MALIGNANT TUMOR OF MARROW

MULTIPLE MYELOMA

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Classification

Predominant tissue	Benign	Malignant
Bone forming	Osteoma Osteoid osteoma and osteoblastoma	Osteosarcoma -central -peripheral -parosteal
Cartilage forming	Chondroma Osteochondroma Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma -Juxtacortical chondrosarcoma -Mesenchymal chondrosarcoma -Dedifferentiated chondrosarcoma -Clear cell chondrosarcoma -Malignant chondroblastoma
Marrow tumors		-Ewing sarcoma -Primitive neuroectodermal tumor of bone (PNET) -Malignant lymphoma of bone -Myeloma

MARROW TUMORS

[MM]

Ewing Sarcoma

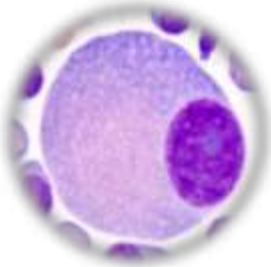
INDIAN INCIDENCE
0.3/ 100000

Multiple Myeloma

INDIAN INCIDENCE
1/ 100000

A 66-year-old woman with polyuria and fatigue has had two bouts of pneumococcal pneumonia during the past year. A pathologic femoral fracture prompts a workup that reveals multiple bony lytic lesions, an elevated creatinine level, and nephrotic-range proteinuria. Her bone marrow biopsy

Calcium slightly elevated and ALP is normal



DIAGNOSIS ??

What is the cause of Proteinuria?

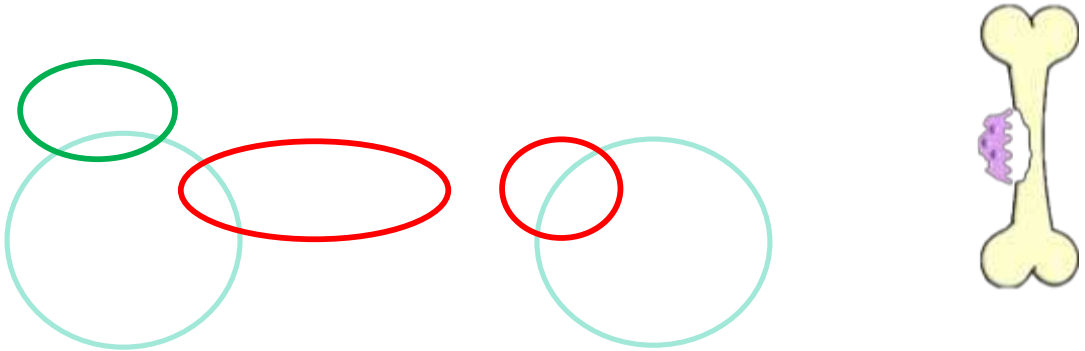
What is the cause of pathological fracture?

What is the reason behind generalized bony pains/ fatigue?

Why Alkaline phosphatase levels are normal despite bone destruction?

Will Bisphosphonates be of use in this case? Regime?

Any monoclonal antibody available for Myeloma treatment?



MULTIPLE MYELOMA [KAHLER'S DISEASE]

- Multiple myeloma is the most common PRIMARY malignancy of the bone <*commonest bone tumour is METASTASIS*>
- It is diagnosed in adults over 40 years of age (median age at diagnosis is 65 years).
- It is nearly twice as common in males as in females.
- Although in about 5% cases, it may present as an isolated bony lesion termed as solitary plasmacytoma, most commonly its a multisystem involvement that this plasma cell dyscrasia presents with.

Plasma cell dyscrasias comprise a group of disorders characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow, which then produces excess of monoclonal immunoglobulins leading to a constellation of clinical signs and symptoms.

MGUS *[Monoclonal gammopathy of undeterminate significance]*

Serum monoclonal proteins < 30 g/L

Bone marrow plasma cells < 10 %

No end organ damage feature **(CRAB)**

- **hyperCalcemia**
- **Renal insufficiency**
- **Anemia**
- **Bone lesions**

Smoldering MM

Concealed state

Serum monoclonal proteins > 30 g/L

and/or

Bone marrow plasma cells > 10 %
But < 60%

No CRAB features

Normal BM plasma cells

2%

Smoldering MM

Solitary plasmacytoma

Solitary biopsy proven bone lesion

Rest Skeletal survey normal

No CRAB features

PLUS

Bone marrow plasma cells 10-60 %

MULTIPLE MYELOMA

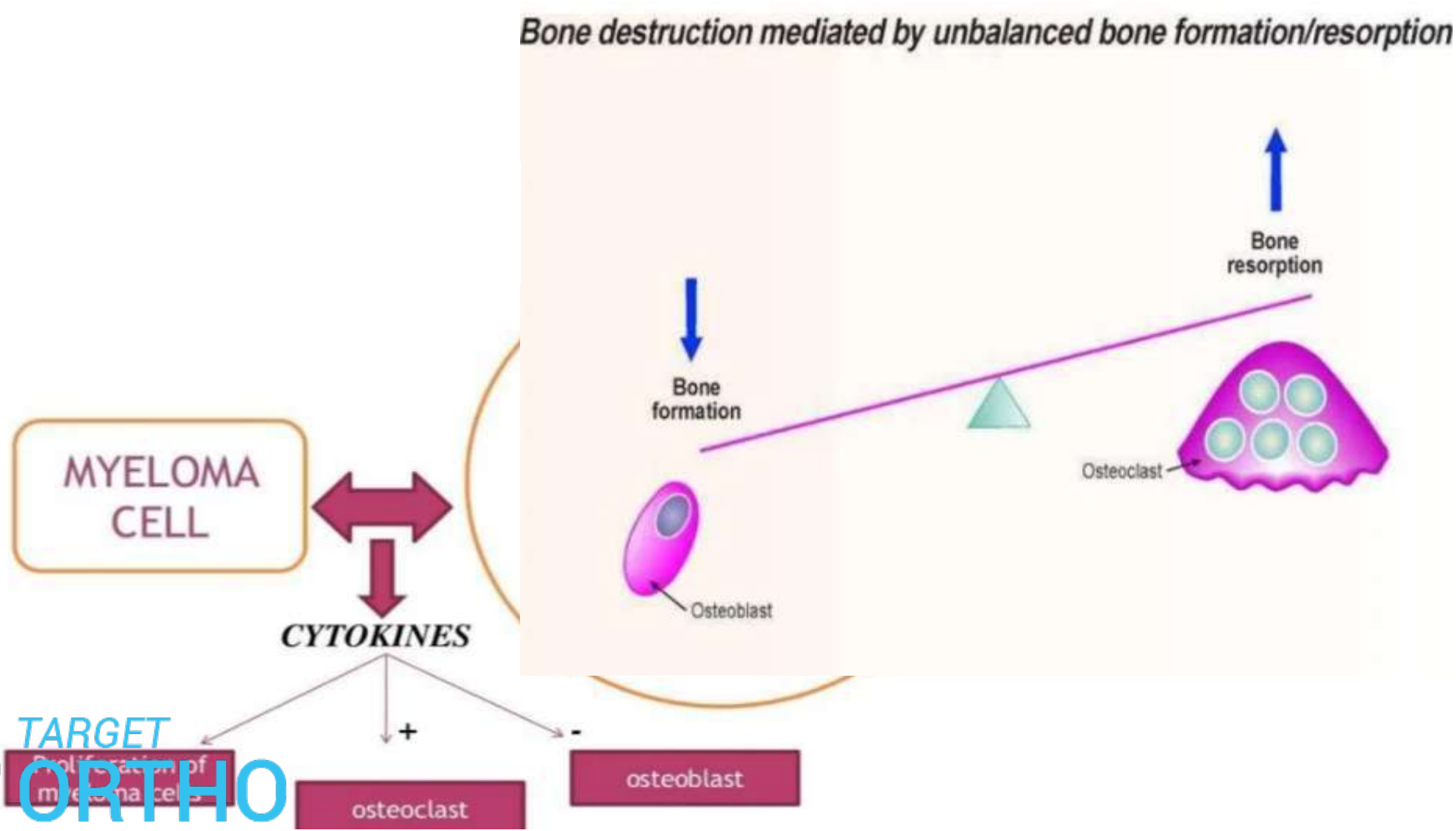
Bone marrow plasma cells > 60 %

OR

Serum monoclonal proteins > 30 g/L

Bone marrow plasma cells 10-60 %

PLUS ≥1 End organ damage feature (CRAB)

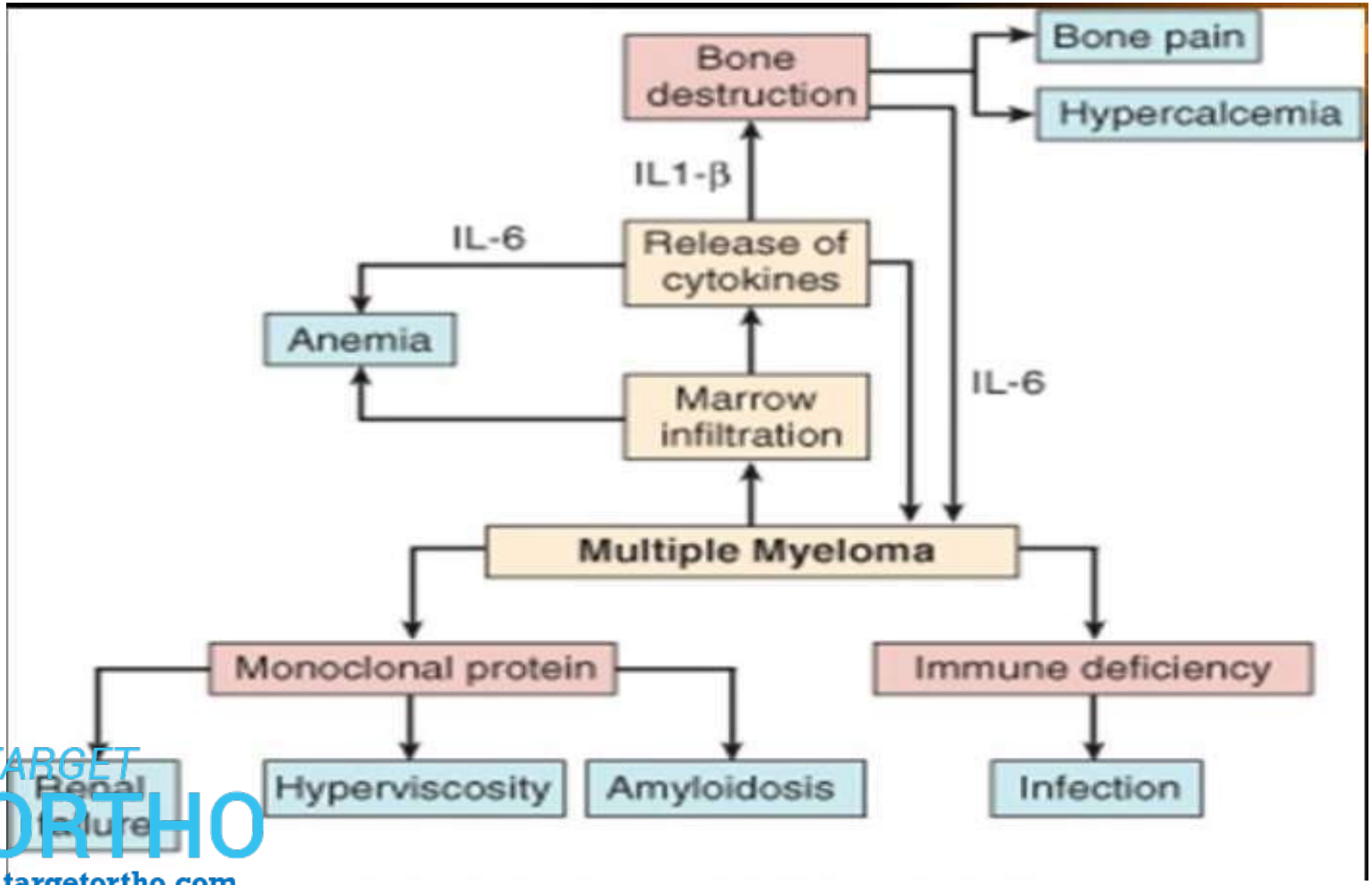


GENETICS

- Hyperdiploidy, 13q14 deletions, translocations t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16), 1q amplification or 1p deletion, and 17p13 deletions
- *N-ras, K-ras*, and *B-raf* mutations are most common

CLINICAL PRESENTATION

Common features	Uncommon features
Anemia	Hyperviscosity syndrome
Bone pain	Paresthesias
Elevated creatinine	Hepatomegaly - splenomegaly
Fatigue/generalized weakness	Spinal cord compression from an extramedullary plasmacytoma - Medical emergency
Hypercalcemia	Lymphadenopathy
Weight loss	Pleural effusion
Infection	



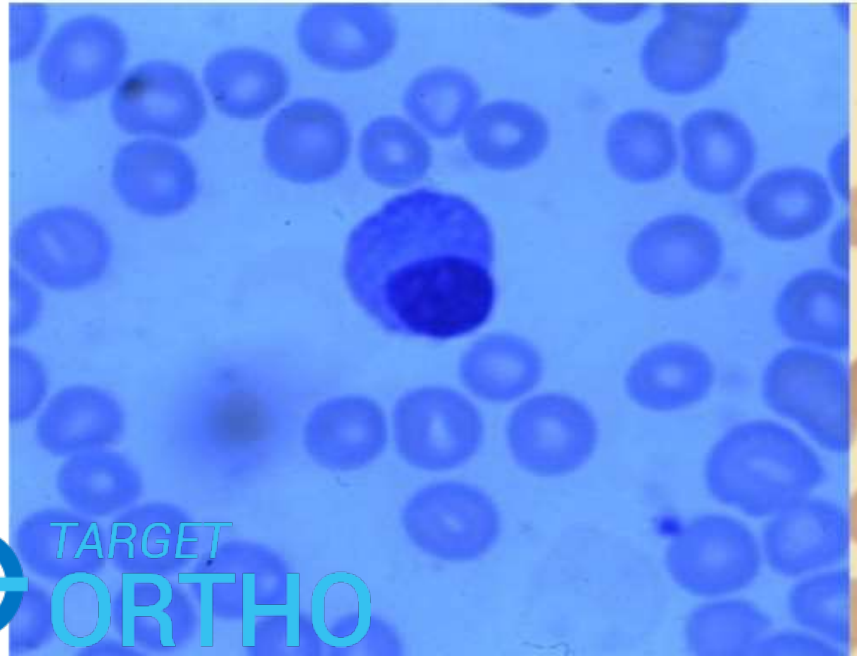
INVESTIGATIONS

- Haemogram- Anemia, Leukopenia, Thrombocytopenia, Raised ESR(often>100)
  - values correlate **neither with tumor burden nor with treatment response.** Hence its importance is uncertain.

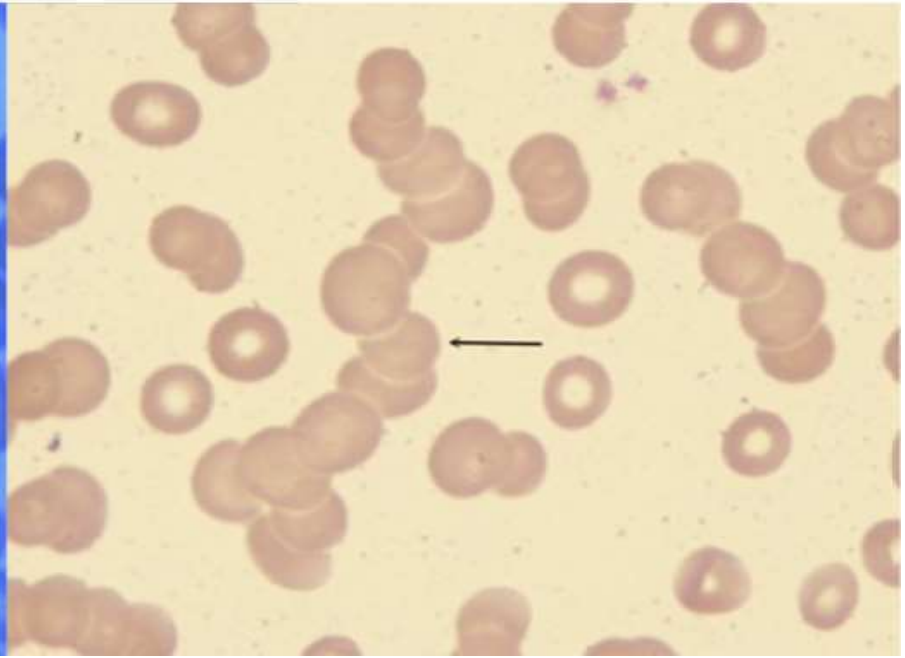
- **Peripheral smear**
  - Rouleaux formation
  - Pancytopenia
  - Monoclonal plasma cells can be seen
    - > 2000/mm^3 **S/O Plasma cell leukemia**

Peripheral smear

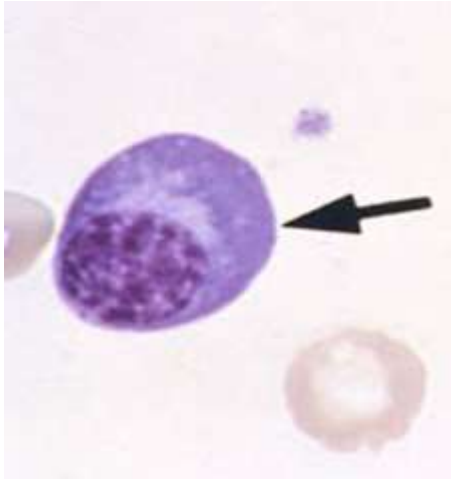
Plasma cells



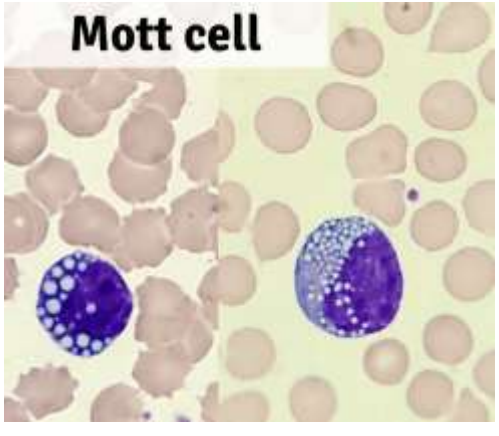
Rouleaux formation



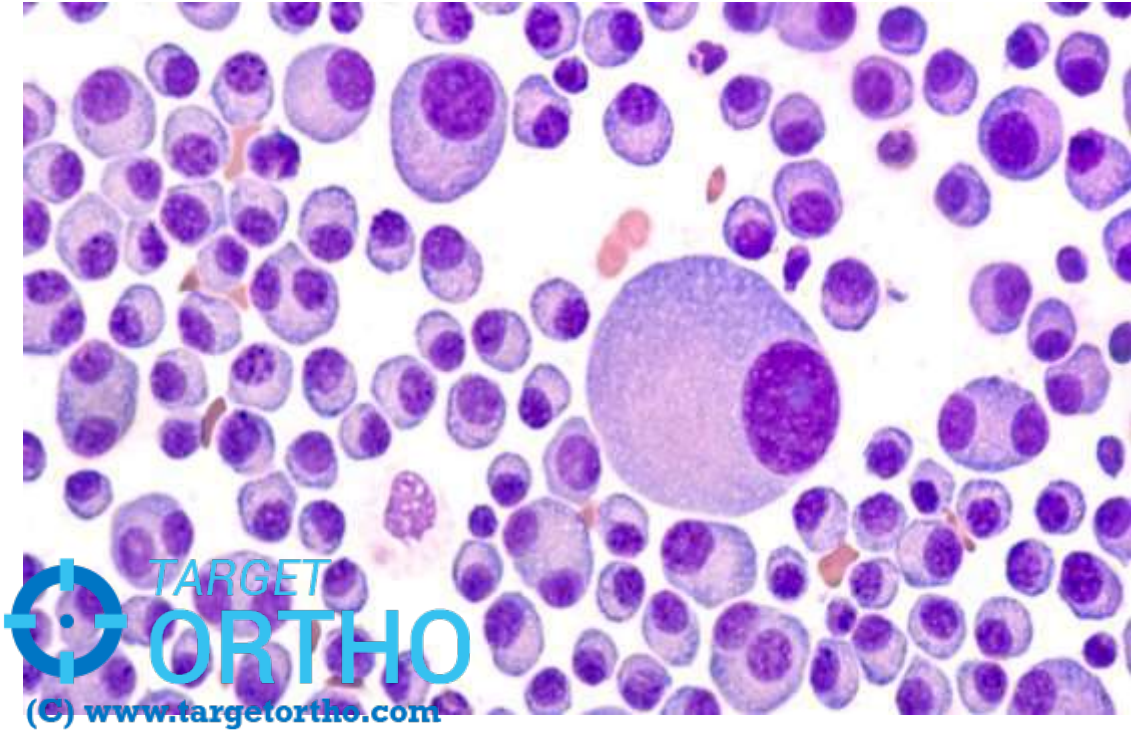
Bone marrow examination

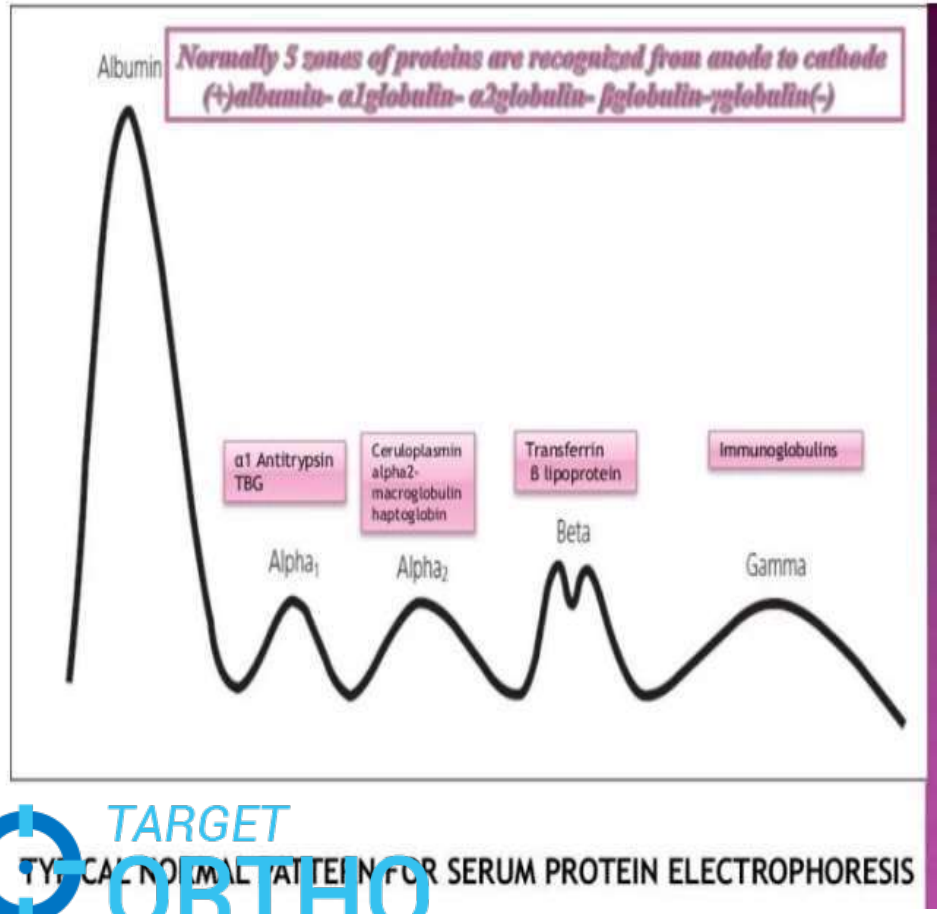


- **Percent monoclonal plasma cells = >10 %**
- **Morphology**
  - Oval with abundant basophilic cytoplasm
  - Nucleus is round and eccentrically located
  - Perinuclear halo
  - "clock-face" or "spoke wheel" chromatin without nucleoli
  - Cytoplasmic immunoglobulin inclusions -Mott cells, Morula cells, Russell bodies

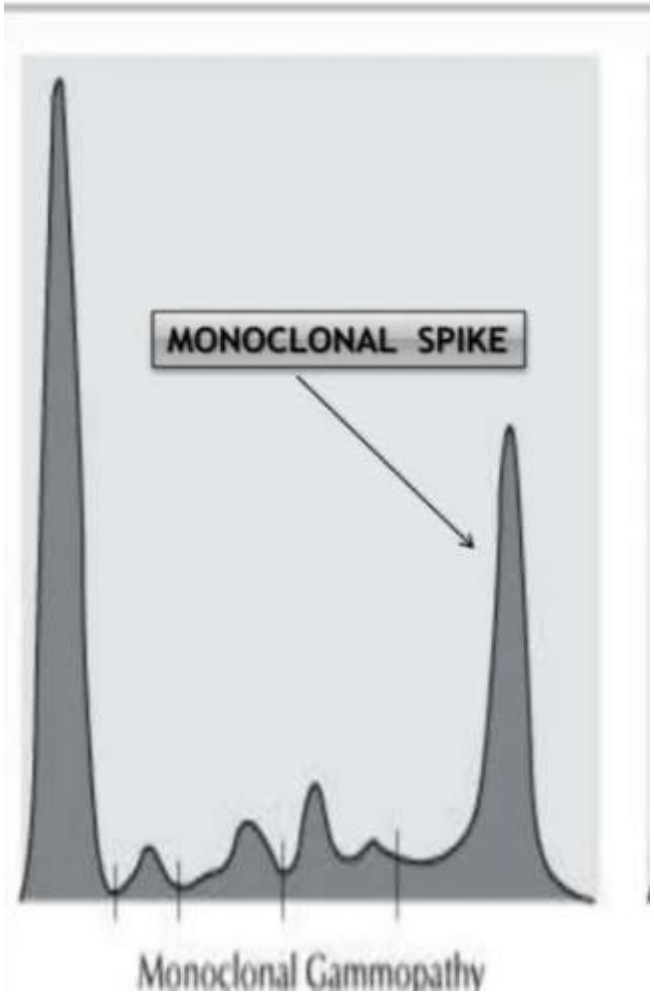


BIOPSY





TYPICAL NORMAL PATTERN FOR SERUM PROTEIN ELECTROPHORESIS



Monoclonal Gammopathy

- **Urinalysis**
  - Protein- near all light chains initially-Bence Jones proteinuria
  - After glomerular involvement
    - non selective proteinuria
    - Albumin
    - Casts
- **KFTs**
  - Elevated urea / creatinine
- Serum calcium- raised
- Serum uric acid- raised
- Serum LDH- raised

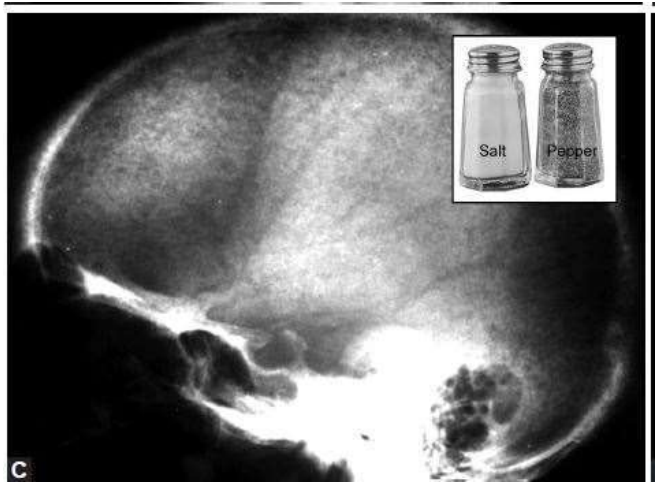
Beta 2 microglobulin

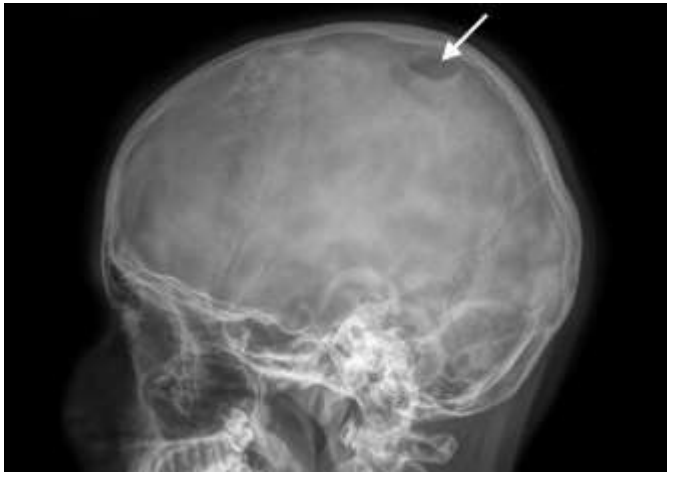
ISS (International Staging System for multiple myeloma)

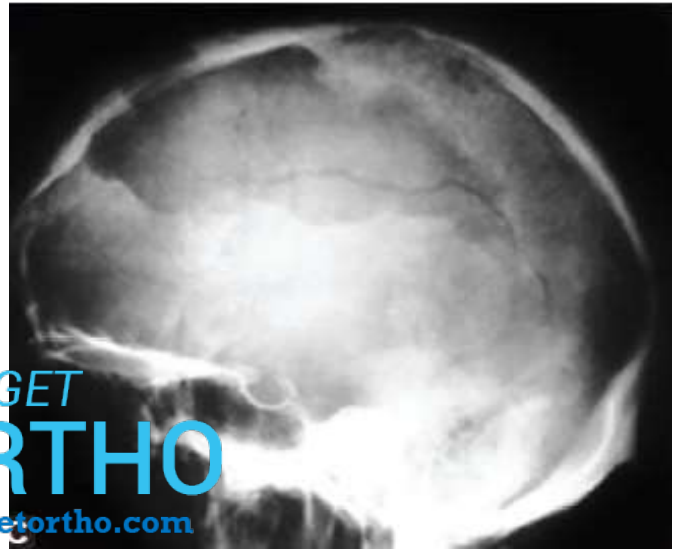
Stage		MOS (months)
I	β2 microglobulin < 3,5 mg/l and albumins > 3,5 g/dl	62
II	No criteria for I and III	44
III	β2 mikroglobulin >5,5 mg/l	29

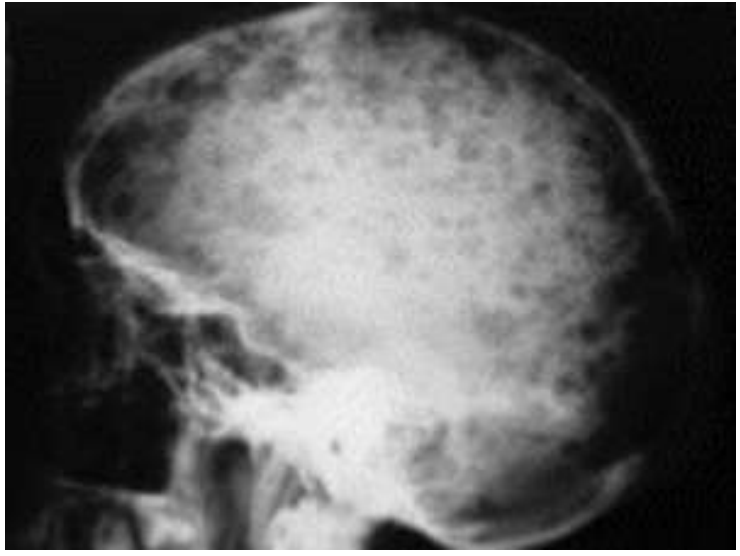
CRAB -- FEATURES

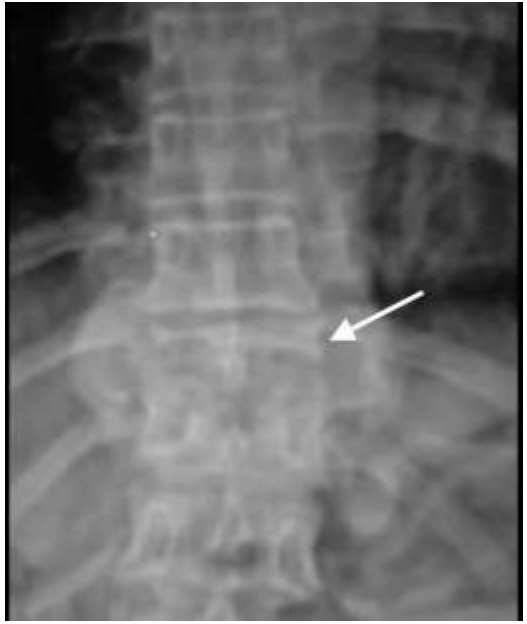
- C (Calcium) (> 2,75 mmol/l)
- R (Renal Insufficiency) creatinine concentration >173 mmol/l (1,96 mg/dl)
- A (Anemia) Hg <10 g/dl
- B (Bone lesions)











LANGERHAN CELL HISTIOCYTOSIS

Ewing sarcoma
Multiple Myeloma <Plasmacytoma>
Lymphoma/ Leukemia
Gaucher's Disease
Aneurysmal bone cyst
Infection- TB (central type)

Management

Smouldering MM: Surveillance

- Bisphosphonates for Osteoporosis <not mandatory though>
- Targeted therapy controversial to slow progression

Solitary plasmacytoma is treated mainly with radiotherapy (external beam radiation therapy) only, with operative stabilization (e.g. Kyphoplasty) employed generally in cases of actual or impending pathological fracture (as per Mirel score).

Management for MM

- Chemotherapy is the mainstay of treatment.
- *Drugs* are mostly used in combination with prednisolone.

- Bisphosphonates are used to decrease bone pain and control hypercalcemia.

  REGIMEN in active myeloma

  Zoledronic acid (slow iv) every 4 weeks x 2 years
  Denozumab (Xgeva): 120 mcg sc in similar manner

- Autologous stem cell transplantation, although not curative (i.e. does not cause remission) improves overall survival by 2–3 years. It is an option in relatively young (<65 years) patients without comorbidities.

Medical Management

- Chemotherapy
- Steroids

} Mainstay

The Newer options

- Targeted therapy: targeting specific genes/ proteins essential to cancer cells' survival
- Immunomodulatory drugs
- Immunotherapy

Chemotherapy

- Drugs include Cyclophosphamide, Doxorubicin, Melphalan (Alkeran, Evomela), Etoposide, Cisplatin, Carmustine (BiCNU), and Bendamustine (Bendeka).

- Melphalan (high dose) is most commonly used and is mostly used in combination with steroids (prednisone/ dexamethsone).

- Side effects: Low counts, Clotting problems, Peripheral neuropathy

Targeted therapy

Drugs against specific genes and proteins that cancer cells are dependant on

Proteasome inhibitors

- Because myeloma cells produce a lot of proteins (IGs) they are particularly vulnerable to this type of drug.
- Bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro) are classified as proteasome inhibitors.
- They target specific enzymes called proteasomes that digest proteins produced by these cells.
- Mainly employed for early stage/ newly diagnosed myeloma.

Targeted therapy

Drugs against specific genes and proteins that cancer cells are dependant on

B-cell maturation antigen (BCMA) targeting agents

- Belantamab mafodotin (Blenrep), an antibody-drug conjugate, is the classical example in this category.
- Belantamab mafodotin uses an antibody to bind to BCMA which is a protein on the surface of myeloma cells. This leads to death of the myeloma cell.
- Its currently approved by the FDA to treat adults with recurrent or refractory multiple myeloma.

Targeted therapy

Drugs against specific genes and proteins that cancer cells are dependant on

Bispecific T-cell engagers

- Bispecific antibodies are monoclonal antibodies that target BCMA. These antibodies can attach to both a T cell (CD3 protein) and a myeloma cell (BCMA) at the same time, activating an immune attack on the cancer cells. Basically by bringing myeloma cells and T cells together, the drug helps the T cell to recognize and destroy the tumor cell.

- Teclistamab (Tecvayli) is the best worked up drug in this category. Presently it is approved for the treatment of recurrent or refractory multiple myeloma.

Targeted therapy

Drugs against specific genes and proteins that cancer cells are dependant on

Monoclonal antibodies

- Monoclonal antibodies bind to myeloma cells and label them for removal by the person's own immune system.
- Elotuzumab (Empliciti), Daratumumab (Darzalex), Isatuximab (Sarclisa) are the available drugs.
- Elotuzumab and Daratumumab are mostly used to treat newly diagnosed multiple myeloma while Isatuximab is approved by the FDA for the treatment of refractory multiple myeloma.
- A drug combination of daratumumab and Pomalidomide (Pomalyst) and Dexamethasone administered by subcutaneous route, has been used quite successfully to treat multiple myeloma.

Immunomodulators

- Thalidomide, lenalidomide (Revlimid), and pomalidomide (Pomalyst) are classified as immunomodulatory drugs, which stimulate the immune system.

- These drugs stimulate immune system against the myeloma cells and also keep new blood vessels from forming and feeding myeloma cells.

- They are mainly are approved to treat newly diagnosed and early staged patients.

Immunotherapy (biological therapy)

- It is designed to boost the body's natural defenses to fight the cancer cells.
- The cellular immunotherapies approved to treat multiple myeloma are Idecabtagene (Abecma) and Ciltacabtagene (Carvykti).
- These are chimeric antigen receptor (CAR) T-cell therapies that target BCMA
- In CAR T-cell therapy, some cells are removed from a patient’s blood. Then, the T cells are changed in a laboratory so they have specific proteins called receptors. These receptors allow the changed T cells to recognize the cancer cells (by binding to BCMA).
- They may be used to treat multiple myeloma that is refractory.

Medical Management

- Chemotherapy
- Steroids

} Mainstay

The Newer options

- Targeted therapy: targeting specific genes/ proteins essential to cancer cells' survival
- Immunomodulatory drugs
- Immunotherapy

Management (Orthopaedic)

- Bisphosphonates/ Denozumab have a role as discussed
- Impending (Mirel score > 8) or actual pathological fractures may require long bone stabilization with intramedullary implants (to splint the entire length of the bone).
- Periarticular fractures are managed with joint replacements or megaprostheses.
- Vertebral fractures are taken up for Kyphoplasty.
- The tumor is radiosensitive so 3 weeks after surgery, radiation is also added to the treatment regimen.

? Queries

MALIGNANT TUMOR OF MARROW

MULTIPLE MYELOMA

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