemia
  - Risk congestive heart failure with transfusion
- Therapy: plasmapheresis/chemotherapy


Thank You