
بسم الله الرحمن الرحيم

PLASMA CELL NEOPLASMS

BY
DR SAIQA ZAHOOR
ASSOCIATE PROFESSOR HAEMATOLOGY
KGMC/MTI

LEARNING OBJECTIVES

- Plasma cell neoplasms
  - Types
- Multiple myeloma
  - Definition
  - Pathogenesis
  - Molecular genetics
  - Clinical features
  - Diagnostic criteria
  - Types

PLASMA CELL NEOPLASMS

- B-cell proliferations
- Neoplastic plasma cells virtually always secrete a monoclonal Ig or Ig fragment
- Also known as plasma cell dyscrasias
- Multiple myeloma is the commonest

PLASMA CELL NEOPLASMS

- A monoclonal Ig identified in the blood - **M PROTEIN**
- MW - 160,000 or higher
- *Neoplastic plasma cells - excess light (usually) or heavy chains along with complete Igs*
- The free light chains are small enough to be excreted in the urine - ***Bence-Jones proteins*** *– tested in urine*

PLASMA CELL NEOPLASMS TYPES

- Multiple Myeloma
- Waldernstorm macroglobuliemia
- Heavy chain disease
- Primary Amyloidosis
- Monoclonal gammopathy of undetermined significance (MGUS)

PLASMA CELL NEOPLASMS TYPES

MULTIPLE MYELOMA:

- *Most important monoclonal gammopathy*
- *Tumorous masses scattered throughout the skeletal system*

SOLATARY MYELOMA/ PLASMACYTOMA

- *Infrequent variant - single mass in bone or soft tissue*

Contd……

WALDENSTRÖM MACROGLOBULINEMIA

- ↑ IgM lead to symptoms related to hyperviscosity of the blood manifested as
- fatigue,
- headache,
- blurred vision,
- mucosal bleeding,
- impaired cognition or coma.

TYPES …

HEAVY-CHAIN DISEASE

- Rare monoclonal gammopathy
- Diverse group of disorders
  - Lymphoplasmacytic lymphoma and an unusual small bowel marginal zone lymphoma that occurs in malnourished populations (so-called Mediterranean lymphoma)
- Common feature - synthesis and secretion of free heavy-chain fragments

TYPES ….

PRIMARY OR IMMUNOCYTE-ASSOCIATED AMYLOIDOSIS:

- Monoclonal proliferation of plasma cells secreting light chains - deposited as amyloid

  - Primary amyloidosis
  - Secondary to multiple myeloma

TYPES ….

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS):

- Defined by less than 10% clonal plasma cells in the bone marrow and less than 30 g/L of an M - protein and absence of end - organ damage.

MULTIPLE MYELOMA

DEFINITION

- **Multiple myeloma (MM) is characterized by the proliferation of a single clone of plasma cells that produce monoclonal protein.**

- **Multiple myeloma is a plasma cell neoplasm commonly associated with lytic bone lesions, hypercalcemia, renal failure, and acquired immune abnormalities.**

DEFINITION

- **A malignant proliferation of plasma cells derived from a single clone involving more than 10 percent of the bone marrow**

- **The multiple myeloma cell produces monoclonal immunoglobulins that may be identified on serum or urine protein electrophoresis**

As a result

Tumour, its products, and the patients response to it, result in a number of organ dysfunctions

- **Fracture/bone pain**
- **Renal failure**
- **Susceptibility to infection**
- **Anemia**
- **Hypercalcemia**
- **Clotting abnormalities**
- **Neurologic symptoms**
- **Vascular manifestations of hyperviscosity**

PATHOPHYSIOLOGY

- **The pathological and clinical features of myeloma are due to:**

1.Tissue infiltration

2. Production of large amount of paraprotein

3. Impairment of immunity.

.

PATHOGENESIS

MM is a B - cell malignancy characterized by the

- **Accumulation of terminally differentiated clonal plasma cells in the bone marrow**
- **Production of a monoclonal immunoglobulin detectable in serum and/or urine**
- **Presence of lytic bone lesions**

PATHOGENESIS

- **Bone disease is one of the hallmarks of MM .**
- **The bone marrow microenvironment provides a sanctuary for myeloma cells by both promoting proliferation and blocking apoptosis, thereby allowing tumour progression.**
- **Osteolysis is mediated by an imbalance between osteoclast activity (increased) and osteoblast activity (decreased).**
- **The proliferation and survival of myeloma cells are dependent on several cytokines, most notably IL-6.**

MECHANISM OF BONE DESTRUCTION

- **Plasma cell produce MIP1α which up-regulates the expression of the receptor activator of NF-κB ligand (RANKL) by bone marrow stromal cells, which in turn activates osteoclasts.**

- **Other factors released from tumor cells, such as modulators of the Wnt pathway, are potent inhibitors of osteoblast function.**

- **The net effect is a marked increase in bone resorption, which leads to hypercalcemia and pathologic fractures.**

- Bone infiltration, causes destruction of medullary and cortical bone due to the stimulation of osteoclast activity by a factor released by the myeloma cells, usually designated osteoclast-activating factor. This leads to osteoporosis and more frequently to localized lytic lesions and pathological features.

- Skeletal destruction results in the release of bone salts,negative calcium balance and hypercalciuria in virtually all cases.

- Hypercalciuria

  osmotic diuresis + Impairment of renaltubular reabsorption

  ↓

- **Dehydration**

  ↓

- **diminished urine output**

  ↓

- **hypocalcemia + azotemia**

  ↓

- **anorexia, nausea,and vomiting and further dehydration.**

Multiple myeloma cell clone produces an excess of

- **Monoclonal immunoglobulins that are nonfunctional and are called paraproteins. (M proteins) recognized as IgA, IgD,IgG, IgE or IgM, depending on their heavy chain class.**
  - Responsible for the hyperviscosity syndrome which interferes with fibrin aggregation and platelet function.

- **Incomplete immunoglobulinsas free light chain proteins(kappa or lambda) in 75% of cases (Bence Jones proteins).**
  - May precipitate and deposit, producing organ damage (kidney)
  - Secreted in the urine

- **1% of multiple myelomas are called nonsecretors because they do not produce any abnormal Ig**

Pathogenesis and Clinical Manifestations of Multiple Myeloma

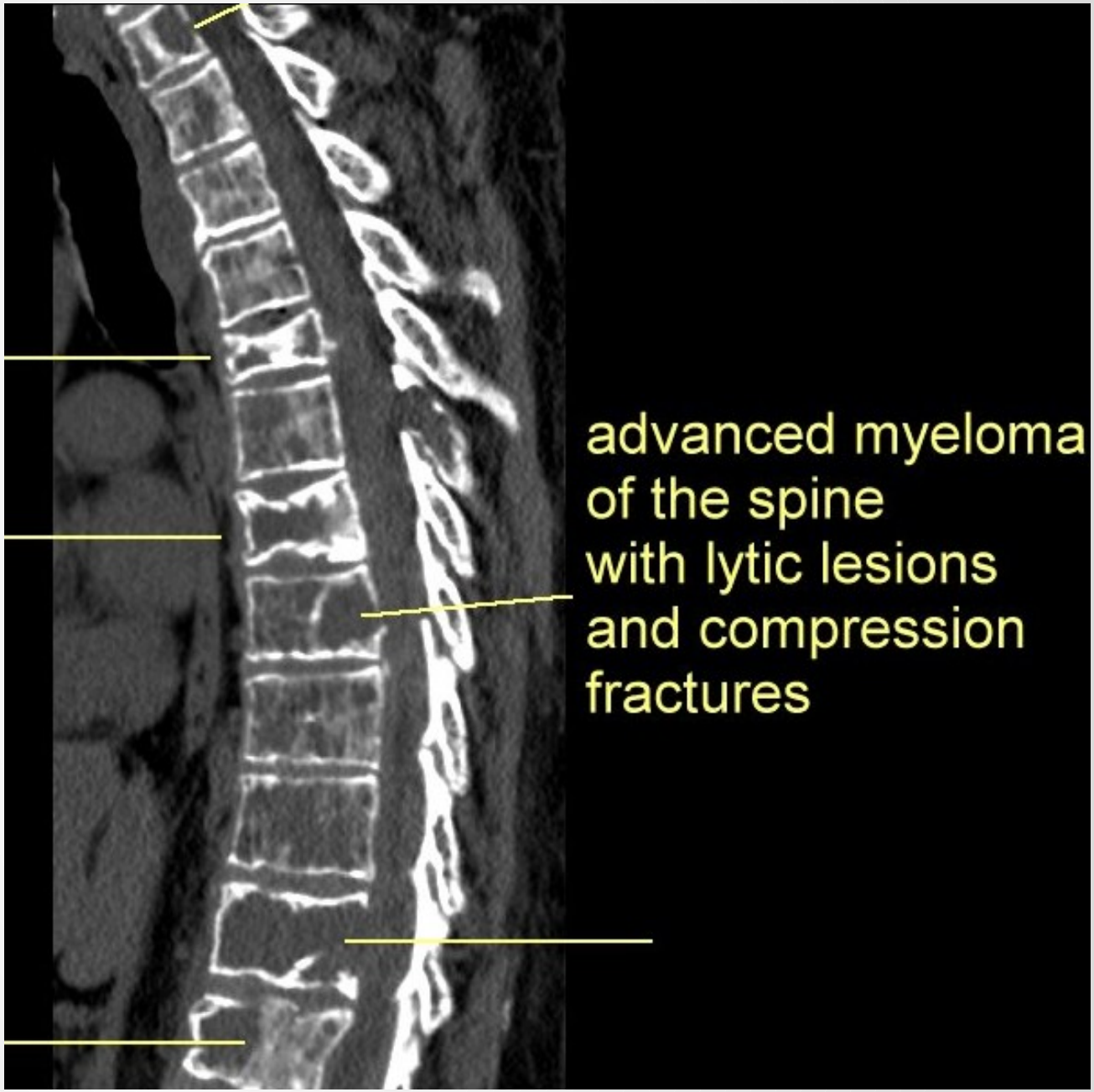
Clinical Finding	Underlying Cause	Pathogenic Mechanism
●Hypercalcemia ●Pathologic fractures ●Cord compression ●Lytic bone lesions ●Osteoporosis ●Bone pain	●Skeletal destruction	●Tumor expansion ●Production of osteoclast activating factors (OAF) by tumor cells
Renal failure	●Light chain proteinuria ●Hypercalcemia ●Urate nephropathy	●Toxic effects of tumor products ●Light chains ●DNA breakdown products
Infections	Pyelonephritis	Hypogammaglobulinemia

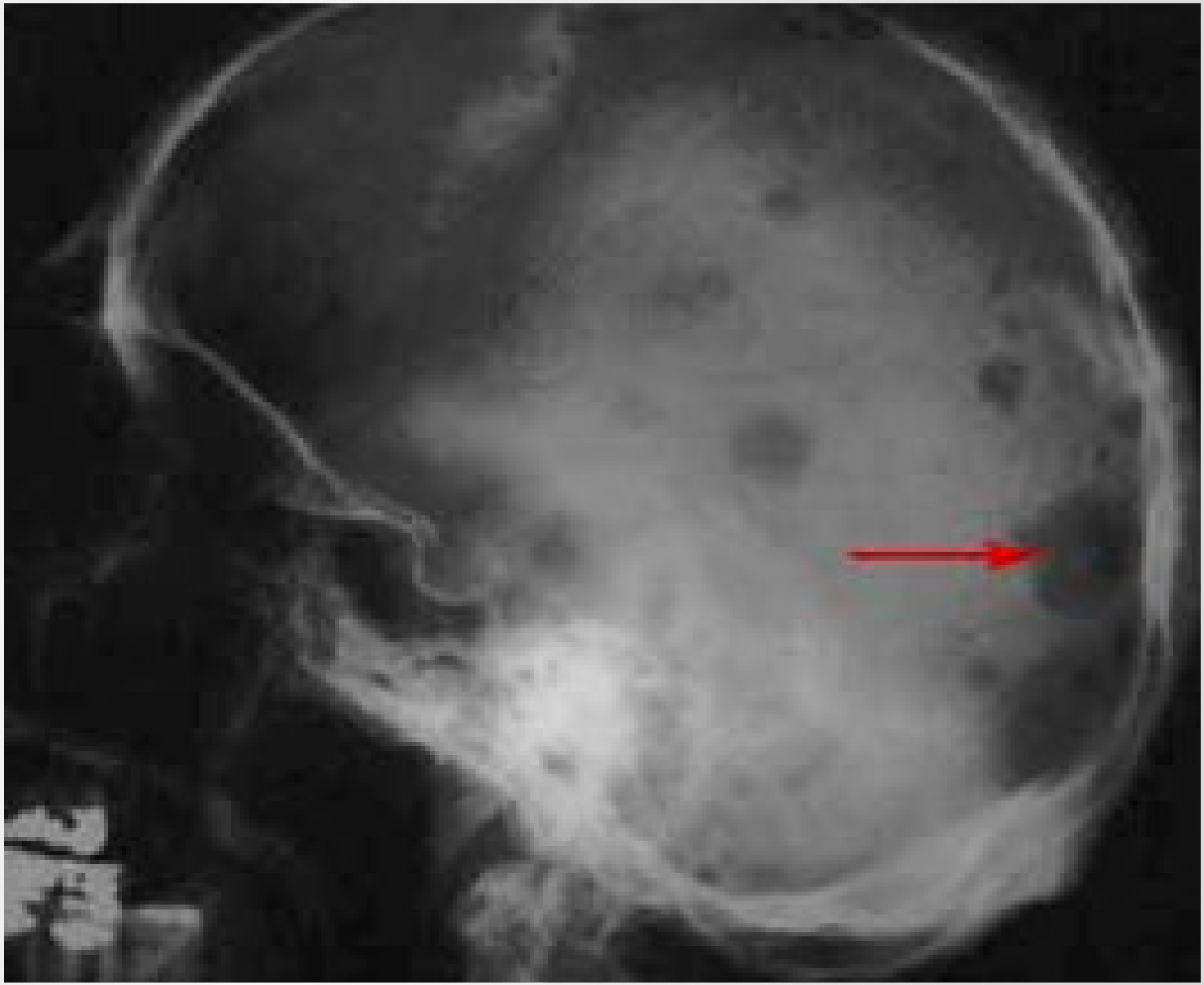
MOLECULAR PATHOGENESIS

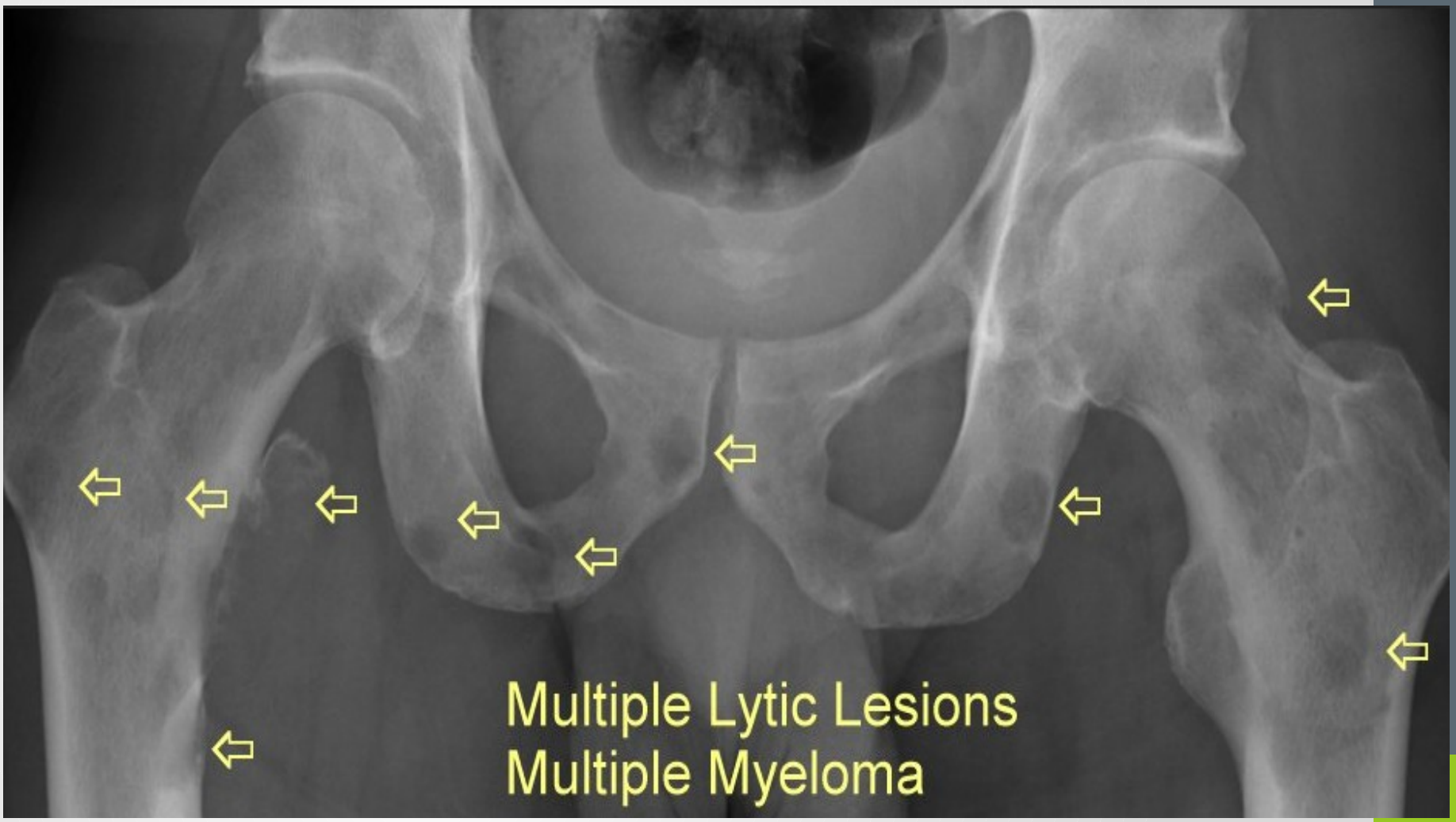
- **Most frequent abnormalities**
  - **del(13q14)**
  - **hyperdiploidy**
  - **t(11;14)**
  - **t(4;14)**
  - ***MYC* translocations, and**
  - **del(17p)**
- **Most frequent translocations involve 14q32**

MORPHOLOGY

- *Destructive plasma cell tumors (plasmacytomas) - axial skeleton*
- **BONES: in descending order of frequency:**
  - **VERTEBRAL COLUMN,**
  - **ribs,**
  - **skull,**
  - **pelvis,**
  - **femur,**
  - **clavicle, and**
  - **Scapula**
- **Radiographically: Punched-out defects, usually 1 to 4 cm in diameter**


advanced myeloma
of the spine
with lytic lesions
and compression
fractures



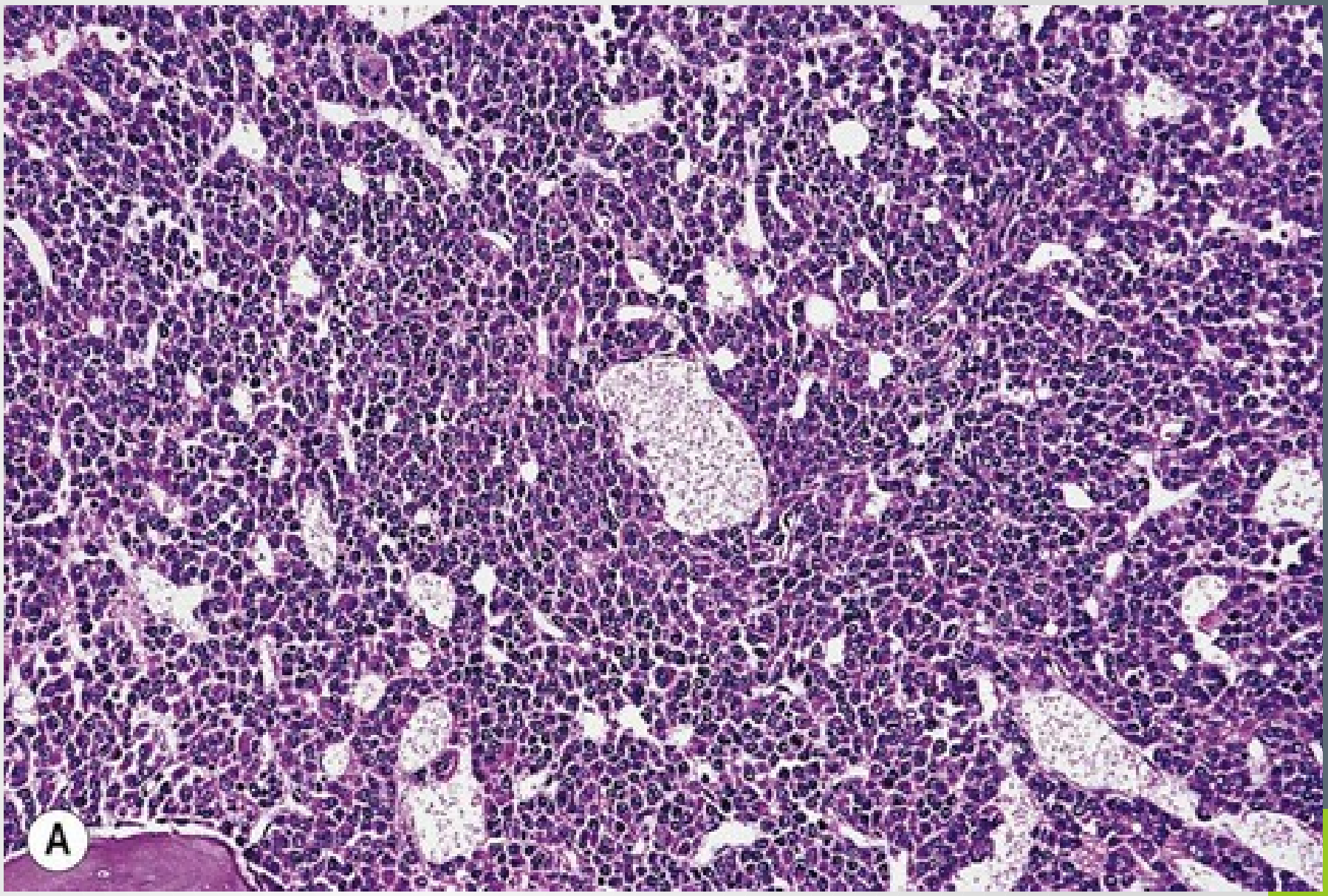

Multiple Lytic Lesions
Multiple Myeloma

MORPHOLOGY

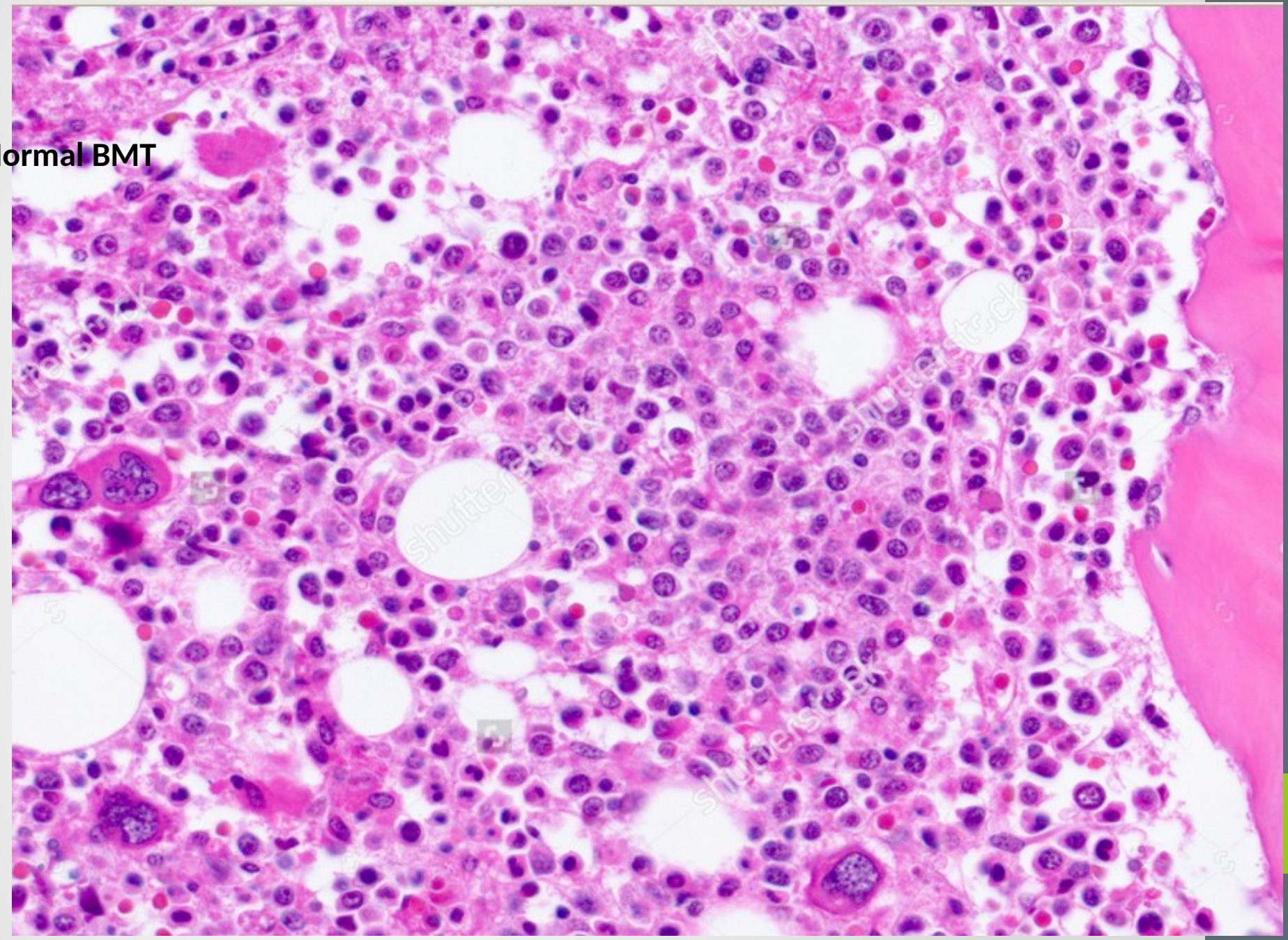
- **High level of M proteins causes red cells in peripheral blood smears to stick to one another in linear arrays a finding referred to as rouleaux formation.**

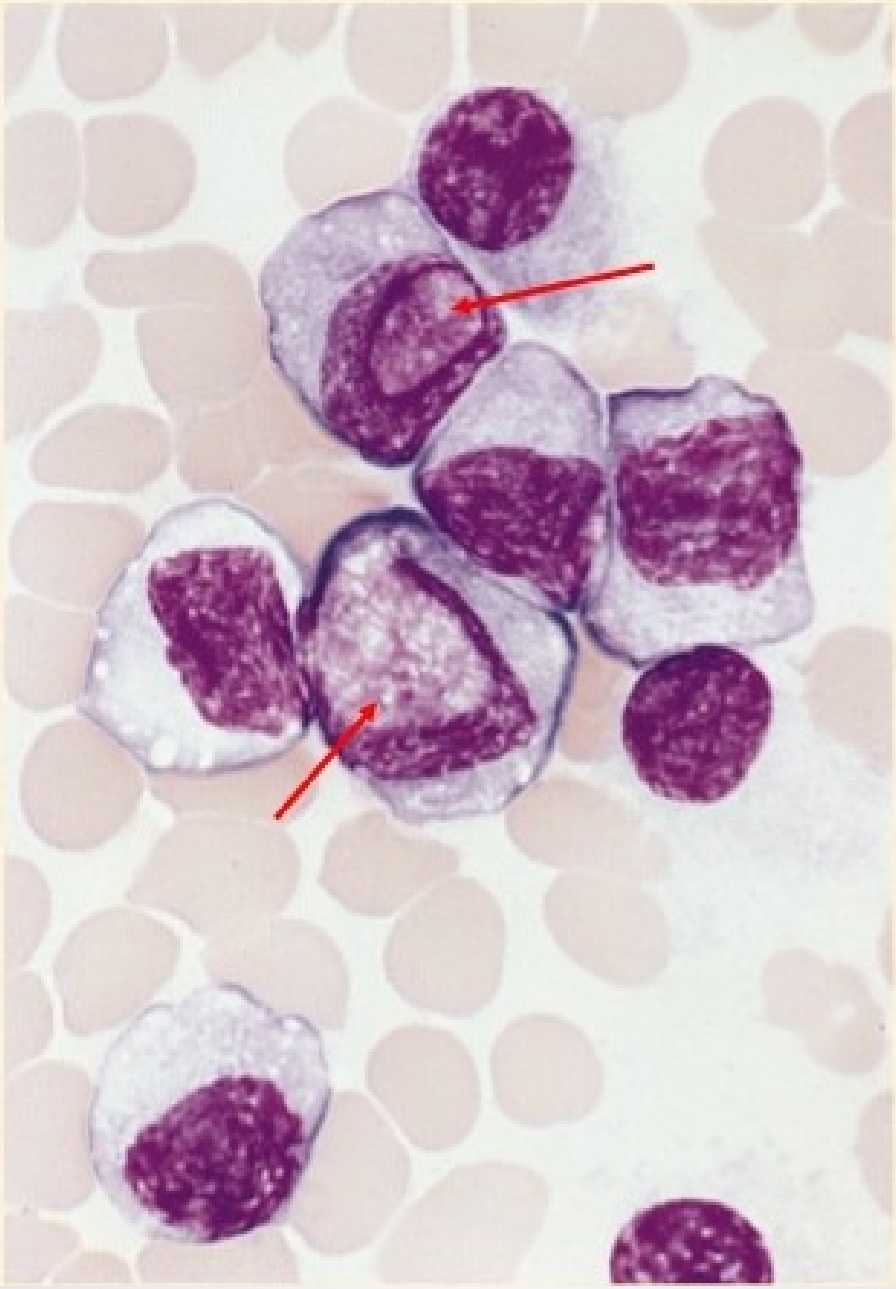
- **Grossly:**
  - **Soft, gelatinous, red tumor masses**

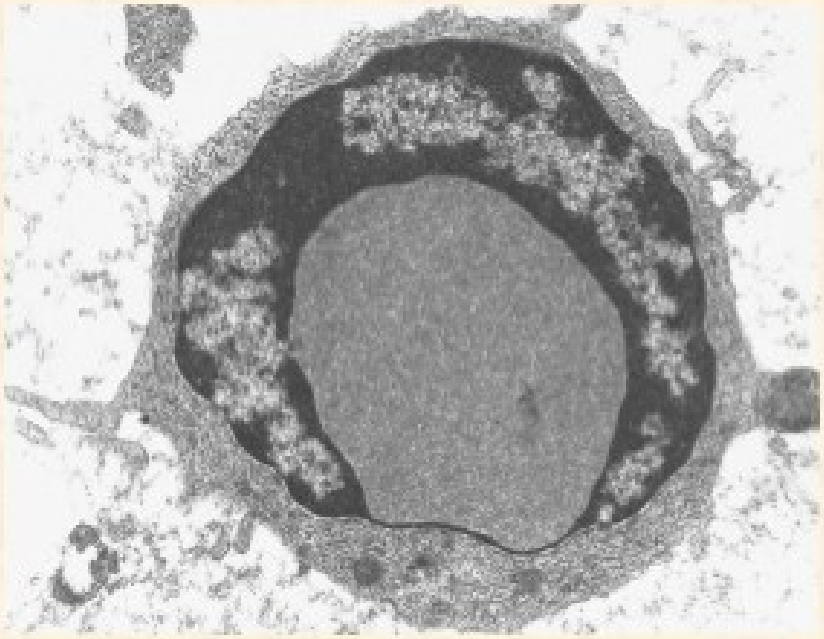
- **Microscopic:**
  - **Marrow - ↑ plasma cells - usually > 30% of the cellularity**
  - **Cytologic varients:**
    - **Plasmablasts**
    - **Bizarre, multinucleated cells**
    - **Flame cells**
    - **Mott cells**
    - **Others - fibrils, crystalline rods, and globules**


A

Normal BMT





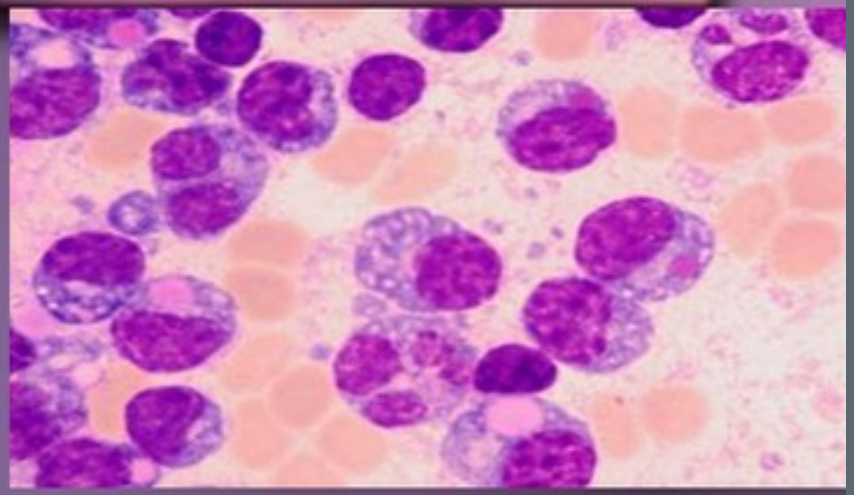


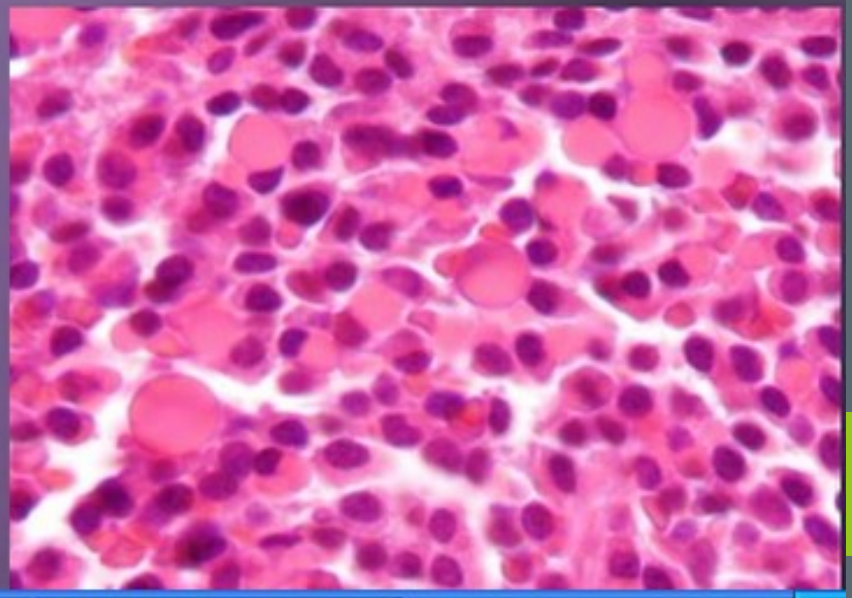
INTRANUCLEAR INCLUSIONS

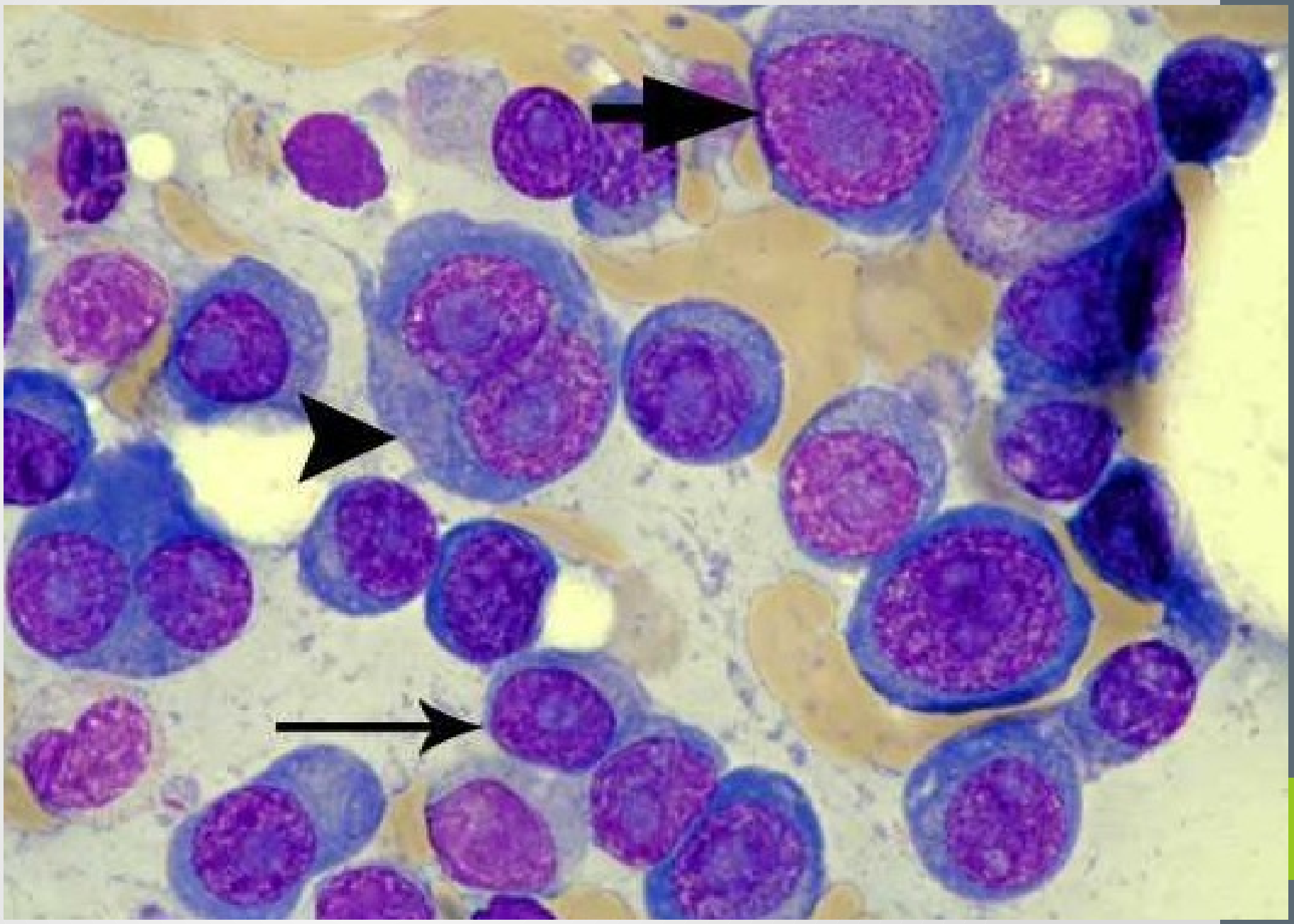
Bone marrow smear from a patient with IgA myeloma. Large nuclear inclusions (**Dutcher bodies**) are present in two of the plasma cells.

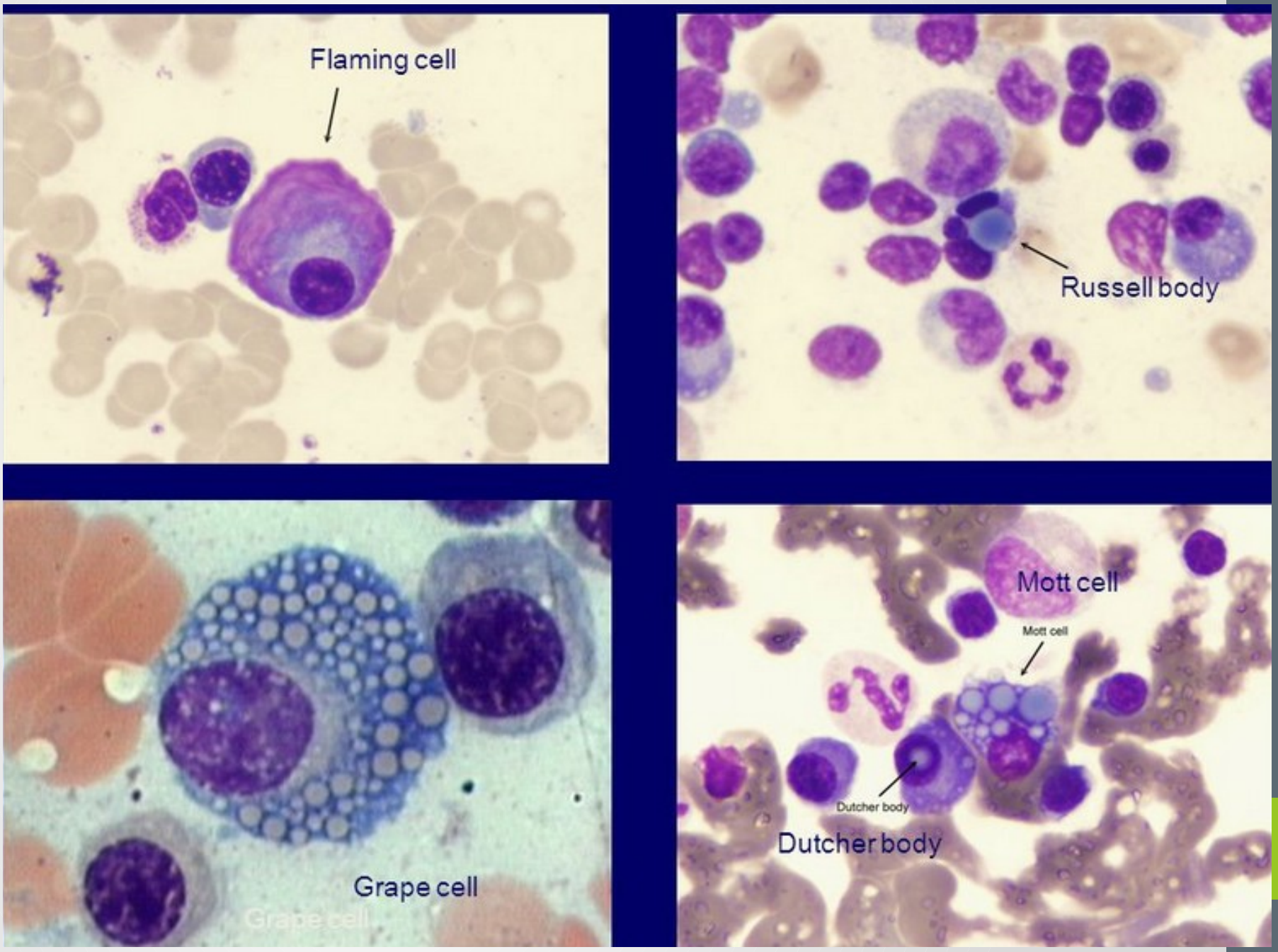
RUSSELL BODIES

- Globules (2-3 μm) of accumulated immunoglobulins in the **cytoplasm** of plasma cells
- Usually round
- May be found in normal bone marrow
- 1st described by William Russell



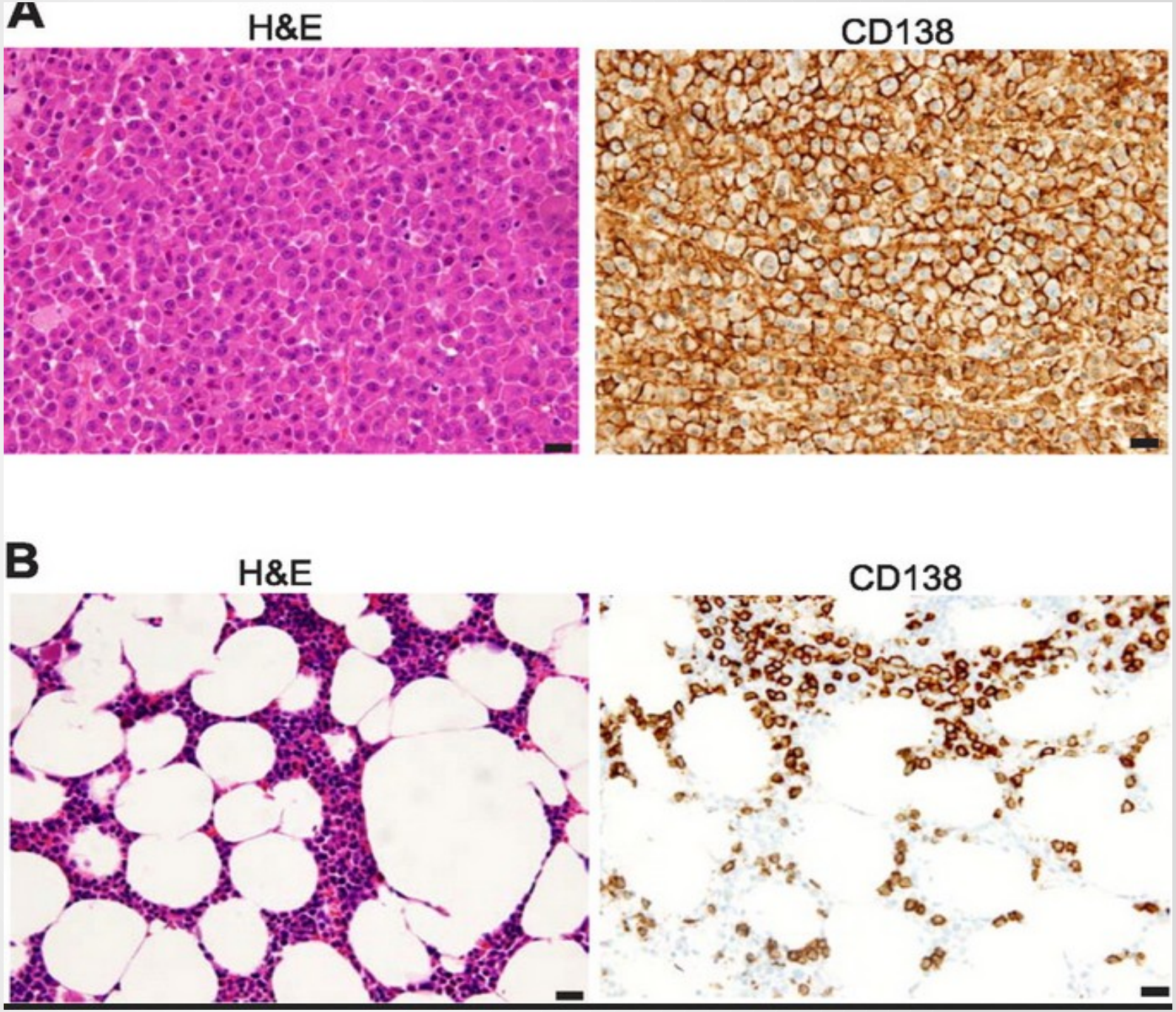





Flaming cell
Russell body
Grape cell
Mott cell
Mott cell
Dutcher body
Dutcher body

MORPHOLOGY….

- **IMMUNOHISTOCHEMISTRY:**
  - **CD 38**
  - **CD138**
  - **Kappa**
  - **Lamda**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H&E
CD138
B
H&E
CD138

SIGNS AND SYMPTOMS

- Calcium Elevation
- Renal Impairment (↑BUN, creatinine)
- Anaemia
- Bone (Pain, Lytic Lesions, Fractures)

CRAB

2008 WHO diagnostic criteria for plasma cell myeloma[614]

Symptomatic plasma cell myeloma

M-protein in serum or urine[a]

Bone marrow clonal plasma cells or plasmacytoma[b]

Related end-organ damage (end-organ damage or bone lesions: hypercalcemia, renal impairment, anemia, bone lesions or myeloma-related symptoms)

Asymptomatic (smoldering) myeloma

M-protein in serum or urine (>30 g/L), and/or

10% or more clonal plasma cells in marrow

No related organ damage or tissue impairment

SOLITARY MYELOMA (PLASMACYTOMA)

Solitary osseous plasmacytoma almost inevitably progresses to multiple myeloma, but this can take 10 to 20 years or longer

SMOLDERING MYELOMA

- **This entity defines a middle ground between multiple myeloma and MGUS**
  - ***Uncommon variant - lack of symptoms and a high plasma M component***

Asymptomatic (smoldering) myeloma

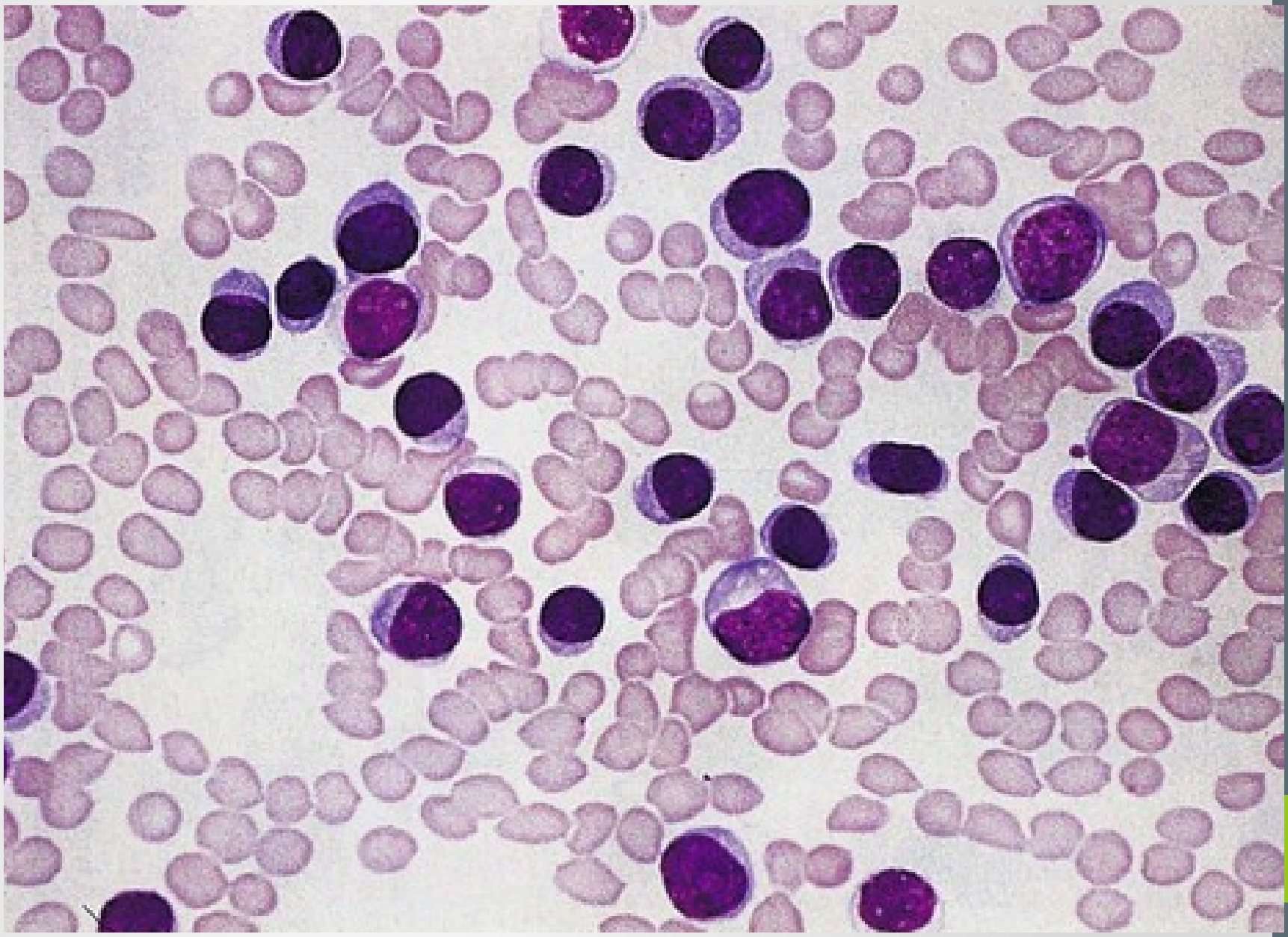
M-protein in serum or urine (>30 g/L), and/or

10% or more clonal plasma cells in marrow

No related organ damage or tissue impairment

PLASMA CELL LEUKEMIA

- **The term plasma cell leukemia is applied to those processes in which a patient presents with a *plasma cell proliferation in the blood;***
  - **Plasma cells exceed *20%* of the blood leukocytes,**
  - **or the absolute plasma cell count exceeds $20 \times 10^9/L$**



THANK YOU