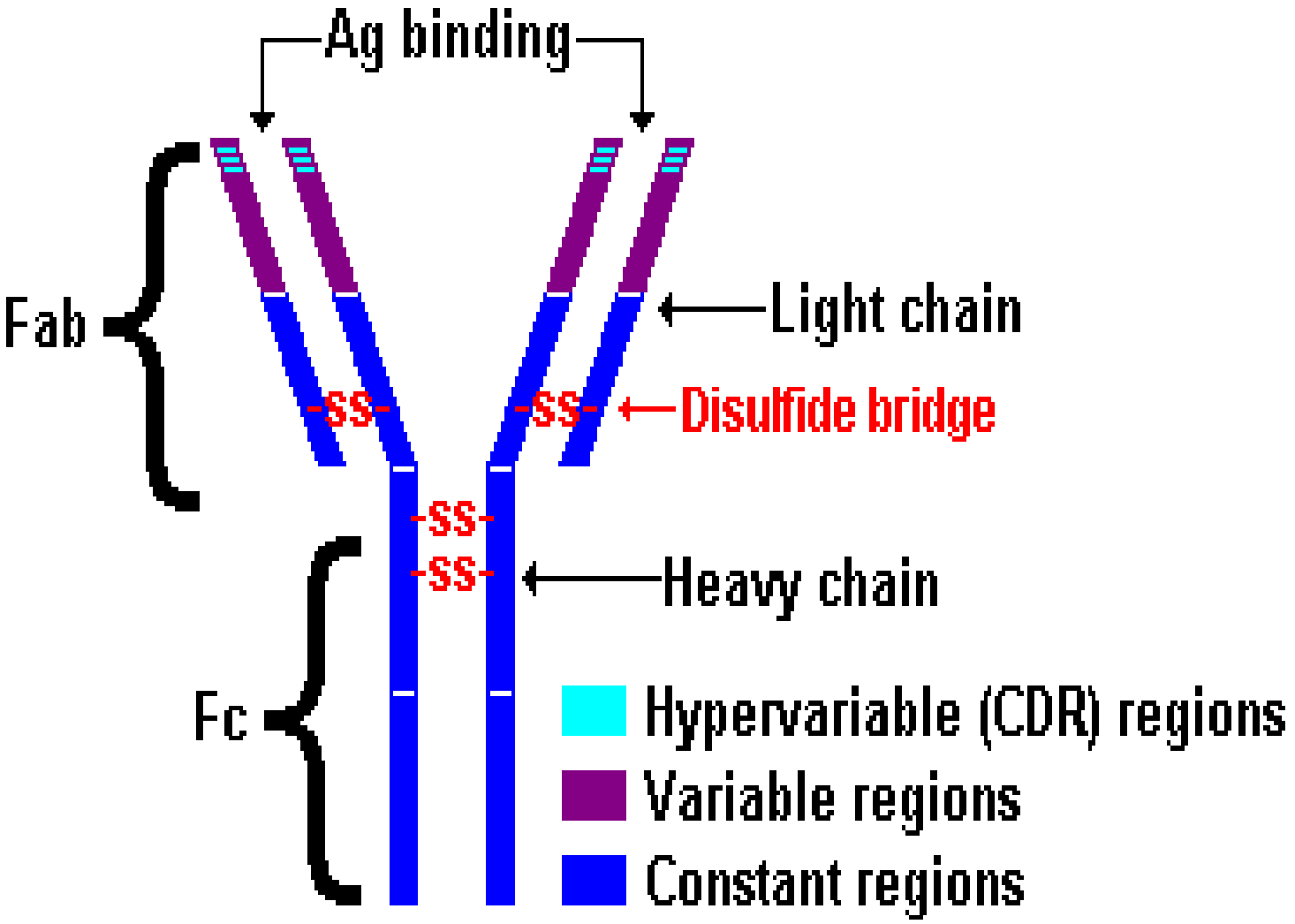
Paraproteinemias

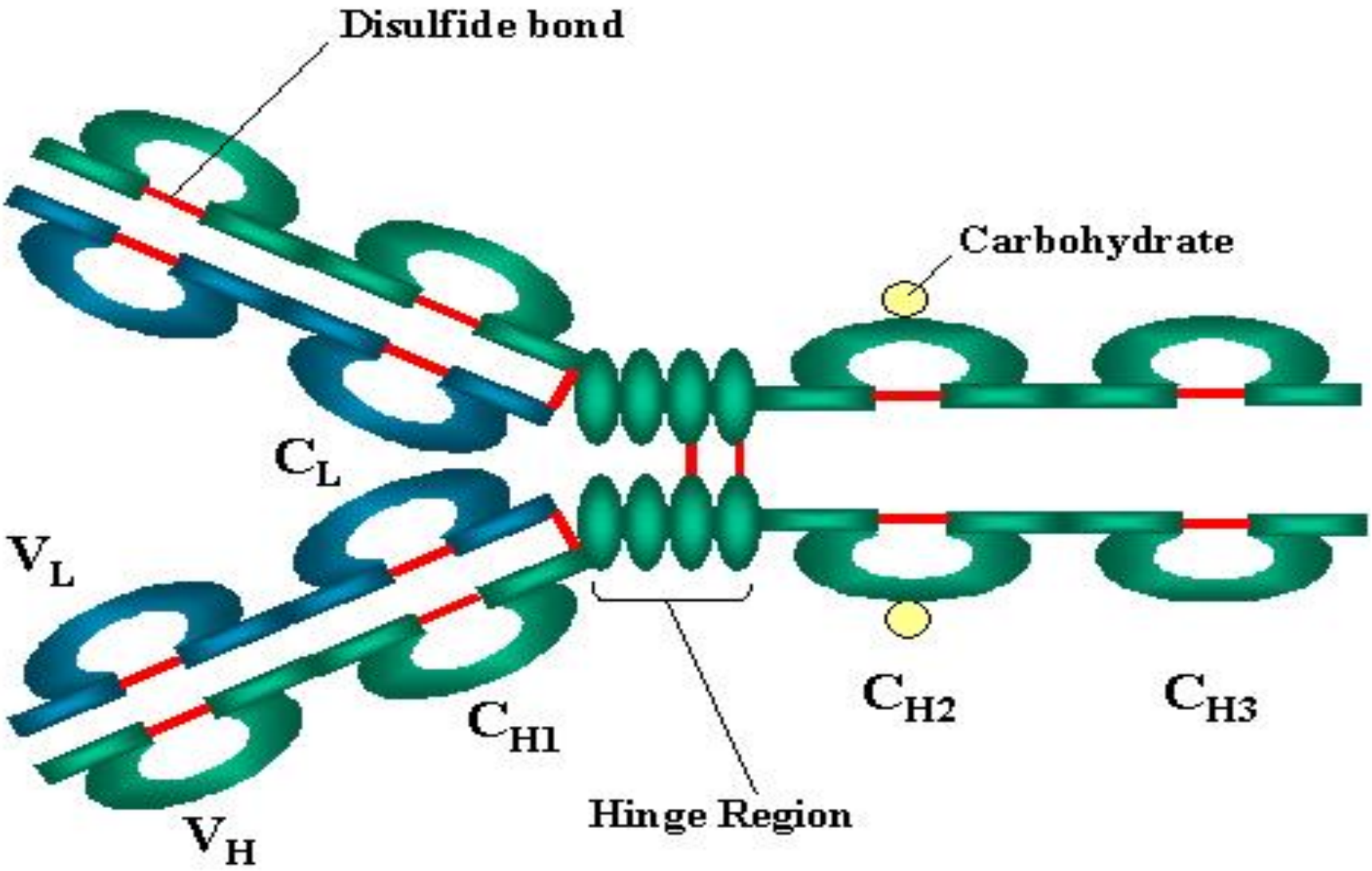
Dr Dina El Dahshan

Lecturer of Clinical Pathology

Ig structure



Ig structure



Paraproteinemias

Definition:

A group of related disorders characterized by secretion of large amount of a single homogenous immunoglobulin product with abnormal physicochemical properties,known as M-component or monoclonal component.

(including dysproteinemias and gammopathy)

Gammopathies

Definition:

A group of ***plasma cell disorders*** resulting in abnormal Ig either quantitative (polyclonal gammopathy) or both quantitative and qualitative (monoclonal gammopathy)

Immunocytic dyscriasis

I-Plasma cell myeloma (Multiple Myeloma)

II-Monoclonal gammopathy of unknown significance (MGUS)

III-Plasma cell myeloma variants:

- Plasma cell leukemia
- Indolent myeloma
- Smoldering myeloma
- Osteosclerotic myeloma
- Non secretory myeloma

VI-Plasmacytomas

- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma

Immunocytic dyscriasis

V-Waldenstrom macroglobulinemia

VI-Heavy chain disease

Gamma HCD, alpha HCD, Mu HCD

VII-Immunoglobulin deposition diseases

Light chain disease

Primary amyloidosis

(Waldenstrom and heavy chain disease more properly Lymphocyte dyscriasis)

Multiple Myeloma

Incidence

Race: black more than white

Age: old age more than 60 yrs

Sex: males

Etiology

- Increased risk in farmers, petroleum, wood, leather, and asbestos workers.
- Exposure to radiation

Multiple Myeloma

Chromosomal alterations:

Trisomy 9,3,19,15,11.

Monosomy 13,14,8.

Overexpressed oncogenes:

C-myc in 80% of patients

N-ras mutation

Bcl2

Supressor genes:

P53 mutation predicts poor survival *(myeloma cells with impaired p53 may have blocked apoptosis)*

Pax 5 gene

Rb gene

Multiple Myeloma

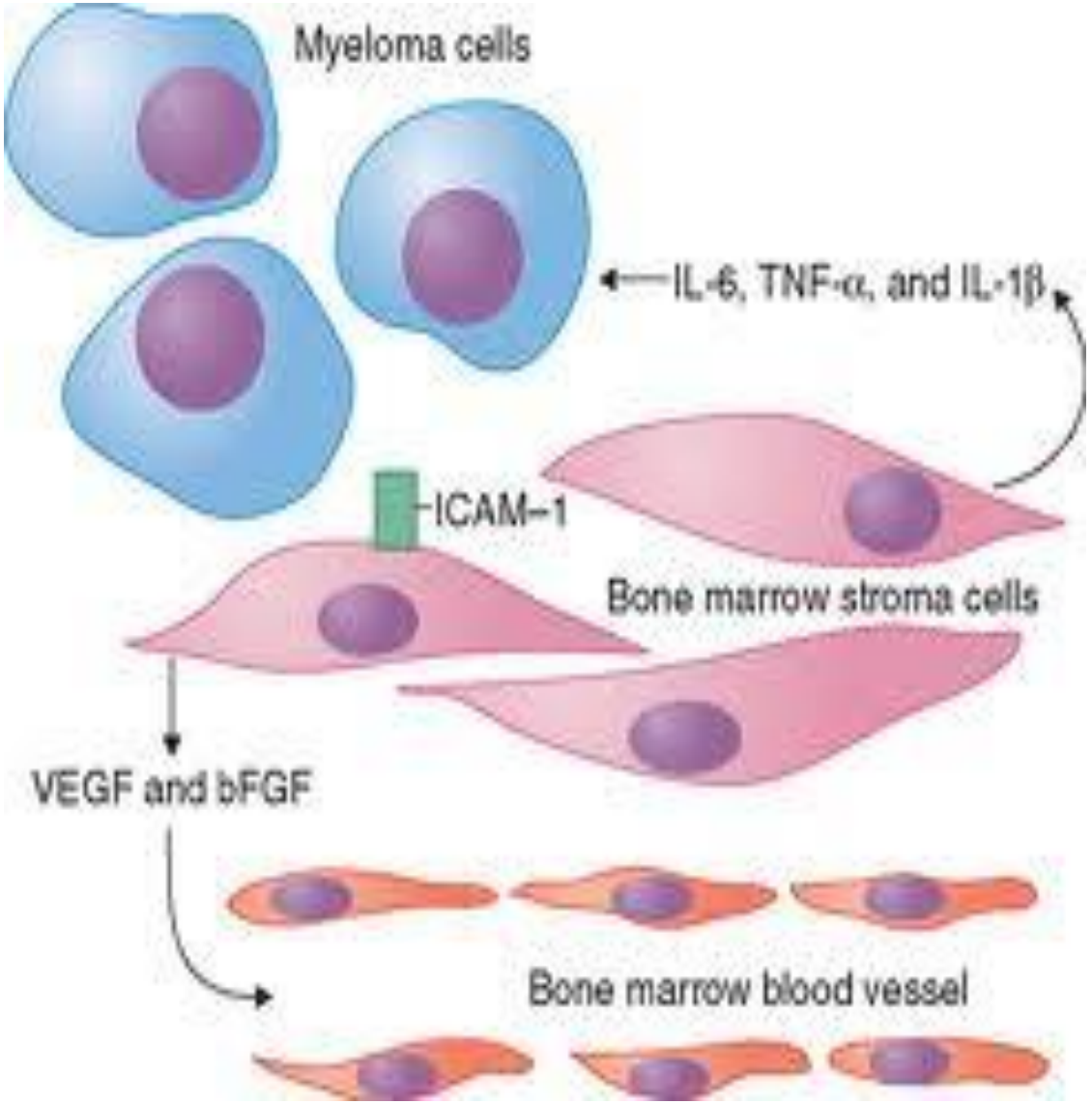
Pathogenesis

Progression of myeloma is intimately linked to the bone marrow microenvironment.

The neoplastic plasma cells express multiple cell adhesion molecules which mediates adhesion of myeloma cells to marrow stroma, triggering secretion of growth promoting cytokines.

Marrow stromal cells provide signals for expansion and maturation of circulating myeloma cells

Pathogenesis



Multiple Myeloma

Role of myeloma cell Adhesion molecules

CD138 (syndecan-1)+osteoblast activation

VLA-4 binding of MM to stroma

VLA-5 binds to fibronectin promotes apoptosis

Role of cytokines

IL6 secreted from BMSC, myeloma cells, osteoblast , osteoclasts.

++proliferation of myeloma cells

IL6 from osteoblasts + osteoclast → release IL6 → osteolytic lesions

Multiple Myeloma

IL1 &TNF → from myeloma cells promotes osteoclastic activity.

GM-CSF → from myeloma cells → promote osteoclastic activity.

GM-CSF → produced from stroma →

Stimulate cell growth.

In multiple myeloma ↑ serum IL6 & soluble receptor = **BAD Prognosis**

Multiple Myeloma

Angiogenic effect of MM cells

Due to expression of VEGF-1

In conclusion

Initial marrow localization of monoclonal B cells may be caused by marrow paracrine stimulations and cell adhesion expression, subsequent autocrine growth by plasma cells may lead to self sustained growth,in addition abnormal gene expression through rearrangement, mutation, or loss of suppressor gene activity due to deletion or alteration could result in myeloma progression.

Multiple Myeloma

Consequences of abnormal plasma cell growth

1-tumour cells in BM ⟹ destruction of bone leading to anemia, leukopenia and thrombocytopenia

2-Immune defficiency and increased susceptebility to infection due to abn Ig & suppression of N immune function by myeloma cells

3-Renal failure is complex but mainly due to excretion of light chain

Diagnosis

- **Clinical**:

-Bone pain

-Weakness, pallor, palpitation, anemia, infections, bleeding.

-Symptoms of Renal failure and hypercalcemia

Common tetrad of multiple myeloma is *CRAB*: C = Calcium (elevated), R = Renal failure, A = Anemia, B = Bone lesions

Diagnosis

- **ESR** ↑
- **CBC** : Normochromic normocytic anemia

  rouleaux appearance

  TLC : Usually normal,

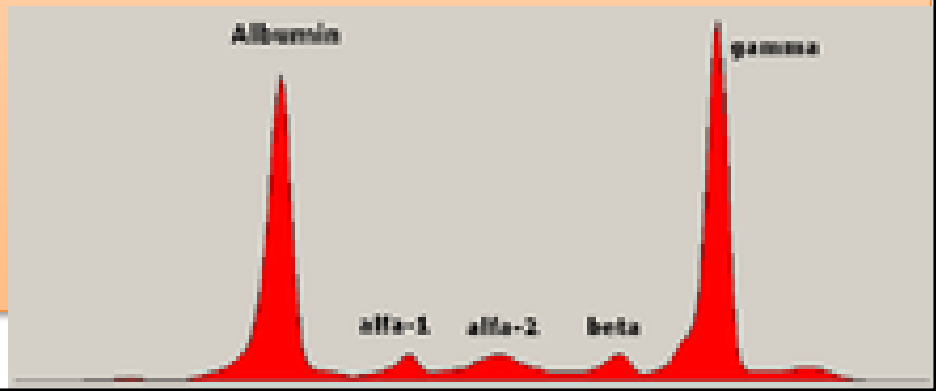
  early leukoerythroblastic picture, immature looking lymphocytes and plasma cells.

  When plasma cells predominate in PB = plasma cell leukemia

Multiple myeloma

- **Serum B2 microglobulin**
- **C-reactive protein**
- **Protein E\P**

of the blood and urine, which might show the presence of a paraprotein (monoclonal protein, or M protein) band, with or without reduction of the other (normal) immunoglobulins (known as immune paresis).



- **Immunoglobulin assay**

-single radial immunodiffusion

-electroimmunodiffusion

-nephelometry

- **Detection of free light chain in urine**

-E\P in 24 hr urine

-immunofixation

-Heat precipitation test

Multiple myeloma

- **Bone Marrow aspirate**

Plasma cells 10% or more

Typical myeloma cells-large , round, ovoid, eccentric nucleus

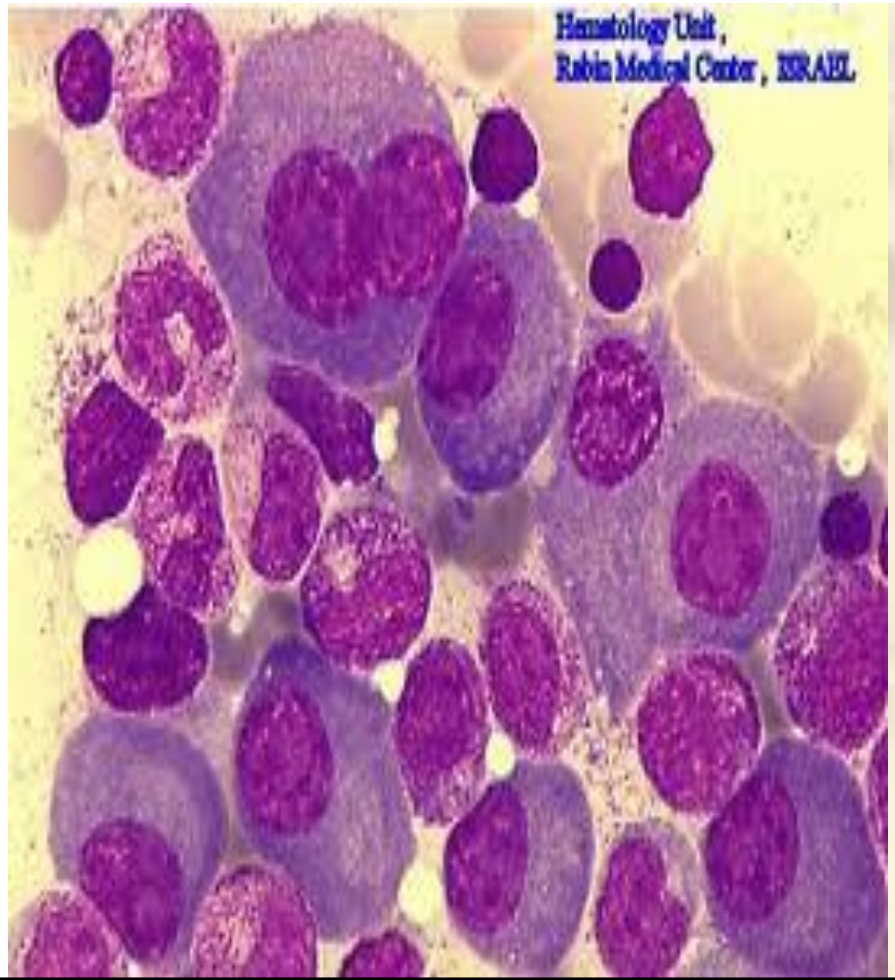
Giant multinucleated

Flame cells

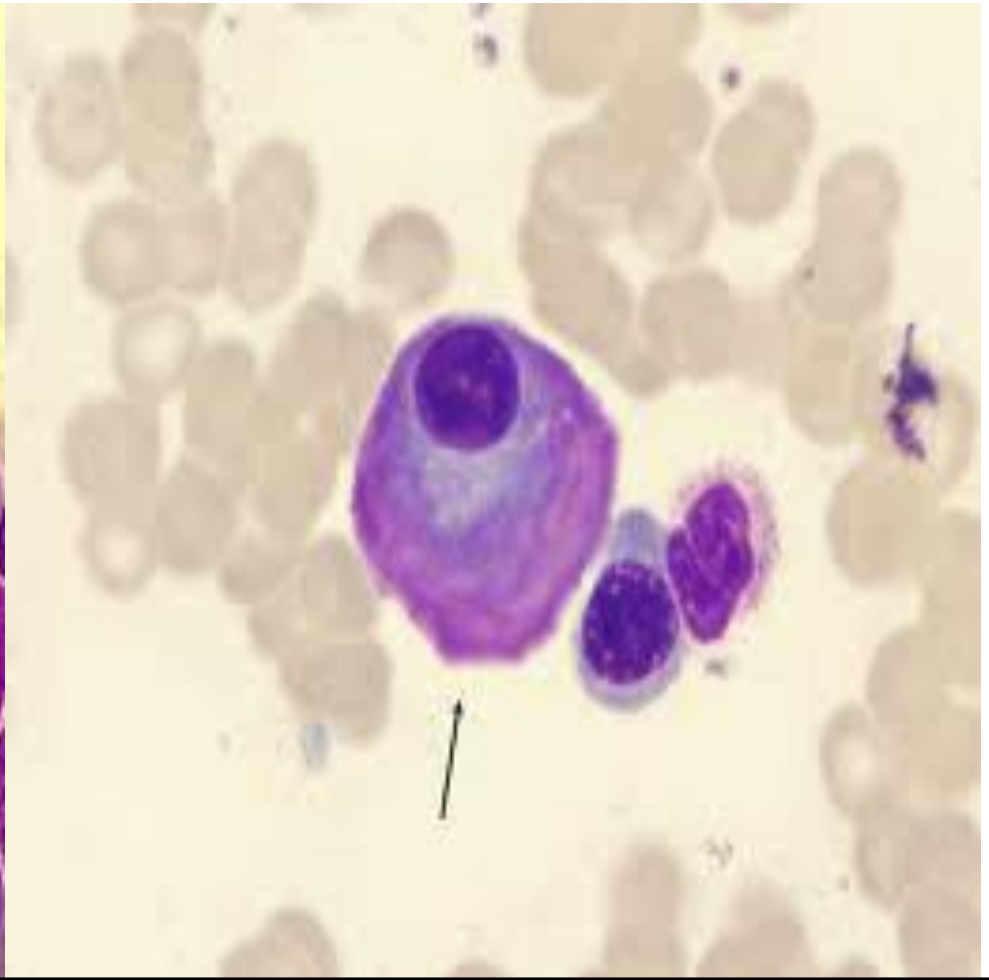
Mott cells

Multiple Myeloma

Plasma cells



Flame cell



Multiple myeloma

- **Bone Marrow Biopsy**

Invasion with plasma cells and displacement of normal hematopoeitic cells. Diffuse or nodular involvement

- **Serum Ca increased**
- Serum uric a increased
- Serum urea, creatinine

Multiple Myeloma

Workout

1-Skeletal survey

2-CT scan

3-MRI

4-Bone marrow biopsy

5- CD56, CD38, CD138+

6-Cytogenetics , fish, karyotyping for prognosis

Diagnostic criteria of MM

I major+ I minor

Or III minor including 1 and 2

Major criteria:

Plasmacytoma of bone

Marrow plasmacytosis 30%

M-component: Ig G 3.5gm%,Ig A 2gm%, urine)1gm\24hr

Minor criteria

Diagnostic criteria of MM

Minor criteria

Marrow plasmacytosis 10-30%

M-component

Lytic bone lesions

Reduced normal Ig

Prognostic criteria

B2 microglobulin level reflects tumour burden

C-reactive protein concentration reflect IL-6 activity

Del 13 Complete or partial

Increased LDH

PCLI (plasma cell labelling index)

Salmon &Durie

Stage I

1-Low M component –Ig G 5gm, -IgA 3gm,Bence jones-4gm

2-Absent or solitary bone lesions

3-N Hb,N serum Ca, Ig level

Stage III

1-High M component +Ig G 7gm, +IgA 5gm, Bence jones+12gm

2-Multiple Lytic lesions

3-Hb less than 8.5gm, serum Ca +12 mg

Staging of MM

Stage II

Between I & II

Variants of MM

- Plasma cell leukemia
- Smoldering myeloma
- Indolent myeloma
- Non secretory myeloma
- Osteosclerotic myeloma

Plasma cell leukemia

-20% of peripheral blood white cells are plasma cells.

Or absolute number exceeds 2000\ul

-1ry or 2ry to MM

-Rapid disease progression with massive marrow replacement

-HSM , anemia, bleeding

-Osteolytic lesions less frequent

-Poor prognosis

Indolent Myeloma

As Myeloma:

-Absent or rare bone lesions

-M-component:Ig G<7g/dl, IgA<5g/dl

-No symptoms or associated disease features: Hg 10g/dl, normal serum calcium, creatinine, and no infections.

Smoldering Myeloma

As indolent Myeloma:

-No demonstrable bone lesions

-Bone marrow plasma cells (10-30%)

Non secretory Myeloma

-Patients of MM lack demonstrable monoclonal protein in the serum or urine.

-difficult to diagnose

-Immunhistochemical studies demonstrate presence of light or heavy chain restricted Ig synthesis

Osteosclerotic Myeloma

-A component of a rare syndrome

-Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin lesions (POEMS)

-Single or multiple sclerotic lesions

-Low level of monoclonal protein

-Nearly all cases has light chain λ, bence jones protein

II-Monoclonal Gummopathy of unknown significance (MGUS)

- Definition:

Monoclonal Ig spike (M component) in serum or urine in a patient with no evidence of a neoplastic plasma cell dyscriasis or any other disorder that causes increase in Ig.

Monoclonal Gummopathy of unknown significance (MGUS)

- Criteria for diagnosis:

Monoclonal Ig in serum

M-component level:-------

Marrow plasma cells<10%

No bone lesions

No bone marrow lesions in MRI

No symptoms

Monoclonal Gummopathy of unknown significance (MGUS)

- MGUS is difficult to differentiate from early myeloma
- With follow up if there is no dramatic increase in M band it is MGUS.

III- Plasmacytomas

- Solitary Plasmacytoma of Bone

-Solitary osteolytic lesion radiologically

- No marrow plasma cells
- Lacking M component or near normal Ig with no spike

Plasmacytomas

- Extramedullary plasmacytoma

-3-5% of all plasma cell neoplasms

-80% in upper respiratory tract (oropharynx, nasopharynx, larynx)

-Surgical excision and local radiotherapy is usually curative

Waldlenstrom's Macroglobulinemia

- Incidence:

Less common than myeloma

2% of hematologic malignancies

Age 63-65 median

Males and whites more

- Pathogenesis:

Chr 9, 10, 11 and 12 are most commonly involved with no particular chromosomal abnormality. monosomy 9 with disease progression

Waldlenstrom's Macroglobulinemia

- ***Clinical Features:***
- ***Its an amalgam of both lymphoma and myeloma***

Fatigue, weakness, wt loss

Lymphadenopathy, HSM

S&S of hyperviscosity syndrome

Bleeding from gums, nasal mucosa

Peripheral neuropathies

Waldlenstrom's Macroglobulinemia

LABORATORY Features:

CBC:NNA, rouleaux, leukopenia

BMA: Hypocellular, dry tap

Lymphocytes , plasmoid lymph

BMB: Hypercellular, infilterates of small lymphocytes, plasmacytoid lymph, plasma cells.

E\P : Monoclonal band in serum in B to gamma region

Immune E\P reveals Ig M

Waldlenstrom’s Macroglobulinemia

- Radiologic diagnosis:

MRI shows lytic bone lesions in flat bones

‘’’’

- NB:

The term macroglobulinemia describes an increase in the blood concentration of Ig M. It is commonly denotes WM, but other disorders can be associated with monoclonal macroglobulinemia as CLL, small lymphocytic lymphoma.

Heavy-chain disease

Rare lymphoplasmacytic disease chch by production of only Ig heavy chain. **Failure of assembly or no production**

<u>l-gamma HCD:</u>

Involves waldeyer ring, uvula oedema

Imuunefixation reads with anti Gamma

No monoclonal band in E\P

<u>ll U HCD:</u>

U HCD

- CLL like
- Fate 1\3 to CLL
- IMM E\P: U +50%K

Alpha heavy chain disease:

Hepatomegaly and mesenteric lymphadenopathy presenting as abdominal mass

Younger ,low socioeconomic, poor hygiene, malnutrition, intestinal infections

- Known as Mediterenian lymphoma
- Early ttt by antibiot
- Late progresses into immunoblastic L

THANK YOU