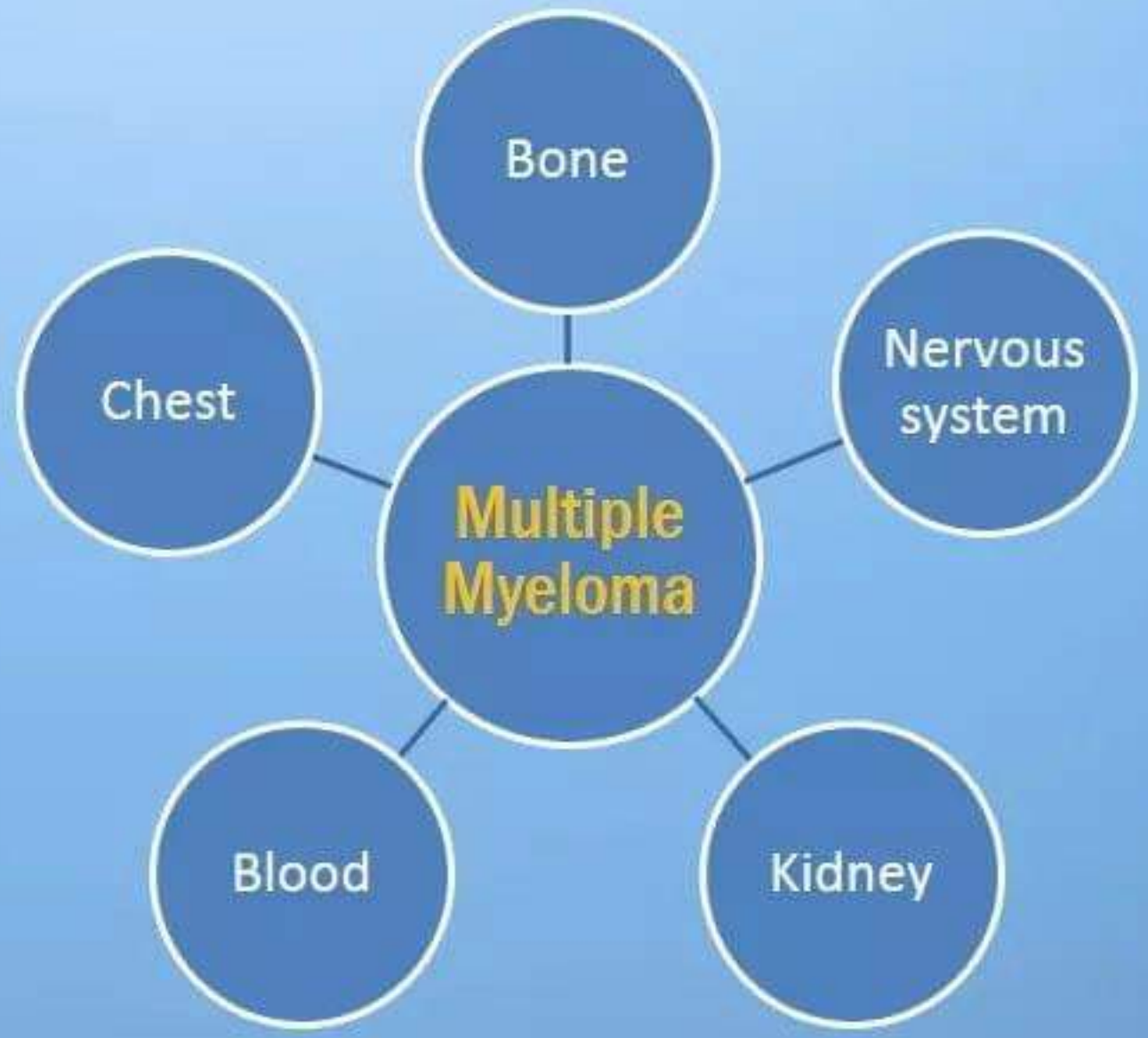
MULTIPLE MYELOMA

- Characterised by a malignant proliferation of plasma cells derived from a single clone
- Most common primary malignancy of bone (~40%)
- Also known as

  -Plasmocytoma

  -Monoclonal gammopathy



Incidence

- Age group – more common in 4^{th} to 6^{th} decade
- Male:Female →2:1
- More in african-americans than caucasians
- Risk factors – radiation
  - exposure to petroleum products
  - 14q. t(4,14), t(14,16), del13

Clinical features

- Early stages → Silent
- Bone pain
- Pathological fractures
- Symptoms of anaemia
- Renal failure
- Recurrent infections
- Hyperviscosity
- Neurological involvement

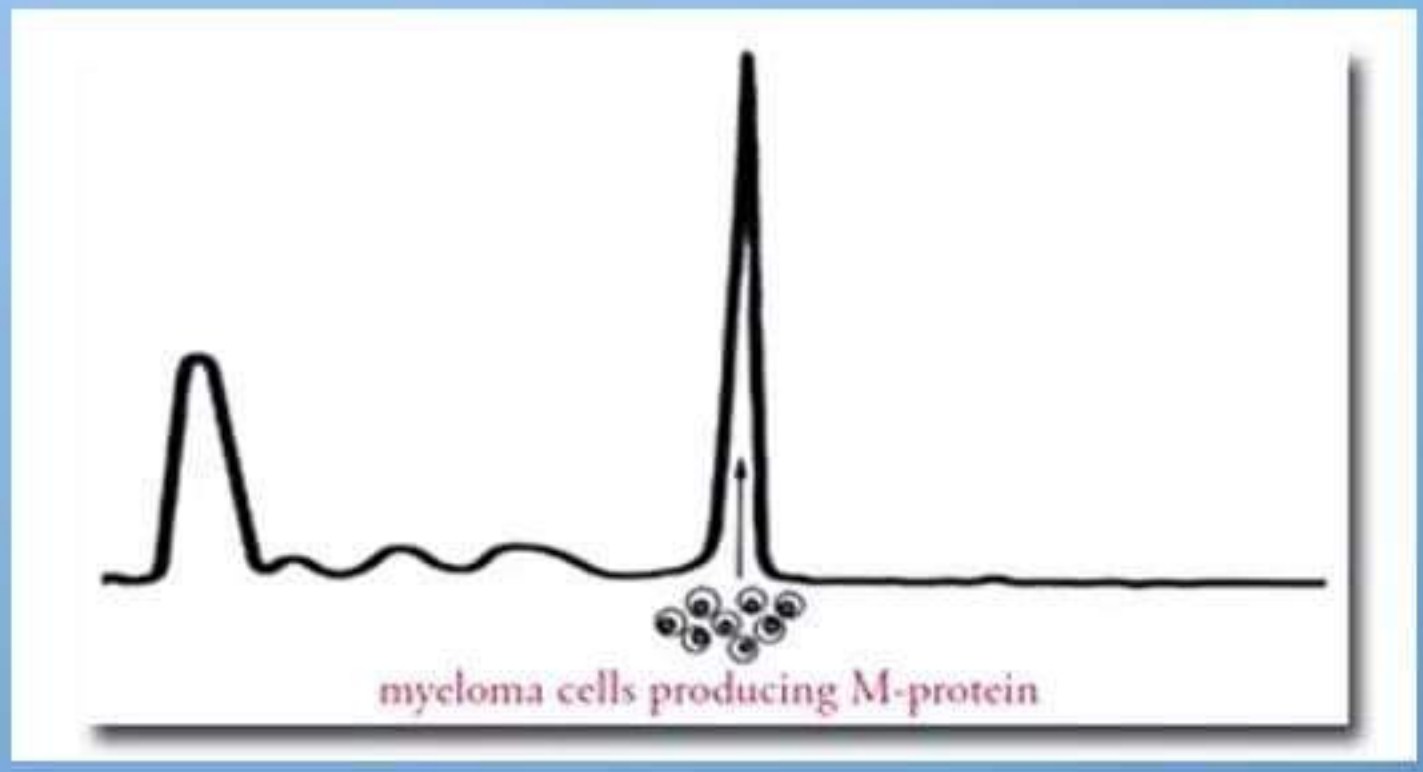
Lab findings

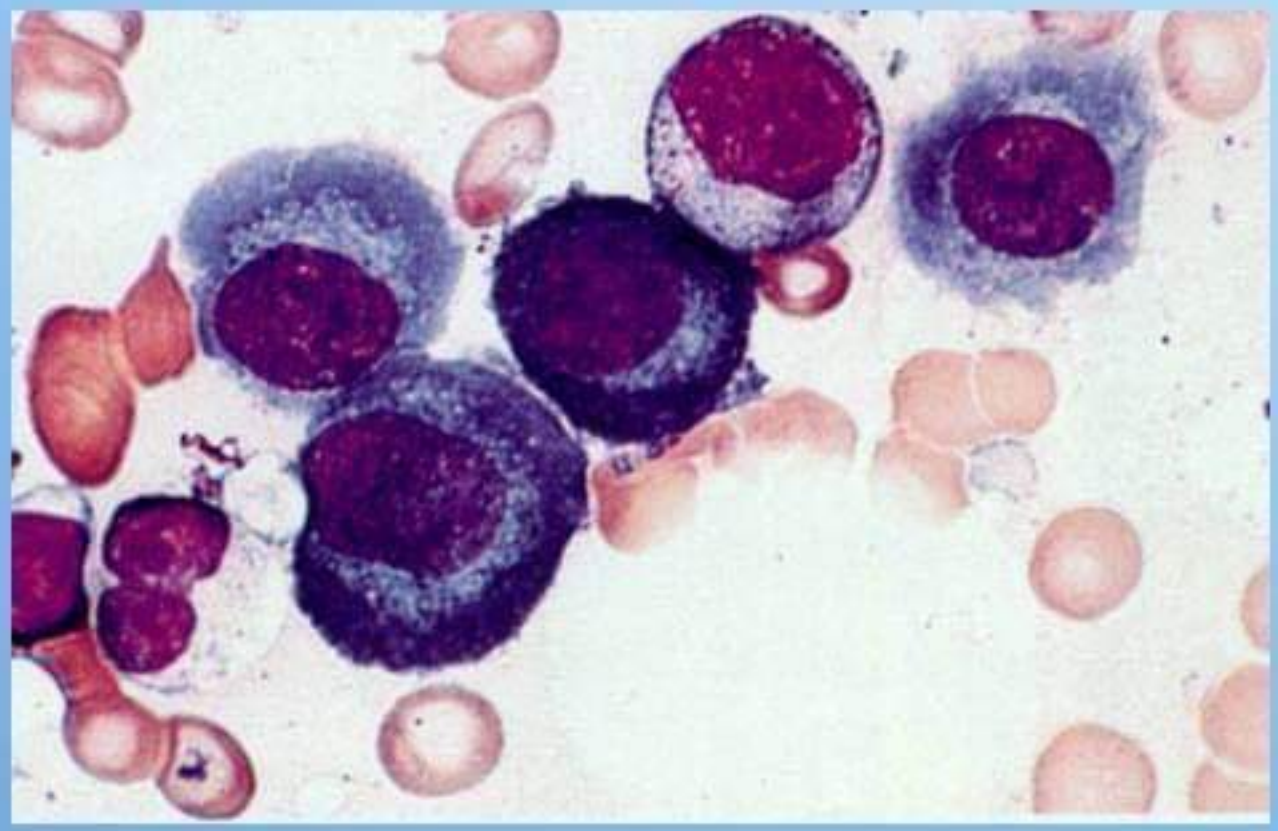
- Anemia, leukopenia, thrombocytopenia
- ⇩ALb, reversed A:G ratio
- ⇧serum creat, uric acid, urea
- Abnormal coagulation
- ⇧Serum Ca
- Proteinuria and cast
- ⇧ESR
- LOW NORMAL ALKALINE PHOSPHATASE
- Red cells show rouleaux formation
- BENCE-JONES PROTEIN in urine in 30%

Lab findings

- **Serum electrophoresis- screening method for detection of Pl. cell disorders.**
- **It reveals monoclonal component (narrow band peak: “church spike”)**
- **found in 98% of patients, in serum, urine or both**

“M” spike or church spike on electrophoresis





***Microscopic appearance –** -

eccentric nucleus with nucleolus

Sparse chromatin in spoke-of-wheel fashion

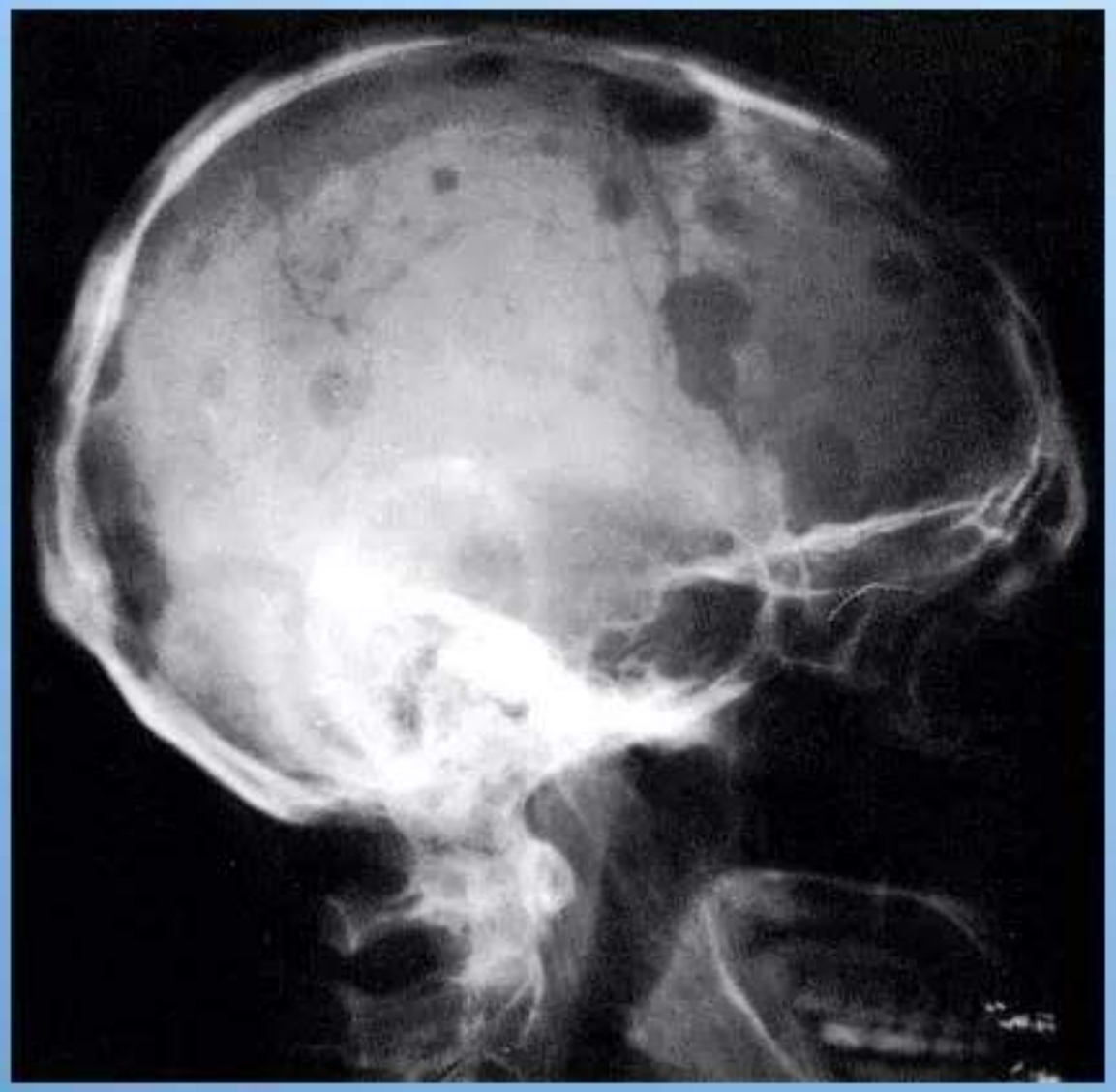
Eosinophilic cytoplasm

No perinuclear halo & does not take PMB stain well

No supporting stroma

Invading vessels seen

Radiology



Multiple, punched-out, sharply demarceted, purely lytic lesion without surrounding reactive sclerosis

Diagnosis

- **I Plasmacytoma on tissue biopsy**
- **II = Bone marrow with greater than 30% plasma cells**
- **III = Monoclonal globulin spike on serum protein electrophoresis, with an immunoglobulin (Ig) G peak of greater than 35 g/L or an IgA peak of greater than 20 g/L, or urine protein electrophoresis (in the presence of amyloidosis) result of greater than 1 g/24 h**

- **a = Bone marrow with 10-30% plasma cells**
- **b = Monoclonal globulin spike present but less than category III**
- **c = Lytic bone lesions**
- **d =Depressed normal Igs**

  The diagnosis of MM requires at least 1 major and 1 minor criterion or at least 3 minor criteria including both a and b

Differential diagnosis

- Other PI cell disorders- MGUS (monoclonal gammopathy of uncertain significance), Waldenstrom`s disease
- Bone metastasis –breast, prostatic Ca
- Hyperparathyroidism
- Other reasons for renal failure-ex. chronic glomerulo-nephritis

Diagnostic features of active or symptomatic myeloma

Organ damage classified as "CRAB"

- **C – calcium elevation (>10 mg/L)**
- **R – renal dysfunction (creatinine >2 mg/dL)**
- **A – anemia (hemoglobin <10 g/dL or ≥2 g/dL decrease from patient's normal)**
- **B – bone disease (lytic lesions or osteoporosis)**

*ONE OR MORE required for diagnosis of SYMPTOMATIC MYELOMA.

Other less common features can also be criteria for an individual patient, including:

- Recurrent severe infections
- Neuropathy linked to myeloma
- Amyloidosis or M-component deposition
- Other unique features

classification

Durie and Salmon Staging System

- **STAGE I (low cell mass) 600 billion myeloma cells***

  All of the following:

  • Hemoglobin value >10 g/dL

  • Serum calcium value normal or <10.5 mg/dL

  • Bone X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only

  • Low M-component production rates

  IgG value <5.0 g/dL

  IgA value <3.0 g/dL

  Urine light chain M-component on electrophoresis <4 g/24h

- **STAGE II (intermediate cell mass) 600 to 1,200 billion myeloma cells***

  Fitting neither stage I nor stage III

STAGE III (high cell mass) >1,200 billion myeloma cells*

One or more of the following:

• Hemoglobin value <8.5 g/dL

• Serum calcium value >12 mg/dL

• Advanced lytic bone lesions (scale 3)

• High M-component production rates

IgG value >7.0 g/dL

IgA value >5.0 g/dL

Urine light chain M-component on electrophoresis >12 g/24h

SUBCLASSIFICATION (either A or B)

• A: relatively normal renal function (serum creatinine value) <2.0 mg/dL

• B: abnormal renal function (serum creatinine value) >2.0 mg/dL

International staging system (ISS)

		SURVIVAL
STAGE 1	β2M <3.5	62 MONTHS
	ALB ≥3.5	
STAGE 2	β2M <3.5	
	ALB <3.5 or	44 MONTHS
	β2M 3.5 – 5.5	
STAGE3	β2M >5.5	29 MONTHS

β2M = Serum β2 microglobulin in mg/L
ALB = Serum albumin in g/dL

MANAGEMENT

1. Chemotherapy
2. High-dose chemotherapy with hematopoietic stem cell transplant
3. Radiation
4. Maintenance therapy
5. Supportive care
6. Management of drug-resistant or refractory disease
7. New and emerging treatments

In asymptomatic myeloma or MGUS

Supportive treatment including

- Erythropoietin
- Pain medication
- Bisphosphonates
- Growth factors
- Antibiotics
- Brace/corset
- Exercise

Systemic anti-myeloma treatment

- Palliative treatment in wide-spread disease with eventual fatal outcome
- Melphalan – with prednisone

  - has stem cell toxicity

➢ If stem cell transplantation is NOT planned –

✓ Melphalan/prednisone/thalidomide (MPT)

✓ Bortezomib/melphalan/prednisone (VMP)

✓ Thalidomide/dexamethasone(thaldex)

✓ levalidomide/low dose dexa (Revlodex)

- ➢ If stem cell harvest is planned
- ✓ Bortezomib/thalidomide/dexamethasone (VTD)
- ✓ VCD -VELCADE/Cyclophosphamide/Dexa
- ✓ VRD - VELCADE/Revlimid/Dexa
- ➢ Induction Therapy Recommendations for Transplant Candidates –
  - Thal/Dex (TD)
  - VELCADE/Dex (VD)
  - VELCADE/Thalidomide/Dex (VTD)
  - Revlimid/Low-Dose Dex (RevloDex)

HIGH-DOSE THERAPY (HDT) WITH AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)

- Front line treatment
- Improved response and survival
- ‘functional cure’ i.e. remission for ≥ 4 years
- Tandem transplantation under clinical trial
- Allogeneic transplantation not recommended

Radiation

- Myeloma is radiosensitive
- Eventually looses its susceptibility
- Relieves pain
- Can be used for control of local disease
- Total body irradiation not advised

Surgical options

- Compression of intraspinal nerves – laminectomy, removal of myelomatous tissue and post-op irradiation
- In cases with instability → spinal fusion
- Intramedullary fixation seldom posible as soft bone retains metal badly

Maintenance therapy

- **Alpha Interferon**
- **Prednisone**
- **Melphalan**
- **Velcade**
- **Revlimid**
- **Dexamethasone**

Supportive therapy

- Erythropoetin
- Biphosphonates
- Antibiotics and GM-CSF
- Anti-virals esp. herpes

Newer drugs

- Pomalidomide
- Next-generation proteasome inhibitors-carfilzomib, NPI-0052
- Doxil-pegylated liposomal doxorubicin
- Histone deacetylase (HDAC) inhibitors-vorinostat, panobinostat
- Monoclonal antibodies-elotuzumab

Thank You