Heavy-chain disease

- Rare disorder
- Bone marrow shows variable increase in plasma cells
- In Heavy chain disease, there is synthesis and secretion of free H chain fragments.
- It is seen in a diverse group of disorders including
  - CLL/SLL,

Waldenstrom macroglobulinemia (Lymphoplasmacytic lymphoma)

- It is rare B cell lymphoproliferative disorder, characterised by lymphoplasmacytic proliferation in marrow with secretion of **IgM** Monoclonal protein
- Classic features are anemia, lymphadenopathy, hepatosplenomegaly & features of hyperviscosity syndrome
- WHO classification has grouped it under **lymphoplasmacytic lymphoma**

- It inevitably progresses to multiple myeloma, although progression can take 10 - 20 years or longer.
- Progression to classic MM is commoner in patients with solitary osseous plasmacytoma then in extraosseous plasmacytomas.

Solitary Myeloma (Plasmacytoma)

- About 3-5% of plasma cell neoplasms present as a solitary lesion of either bone or soft tissue.
  - The **bony lesions**, with single localised collection of plasma cells in bone, tend to occur in the same locations as in multiple myeloma.
  - **Extraosseous lesions**- in the lungs, oronasopharynx or nasal sinuses.

MGUS → AMM → IM → MM

MGUS Vs Smoldering MM Vs Multiple Myeloma

Investigations	MGUS	Smoldering MM	Multiple myeloma
Bone marrow plasma cells	<10%	>10-60%	>60% clonal or >10% clonal plasma cells with CRAB/ MDE
M component	<30g/L	>30g/L	>35g/L
Lytic lesions in bones	No bony lesions	No bony lesions	Present
Myeloma related organ damage/	Not present	Not present	Present

Indolent myeloma

- Have upto 3 lytic bone lesions without bone pain
- Marrow plasmacytosis 10-30 %
- M component at intermediate levels
- No anemia, Normal calcium & creatinine levels

Asymptomatic/ Smoldering MM

- It is an intermediate stage between MGUS and MM, (formerly known as smoldering multiple myeloma).
- Clonal bone marrow plasmacytosis: 10-30%
- Serum M component >3gm%
- Patients are asymptomatic, without any anemia or lytic bone lesions,
- No myeloma related end organ damage (CRAB)
- 75% of patients progress to MM

- Approx 1% of patients with MGUS progress to an overt multiple myeloma per year. Therefore, it is considered pre-neoplastic condition.
- Life long follow up with serum M component levels and Bence Jones protein in urine is warranted.

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- MGUS is a relatively benign proliferation of plasma cells resulting in secretion of Monoclonal proteins
- It is the m/c plasma cell dyscrasia, occurring in about 3-5% of patients > 70 yrs of age.
- Patients with MGUS have
  - <3 gm/dL of monoclonal protein in the serum
  - No Bence Jones proteinuria,
  - Clonal BM plasma cells <10%,

CLINICAL VARIANTS

- Non-secretory myeloma: rare (1%), myeloma cells synthesize Igs but do not secrete Igs in plasma, so, Ig levels are not increased, therefore M component is absent
  - Ig is demonstrated in cytoplasm of myeloma cells by IF or Immunoperoxidase studies
  - Have low incidence of renal insufficiency
  - Lytic bone lesions are present, bone marrow reveals increase in plasma cells.
- Plasma cell leukemia: when plasma cells in PBF have a count $>2x10^9/L$ or >20% of

Treatment

- Despite advancement in therapy of myeloma, it is still incurable disease
- Asymptomatic myeloma patients do not require therapy
- The main aim is to have prolonged progression free survival & symptomatic improvement.
- Treatment is started if there is evidence of end organ damage (CRAB)
  - Melphalan, prednisolone
  - Bisphosphonates (inhibitors of osteoclast mediated bone resorption)

Prognosis

- Prognosis is variable; median survival is 4-7 years.
- Patients with multiple bony lesions, if untreated, rarely survive for more than 6-12 months,
- Translocations involving cyclin D1 are associated with a good outcome,
- **Poor prognostic factors are**
  - Deletions of 13q, 17p, and the t(4;14)
  - High tumour load, Higher stage of MM

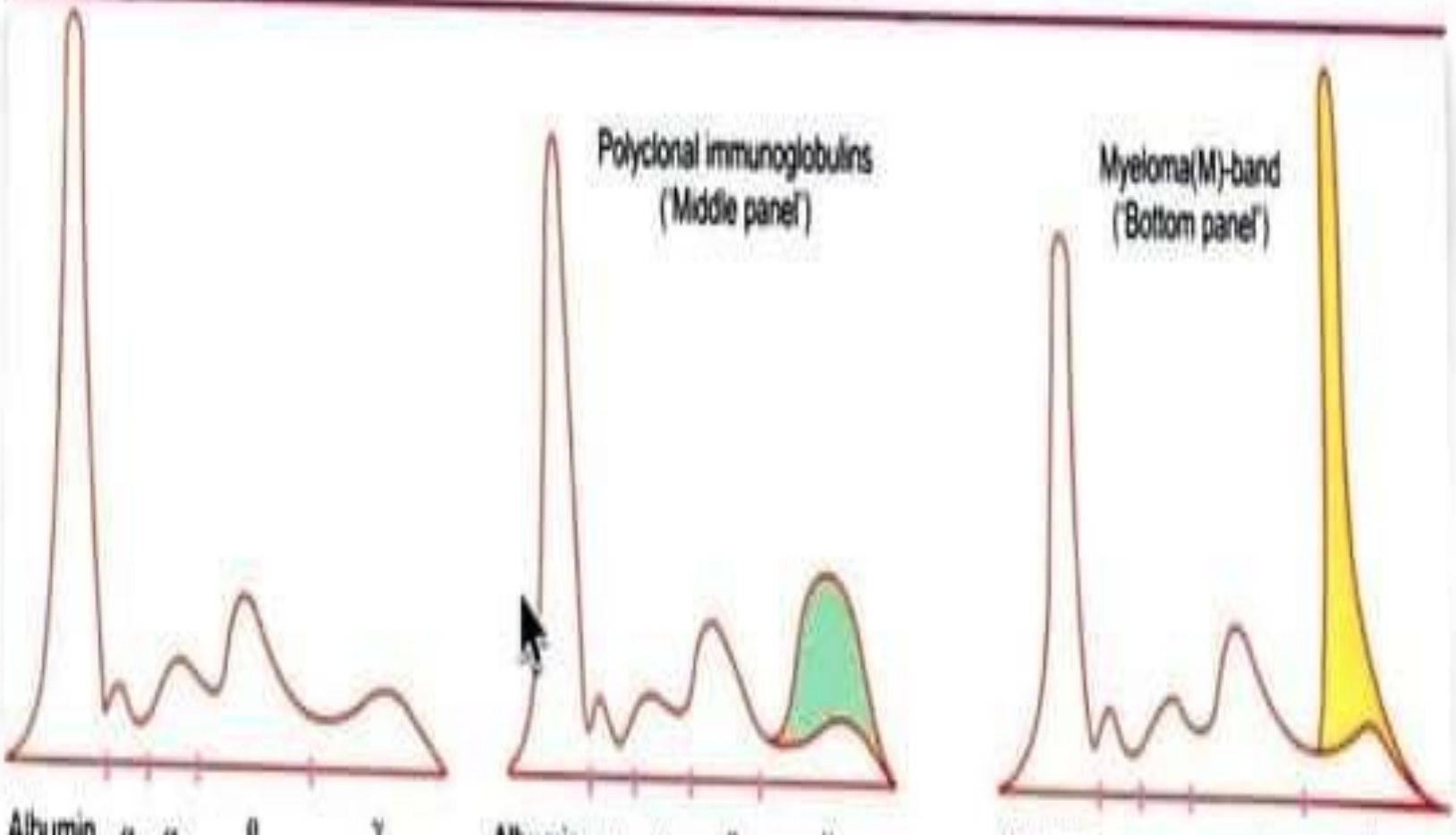
Durie–Salmon staging system

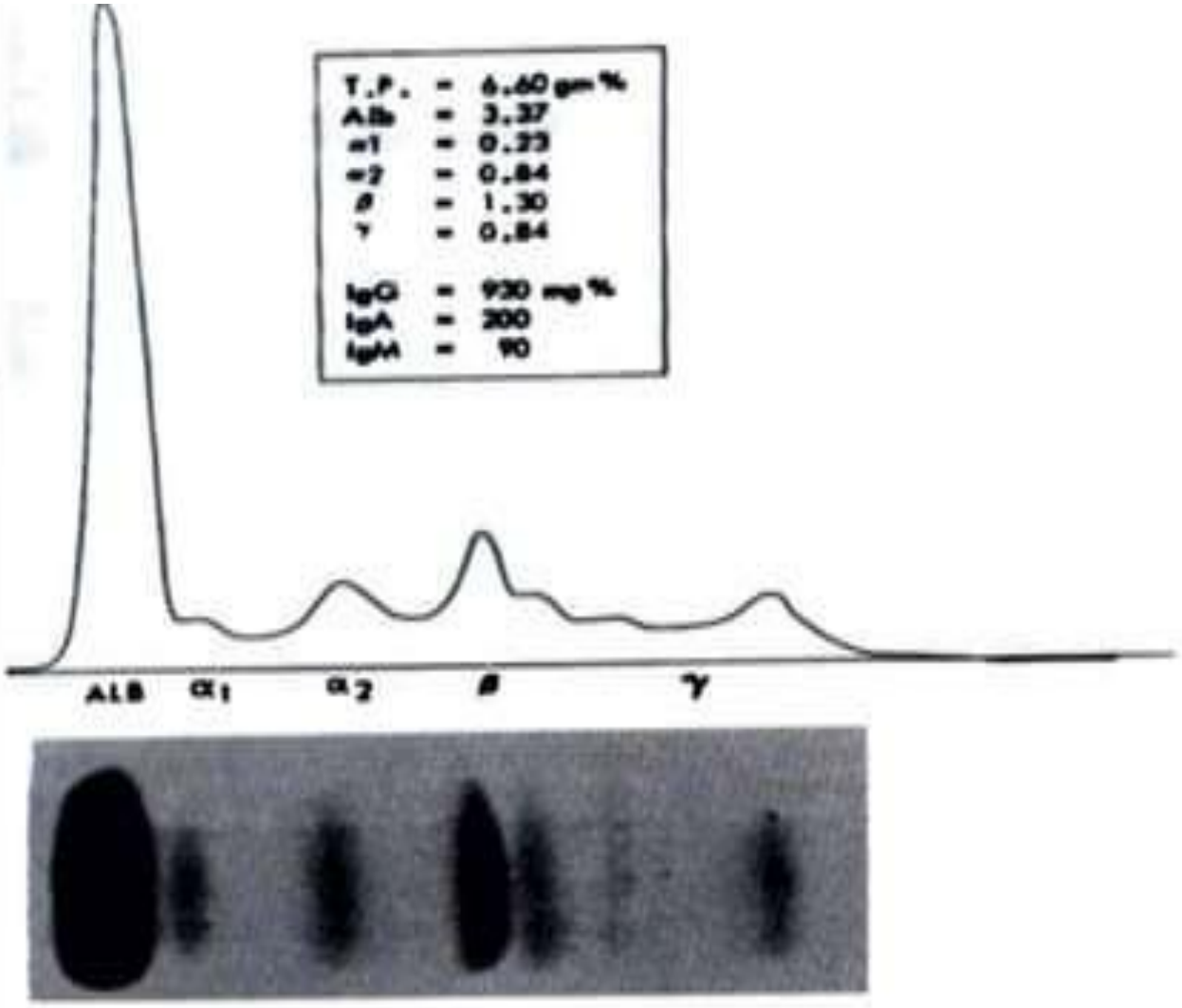
- International staging system, developed over 40 years ago to provide a practical way **to measure MM tumor burden**
- Patients are categorized as stage I, II or III depending on the degree of anemia, hypercalcemia, levels of M protein in the serum and urine, and bone lesions.
- In addition, stages are further divided into category A or B if serum

Diagnosis

- The diagnosis depends on the
  - Identification of abnormal monoclonal plasma cells in the bone marrow,
  - M protein in the serum or urine on electrophoresis,
  - Evidence of end-organ damage

Serum protein electrophoresis





Normal Electrophoretic Pattern

- **Urine examination** for presence of Bence Jones proteins.
- **Electrophoretic studies on Serum or urine**: to screen patient for presence of monoclonal immunoglobin or M band
  - In 99% of patients, there is increased levels of M Igs in the blood and/or light chains, i.e. Bence Jones proteins, in the urine
- **Immunofixation:** done to confirm the suspected monoclonal Ig and classify it. The most common serum monoclonal Ig is IgG (in 55% of pts), IgA-25%,

Investigations

- PBF:
  - Anemia; normocytic normochromic with rouleaux formation
  - TLC, DLC is normal, Raised ESR
  - Platelet count normal with increased bleeding time
- Bone marrow shows increased number of plasma cells (30-90%),
- Raised S. calcium due to extensive osteolytic lesions

Clinical features

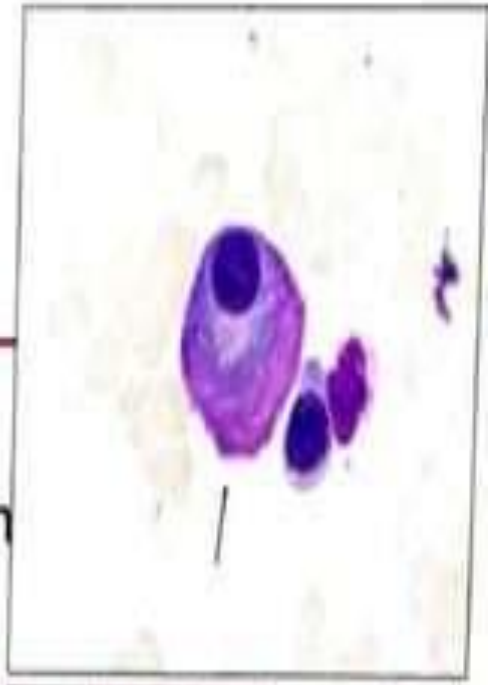
- In early stages, patient complains of weakness, fatigue & weight loss,
- Later, various clinical manifestations are
  - Pallor
  - Bone pains, pathological fractures, leading to Hypercalcemia due to bone resorption,
  - Neurological manifestations like confusion, lethargy
  - Recurrent infections (due to decreased production of normal Ig)

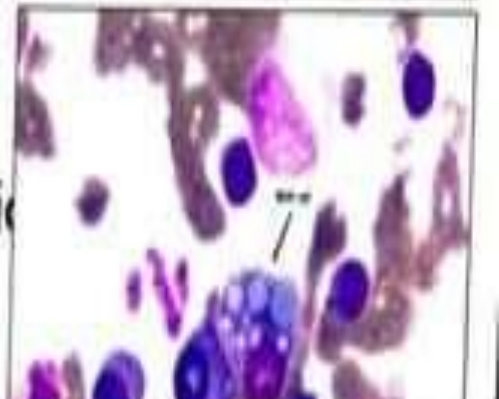
Clinical features

- Insidious onset
- The clinical features are due to the effects of
  - Infiltration of organs, particularly bones, by the neoplastic plasma cells;
  - Production of excessive immunoglobulins,
  - The suppression of normal humoral immunity

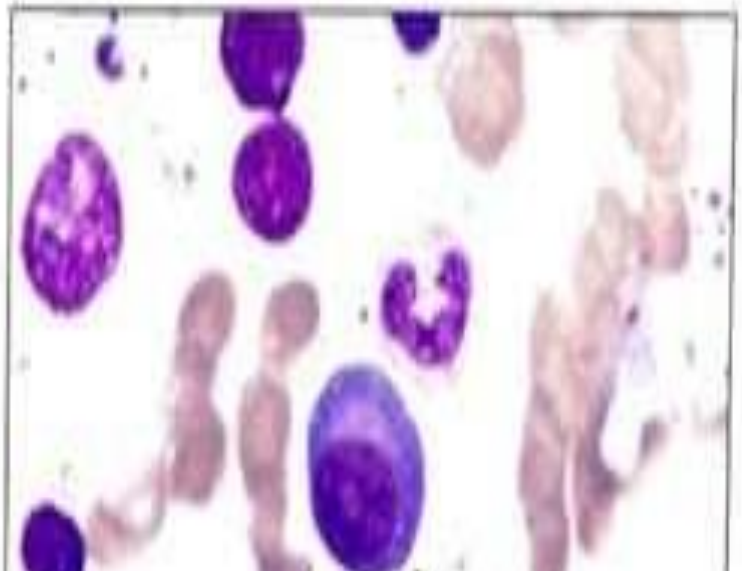
- With progressive disease, plasma cell infiltrate is seen in spleen, liver, kidneys, lungs, lymph nodes or other soft tissues.

- **Cytologic variants** are d/t abnormal synthesis and secretion of Ig, which leads to intracellular accumulation of intact or partially degraded Ig. Such variants include
  - Flame cells with fiery red cytoplasm;
  - Mott cells having multiple, blue, grapelike cytoplasmic droplets;



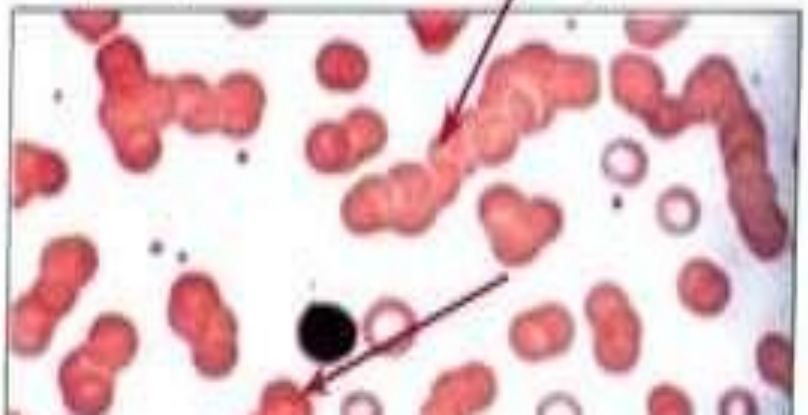


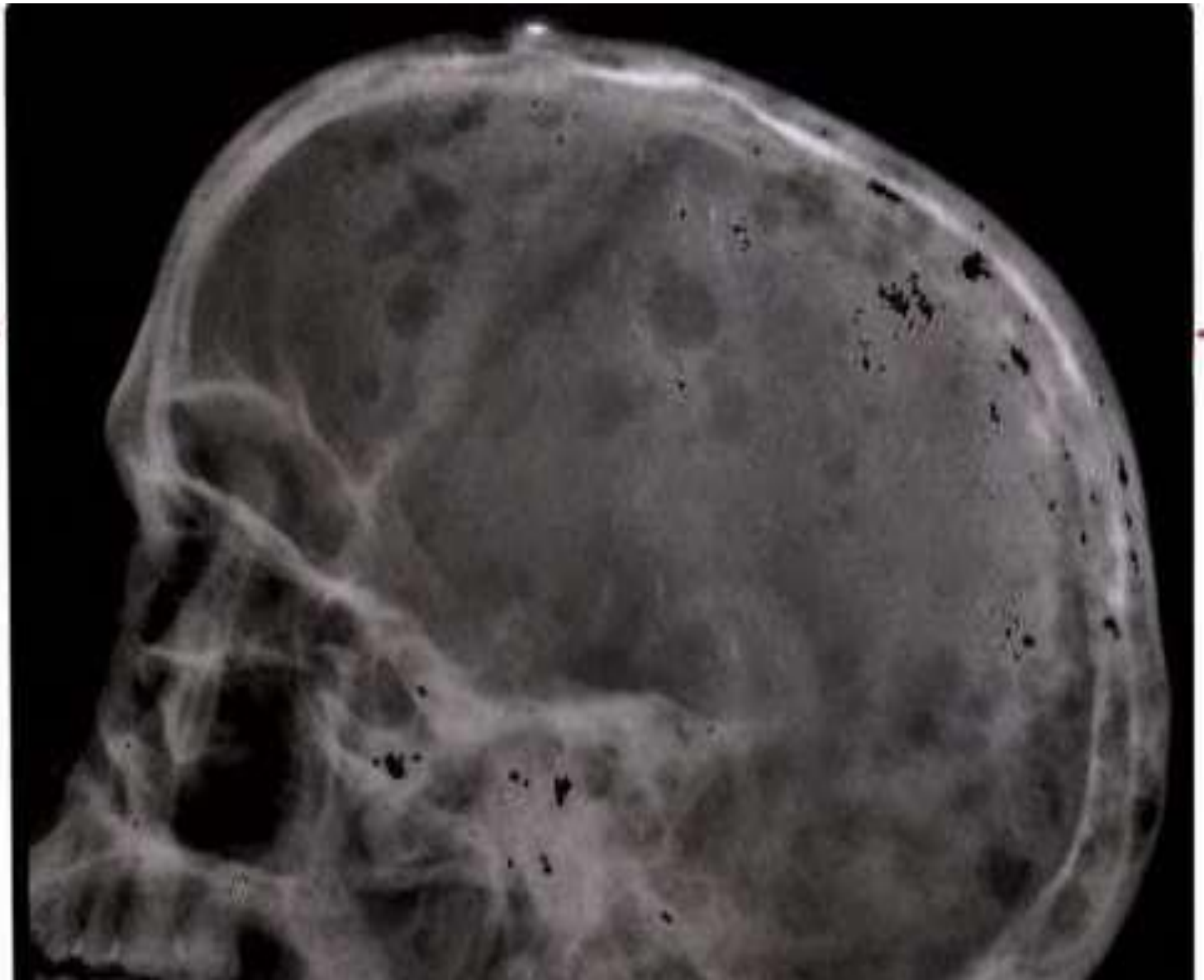
- Neoplastic plasma cells like their benign counterpart usually have a perinuclear clearing and an eccentrically placed nucleus.



- **Bone marrow examination** reveals increased number of monoclonal plasma cells, plasmablasts (with vesicular nuclear chromatin & a prominent single nucleolus), or bizarre, multinucleated cells (10-90%).
- Plasma cells infiltrate the marrow diffusely or in sheets that completely replace normal hematopoietic elements.

- High level of serum M proteins causes red cells in smears of peripheral blood to appear as a stack of coins, referred to as rouleaux formation. Although characteristic, it is not specific.
- Rarely, tumor cells flood the peripheral blood, giving rise to **Plasma cell leukemia.**





Morphology

- MM presents most often as multifocal, destructive bone lesions composed of plasma cells throughout the skeletal system.
- Most commonly affects **axial skeleton** bones & other bones including
  - Vertebral Column, Ribs, Skull, Pelvis, Femur, Clavicle & Scapula.
- The bone lesions appear radiographically as **punched-out defects**, usually 1-4 cm in diameter.

Revised IMWG criteria for diagnosis of Multiple Myeloma (2014)

- Out of proposed 3 **myeloma defining events** (MDEs) one must be present regardless of presence or absence of CRAB features. These are:
  - ≥60% clonal plasma cells in BM
  - Involved/ uninvolved free light chain ratio > 100
  - >1 focal lesion on MRI (>5mm in size)

Diagnostic criteria for multiple myeloma (IMWG 2011)

- Clonal plasma cells ≥10% on bone marrow biopsy,
- Monoclonal protein in serum or urine,
- Evidence of myeloma related end organ damage (**CRAB**)
  - Hyper**C**alcemia (S. Ca>11.5mg%)
  - **R**enal insufficiency (S. Creatinine>1.9mg%)
  - **A**nemia (Hb<10gm%)

- The proliferation & survival of myeloma cells is dependent on various cytokines, like IL-6, which is produced by neoplastic plasma cells and normal stromal cells in the marrow.
- IL-6 and MIP-1α, activate osteoclasts, resulting in bone destruction (the major pathological feature of MM).
- Other factors released from tumor cells, like modulators of Wnt pathways, are potent inhibitors of osteoblast function.

Etiology and Pathogenesis

- MM is associated with rearrangements involving Ig Heavy chain gene locus and various proto-oncogenes.
- Translocations involving chr 14 with oncogene cyclin D1 on chr 11q13 and cyclin D3 on chr 6p21.
- Deletions of chromosome 17p (poor outcome).
- Plasma cell leukemia (a highly aggressive form of the ds) is associated with rearrangements involving MYC gene.

Multiple Myeloma

- Multiple myeloma is a malignant neoplasm of plasma cells; B cell neoplasm.
- Usually presents as multiple tumor masses of neoplastic plasma cells scattered throughout the skeletal system.
- Accounts for 1% of all malignancies & 10-20% of all hematologic malignancies.

MULTIPLE MYELOMA

- ✓ Benign proliferations are important as there is increased risk of their transformation to MM
- ✓ Of all the plasma cell dyscrasias, Multiple Myeloma is the commonest & clinically most important.

Plasma cell Neoplasms/ dyscrasias

- Plasma cell dyscrasias are subclassified into 2 groups:

1. Malignant proliferations:

- ✓ Multiple myeloma
- ✓ Waldenstrom macroglobulinemia
- ✓ Solitary Plasmacytoma
- ✓ Heavy chain disease

2. Relatively benign proliferations:

- ✓ Monoclonal Gammopathy of Uncertain Significance (MGUS)

Plasma cell Neoplasms

- **Monoclonal Ig, or** M component refers to structurally homogenous proteins synthesized by neoplastic plasma cells.
- These have high MW (≥ 1,60,000), so they are restricted to plasma and extracellular fluid and are not excreted in urine in absence of glomerular damage.
- Neoplastic plasma cells synthesize complete immunoglobulins of same class, with excess of light chains or rarely, heavy chains.

Plasma cell Neoplasms

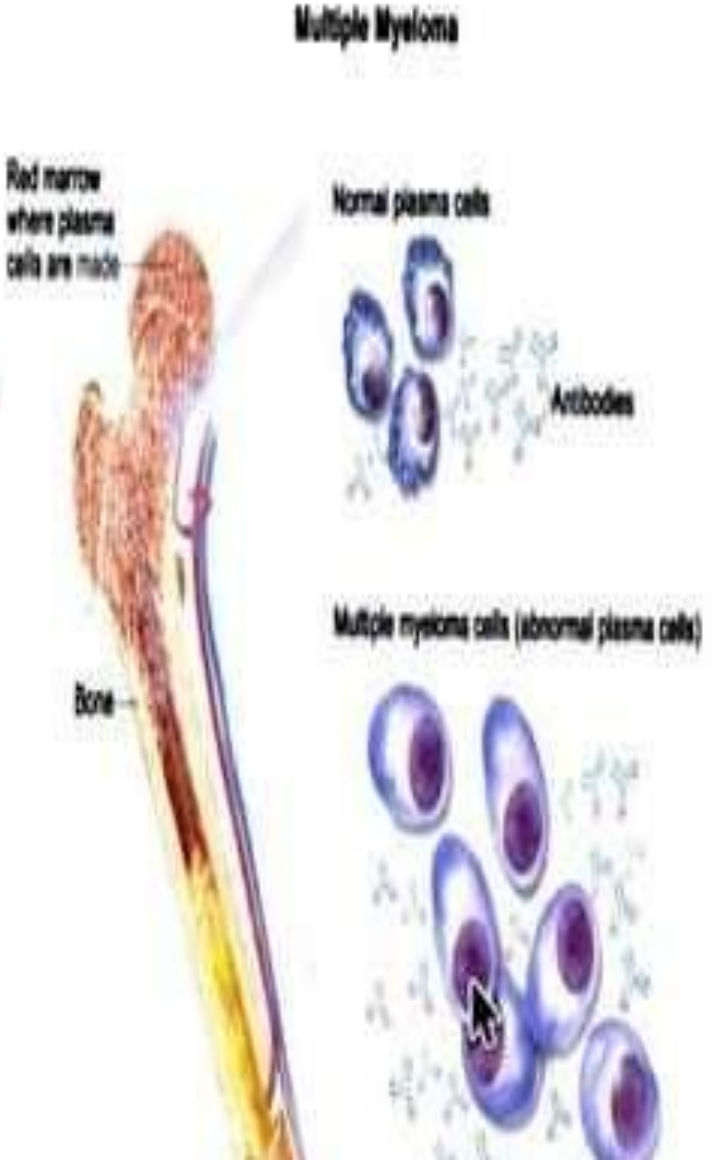
- In immunoglobulins produced by normal plasma cells, the production and coupling of heavy (H) and light (L) chains are tightly balanced, but neoplastic plasma cells usually synthesize excess of light chains or rarely, H chains.
- **Light chains** produced are either Kappa or Lambda (never both) & **Heavy chains** are either alpha, gamma or mu depending on particular class of immunoglobulins.

Plasma cell Neoplasms

- Normal plasma cells transform into malignant plasma cells (known as **myeloma cells)** and produce large quantities of an abnormal immunoglobulins called **Monoclonal** proteins (M component).
- Collectively, the plasma cell neoplasms account for about 15% of the deaths caused by lymphoid neoplasms.

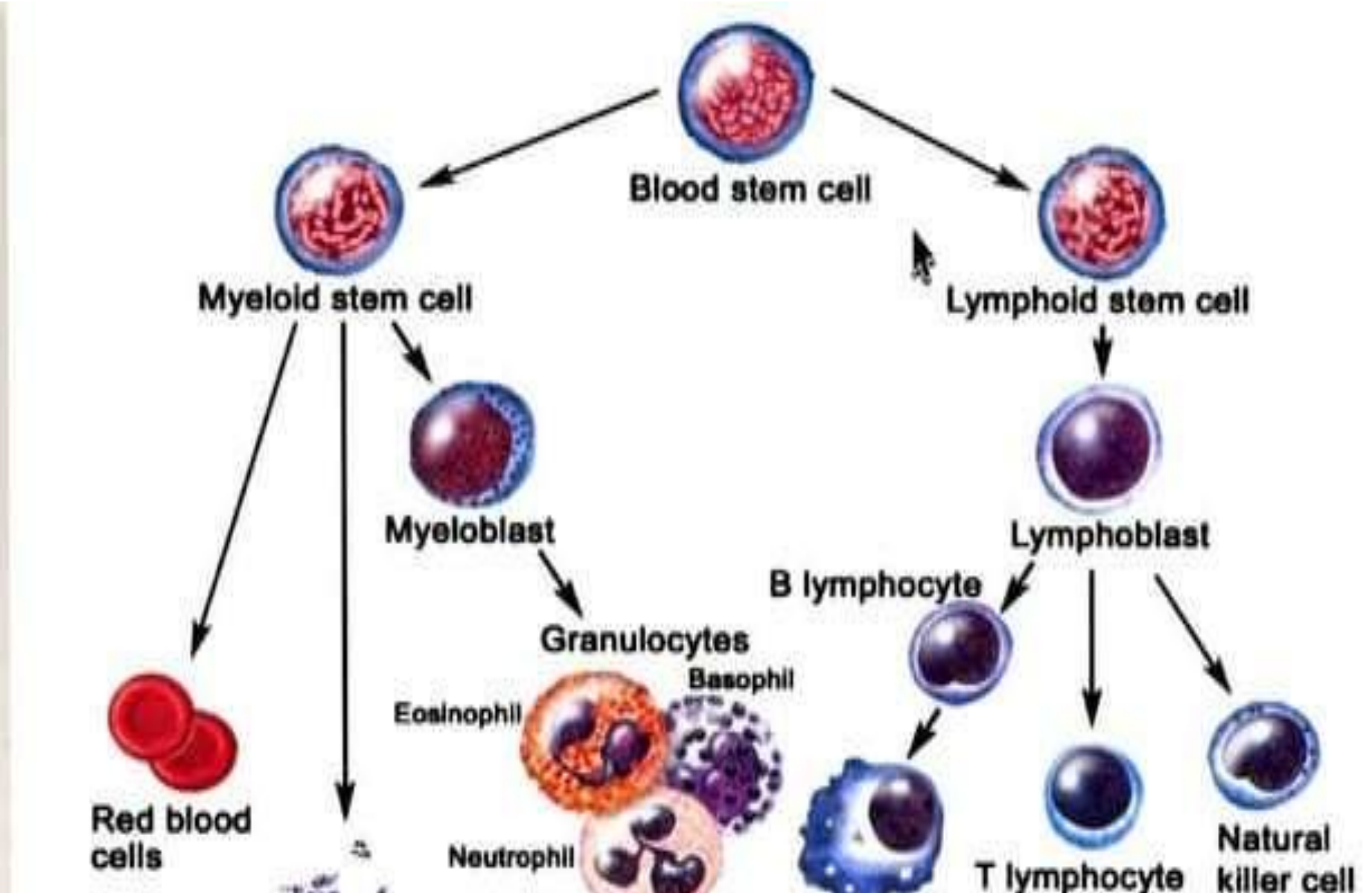
Plasma cell Neoplasms

- Plasma cell neoplasmsare abnormal proliferation of plasma cells and represent a spectrum of diseases called plasma cell dyscrasias.
- It is associated with production of monoclonal immunoglobulins (Igs), which serve as tumour markers.



Plasma cells

- **Plasma cells**, also called **plasma B cells**, are white blood cells that originate in the bone marrow and secrete large quantities of proteins called antibodies in response to specific substances called antigens.
- These cells are large lymphocytes with abundant basophilic cytoplasm, an eccentric nucleus


Blood stem cell
Myeloid stem cell
Lymphoid stem cell
Myeloblast
Lymphoblast
B lymphocyte
Granulocytes
Basophil
Eosinophil
Neutrophil
Red blood cells
T lymphocyte
Natural killer cell

COMPETENCY 20.1

Describe the features of Plasma Cell Myeloma