



**Internal medicine
Hematologic Diseases**



Plasma Cell Disorders Multiple Myeloma

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Intended Learning Outcomes

By the end of the lecture, you should be able to:

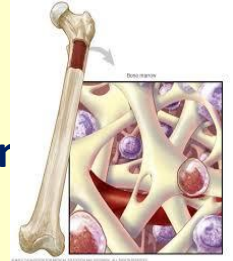
A- Knowledge and understanding:

A1- Describe a definition , epidemiology and causes of Multiple Myeloma

B- Intellectual Skills:

B1- Formulate history and approach to the patients with Multiple Myeloma.

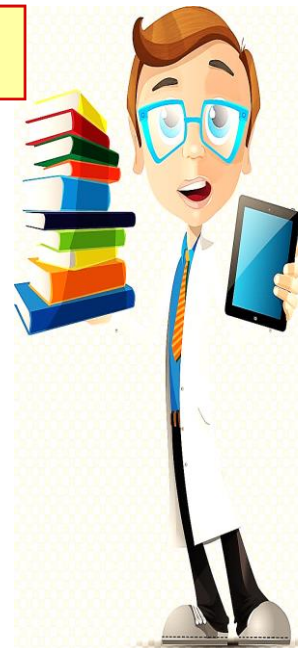
B2-Select diagnostic investigations and management strategy of Multiple Myeloma



History of present illness training learning objectives

After this lecture, you should be able to identify items of Multiple Myeloma:

- ☐ Definition and Epidemiology
- ☐ Etiology and Types.
- ☐ Clinical Manifestations and Diagnostic Evaluation .
- ☐ Treatment





Items of Plasma Cell Disorders

- ☐ **Definition**
- ☐ **Epidemiology** (**statistics, race, age, sex, mortality/morbidity**)
- ☐ **Etiology**
- ☐ **Pathophysiology of Multiple Myeloma**
- ☐ **Types.**
- ☐ **Clinical Manifestations and complication**
- ☐ **Diagnostic Evaluation.**
- ☐ **Differential Diagnosis of plasma cell disorders**
- ☐ **Treatment**



- A- Supportive treatment of patients with MM**
- B- Immunosuppressive treatment (IST) of MM**
- C- Haemopoietic stem cell transplant in MM**

Definition of Multiple Myeloma (MM)

- ❑ MM is defined as neoplastic proliferation of a single clone of plasma cells engaged in the production of a monoclonal immunoglobulin.





Epidemiology

☐ International statistics

- The most common plasma cell malignancy

☐ Race and Sex

- MM occurs in all races and all geographic locations
- Male > female
- A male preponderance is observed



☐ Age-related demographics

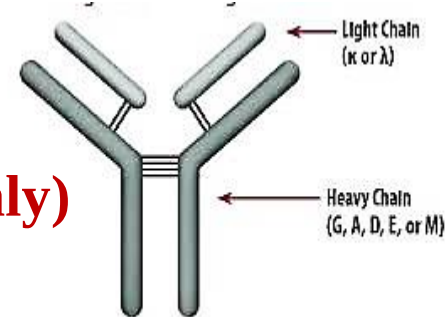
- Increased frequency with age; median age of diagnosis is 68 yr



Pathophysiology

Malignant plasma cells secrete monoclonal antibody

- **95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)**

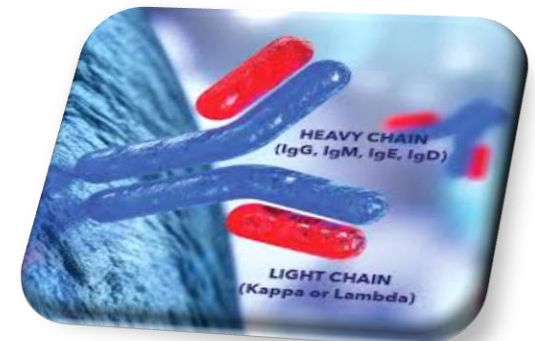
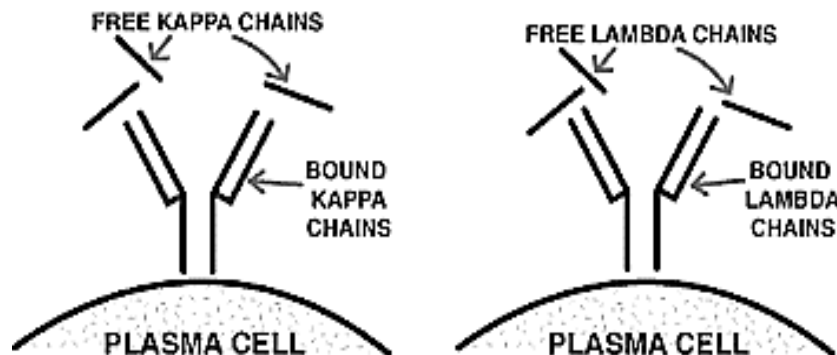


- ◆ **IgG 50%**

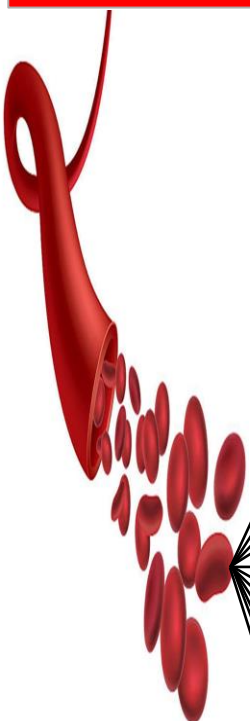
- ◆ **15-20% produce free light chains or light chains alone found in either:**

- Serum as an increase in the quantity of either kappa or lambda
- Urine has Bence-Jones protein

- **<5% are non-secretors**



Clinical Features and Complications



Bone disease

- Bony pain, pathologic fractures
- Lytic lesions (skull, spine, ribs)

Anemia

- Fatigue, due to BM suppression

Infections

- Respiratory and urinary tract

Hypercalcemia

- Bone resorption, Constipation, polyuria

Renal disease

- Myeloma kidney:-light chains or hypercalcemia, amyloidosis

Weight loss

Bleeding

- From thrombocytopenia or coating of platelets with M protein

Extramedullary

- Soft issue mass composed of monoclonal plasma cells

Hyperviscosity

Amyloidosis

- Accumulation of insoluble fibrillar protein (Ig light chain)

Neurologic disease

- Radiculopathy
- Spinal cord compression

Investigations

A- CBC

1. Full blood count
 - Normocytic anemia, thrombocytopenia, leukopenia
2. Blood film examination
 - Rouleaux formation on peripheral film

B- Biochemistry

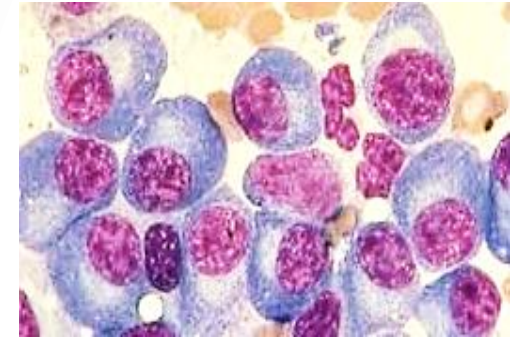
1. Increased Ca
2. Increased ESR
3. Increased Creatinine
4. Increased Total protein
5. Increased Uric acid
6. Increased β 2-microglobulin
7. Proteinuria (24 h urine collection)
8. **Decreased** anion gap
9. β 2-microglobulin, LDH, and CRP are **poor prognosticators**



Investigations

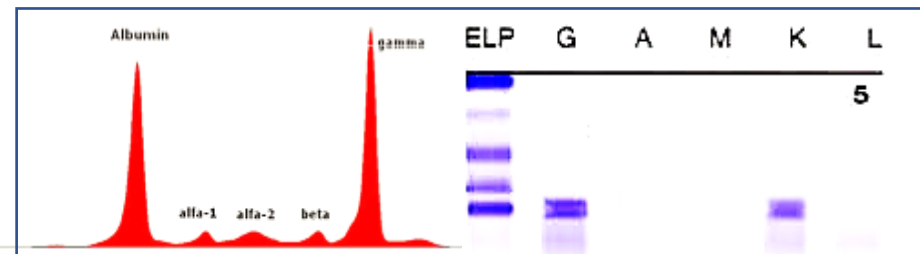
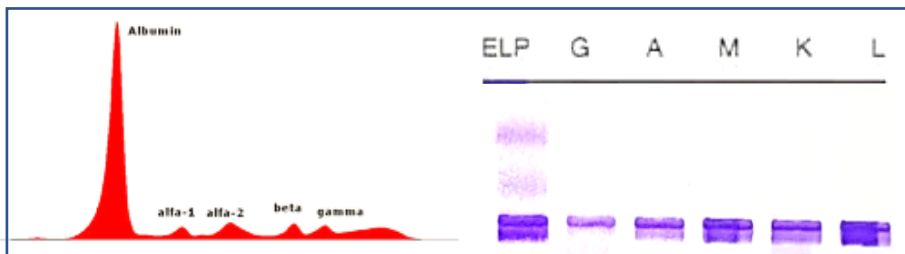
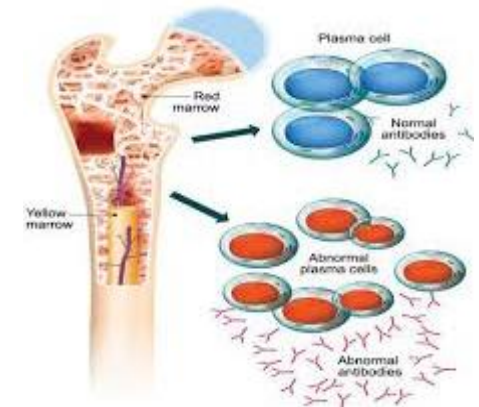
C- Bone Marrow Aspiration and Biopsy

- Greater than 10% plasma cells, abnormal morphology,
- Clonal plasma cells;
- Send for FISH or cytogenetics (prognostic implications)



D- Monoclonal proteins

1. **Serum protein electrophoresis (SPEP):** demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
2. **Urine protein electrophoresis (UPEP):** demonstrates light chains in urine = Bence-Jones protein (15% light chains)
3. **Immunofixation:** demonstrates M protein and identifies Ig type; also identifies light chains
4. **Serum free light chain quantification:** kappa and lambda light chains, calculated ratio

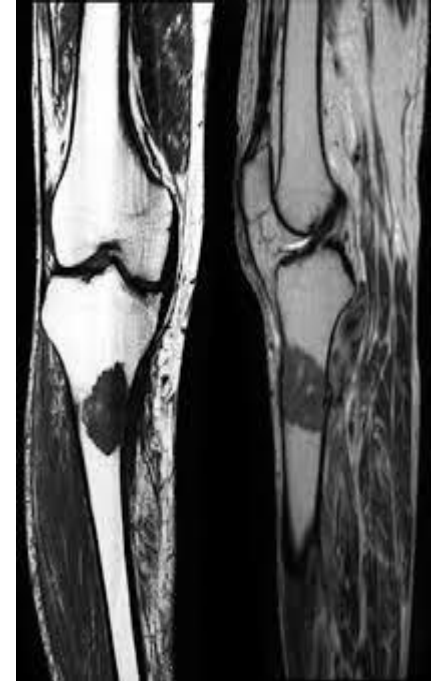
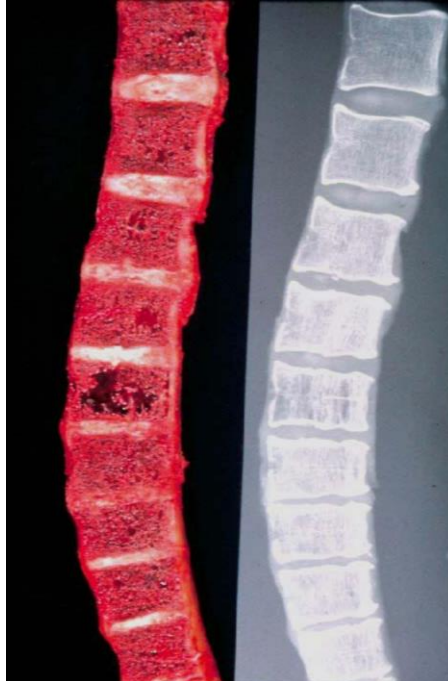


Investigations

E- Skeletal series

x-rays, MRI if symptoms of cord compression

- Presence of lytic lesions and areas at risk of pathologic fracture
- Bone scans are not useful since they detect osteoblast activity





MM: 2020 update on diagnosis

To diagnose MM

Both criteria must be met as:

- Clonal bone marrow (BM) plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma
- Any one or more of the myeloma defining events (MDE)

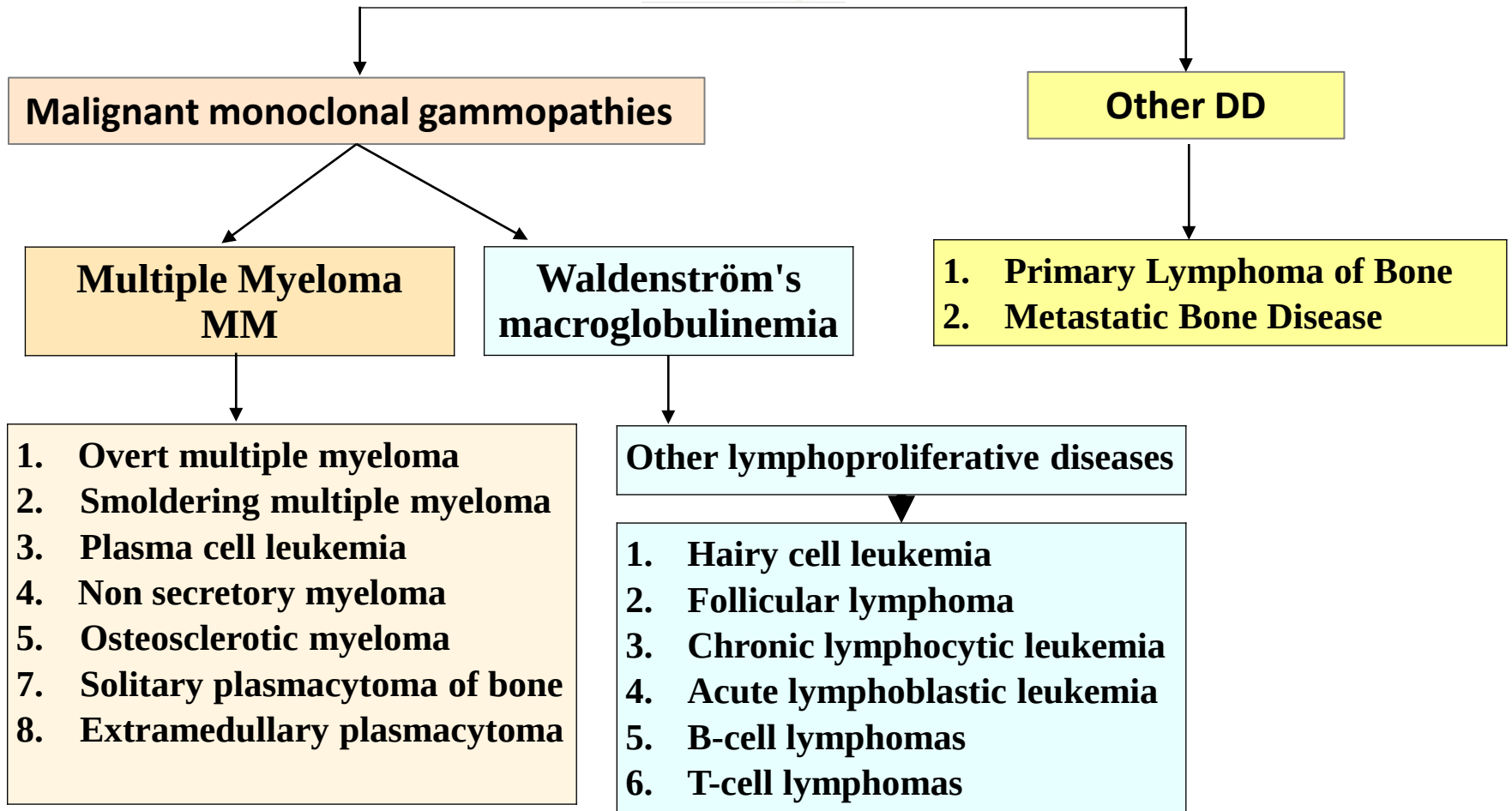
1. **Hypercalcemia:** >11 mg/dL
2. **Renal insufficiency:** Creatinine clearance <40 mL/min or serum >2 mg/dL
3. **Anemia:** Hb value <10 g/dL
4. **Bone lesions:** One or more osteolytic lesions on skeletal radiography

Or three specific markers

- Clonal BM plasma cell percentage $\geq 60\%$
- Serum free light chain (FLC) ratio ≥ 100
- >1 focal lesions on MRI studies (at least 5 mm in size)



Differential Diagnosis





Treatments

A- Supportive treatment of patients with MM

1. Hypercalcemia

1. Hydration, preferably with isotonic saline plus prednisone (25 mg/4/day)
2. Bisphosphonates such as zoledronic acid or pamidronate

2. Renal Insufficiency

1. If the patient is not oliguric, IV fluids and furosemide.
2. Hemodialysis is necessary for symptomatic azotemia.
3. Allopurinol is necessary if hyperuricemia is present

3. Infection

1. Prophylactic antibiotics.
2. Pneumococcal and influenza immunizations

4. Skeletal Lesions

1. Bisphosphonates for those with osteopenia or lytic bone lesions
2. Local XRT for bone pain, spinal cord compression
3. Kyphoplasty for vertebral fractures to improve pain relief and regain height

5. Miscellaneous Complications

1. Erythropoietin for anemia, DVT prophylaxis.



B- Autologous stem cell transplant if <65 yr old

Usually preceded by 4-6 months of cytoreductive therapy:
Steroid based with novel agents
(i.e. immunomodulatory drugs or proteasome inhibitors)

C- Allogeneic Bone Marrow Transplantation

D- Chemotherapy if >65 yr old or transplant-ineligible

- **Melphalan, prednisone, cyclophosphamide and proteasome inhibitor**
- **Recently Approved Drugs (2013-2015)**
 - ☐ **Carfilzomib**
 - ☐ **Daratumumab**
 - ☐ **Elotuzumab**
 - ☐ **Panobinostat**
 - ☐ **Ixazomib**
 - ☐ **Pomalidomide**
- **Future Drugs.....**

E- Radiation Therapy



Lymphoplasmacytic Lymphoma (Waldenstrom's Macroglobulinemia)

Definition

- Proliferation of **lymphoplasmacytoid** cells
- Presence of **monoclonal IgM** paraprotein

Clinical Features

- **Elderly patients**; median age 64 yr
- Symptoms: weakness, fatigue, bleeding weight loss, recurrent infections,
(**triad of anemia, hyperviscosity, plasma volume expansion**),
peripheral neuropathy, cerebral dysfunction
- Signs: pallor, **splenomegaly, hepatomegaly, lymphadenopathy**, retinal lesions
- key complication to avoid: **hyperviscosity syndrome**
 - because **IgM** (unlike IgG) confined largely to intravascular space





Lymphoplasmacytic Lymphoma (Waldenstrom's Macroglobulinemia)

Investigations and Diagnosis

- Bone marrow shows **plasmacytoid lymphocytes**
- **Bone lesions** usually **not** present
- Blood work **rarely** see **hypercalcemia**
- Cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia
- Normocytic anemia, rouleaux, high ESR if hyperviscosity not present
- Immunofixation **IgM**

Treatment

- Bendamustine – R/R-CVP chemotherapy, alkylating agents (chlorambucil), nucleoside analogues (fudarabine), rituximab, or combination therapy
- Corticosteroids
- Plasmapheresis for hyperviscosity: acute reduction in serum IgM





Amyloidosis

Accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system:

- **Cardiac infiltration** – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death;
- **GI involvement** – malabsorption, beefy large or laterally scalloped tongue;
- **Neurologic involvement** – orthostatic hypotension, carpal tunnel syndrome
- **Factor X deficiency-** fibrils bind Factor X → bleeding (raccoon eyes)





List of references & Recommended books

Essential Books:

- Goldman-Cecil Medicine, 26 th Edition, 2019.
- Kumar and Clark's Clinical Medicine, 10 th Edition, 2020.



Recommended Books:

- Davidson's Principles and Practice of Medicine. 23rd Edition, 2018

Periodicals and Web Sites of Medicine



**THANK
YOU
FOR YOUR
LISTENING**