MULTIPLE MYELOMA

Presented by :

Eman Al-Etawi

Roa’a Alfraijat

Rahaf AlRababha

OBJECTIVES :

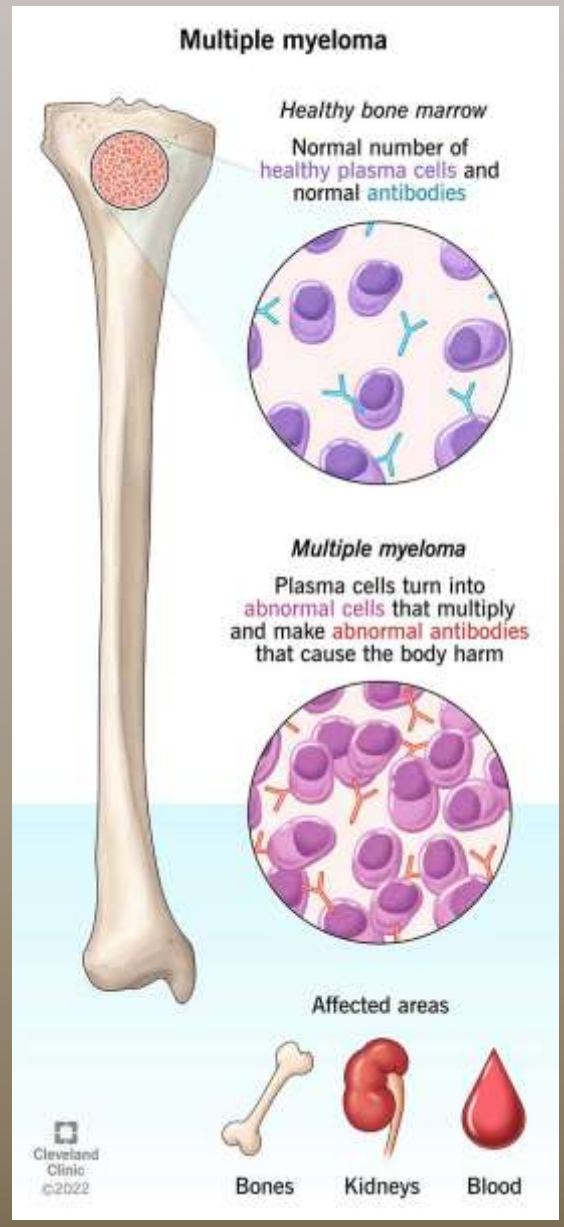
- DEFINITION
- GENETIC MUTATIONS
- MORPHOLOGY
- CLINICAL FEATURES
- LAB FINDINGS & DIAGNOSIS
- MANAGEMENT

INTRODUCTION

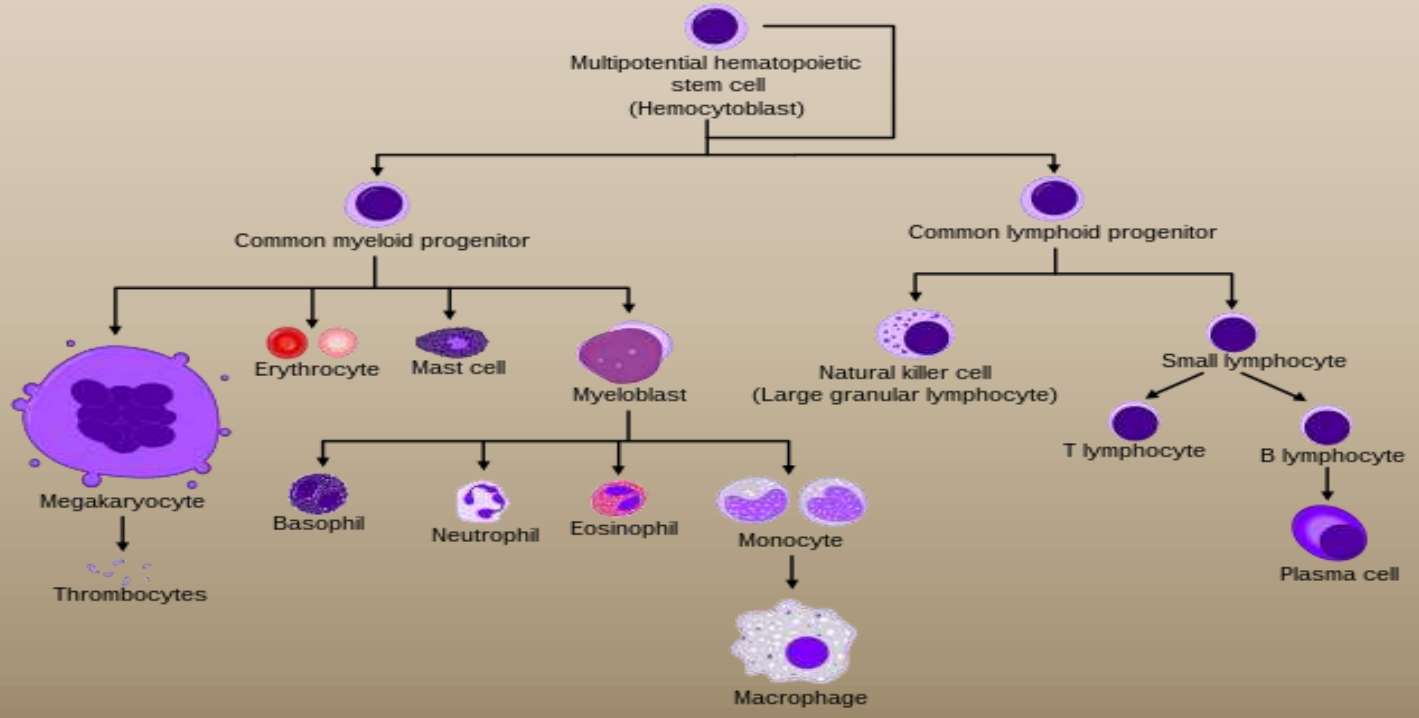
Multiple Myeloma, also known as **Plasma Cell Myeloma**

and **the second most hematological** malignancy,

resulting in **1% of cancer deaths** each year.



- Plasma cell is the activated form of B-cell that produces Immunoglobulin (antibodies) against specific infection and each cell produces Ig against specific antigen **(monoclonal)**
- **Shape: Cartwheel nucleus** & abundant **eosinophilic cytoplasm.**



DEFINITION:

- It’s a bone marrow cancer that is characterized by the neoplastic proliferation of a single plasma cell line that produces monoclonal immunoglobulin, leading to enormous copies of one specific immunoglobulin (usually **IgA** or **IgG** type).
- As the disease process advances, bone marrow elements are replaced by malignant plasma cell, resulting in **anemia**, **leukopenia**, and **thrombocytopenia**.

Normally these immunoglobulins are polyclonal (IgG, IgA,…), but in multiple myeloma plasma cells produce immunoglobulin of a single type of heavy and light chains.

- These neoplastic cells might produce whole immunoglobulins and are called **M Proteins.**
- In some cases, only light chains are produced in excess, which can be **detected in urine** because of their small size which are **Bence Jones proteins.**

TABLE BELOW SHOWS THE FREQUENCY OF DIFFERENT ISOTYPES OF MONOCLONAL PROTEIN IN MYELOMA.

23.58 Classification of multiple myeloma

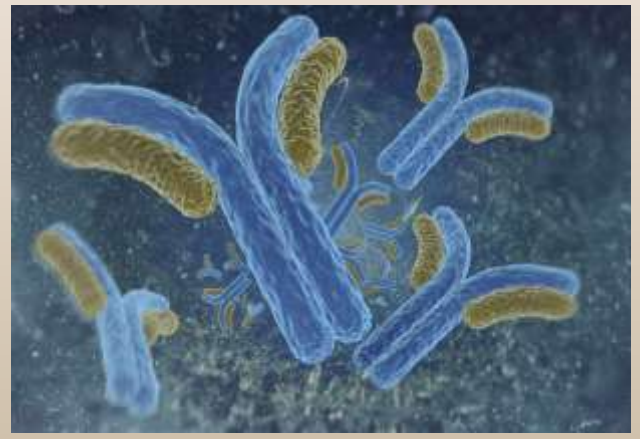
Type of monoclonal (M)-protein	Relative frequency (%)
IgG	55
IgA	21
Light chain only	22
Others (D, E, non-secretory)	2

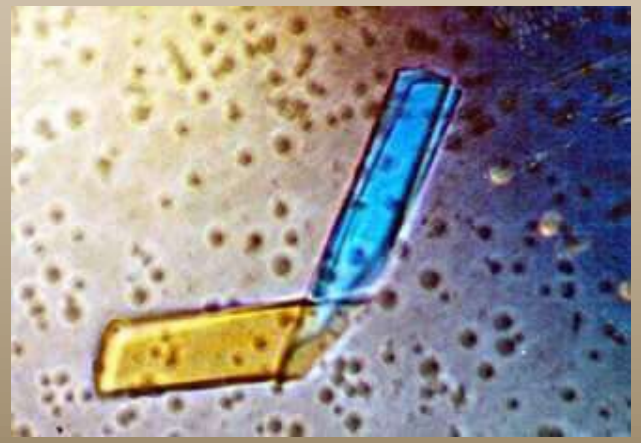
RISK FACTORS / CAUSES

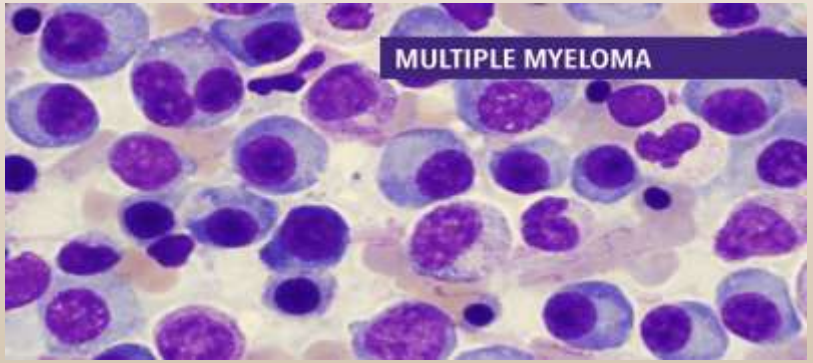
- Sex: ♂ > ♀ (3:2)
- Peak incidence: **50–70** years
- African – American ethnicity
- Obesity and alcohol consumption
- Chemical exposure (as AGENT ORANGE)

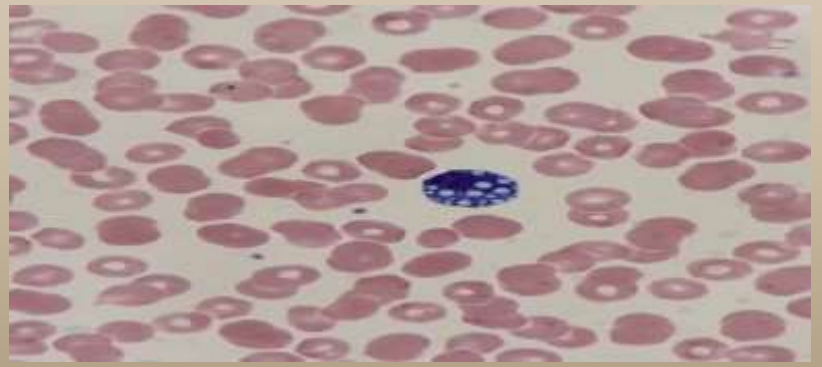
GENETIC MUTATIONS :

• myeloma often has chromosomal translocations that fuse the **IGH locus** on **chromosome 14** to oncogenes such as the **cyclin d1** and **cyclin d3** genes .







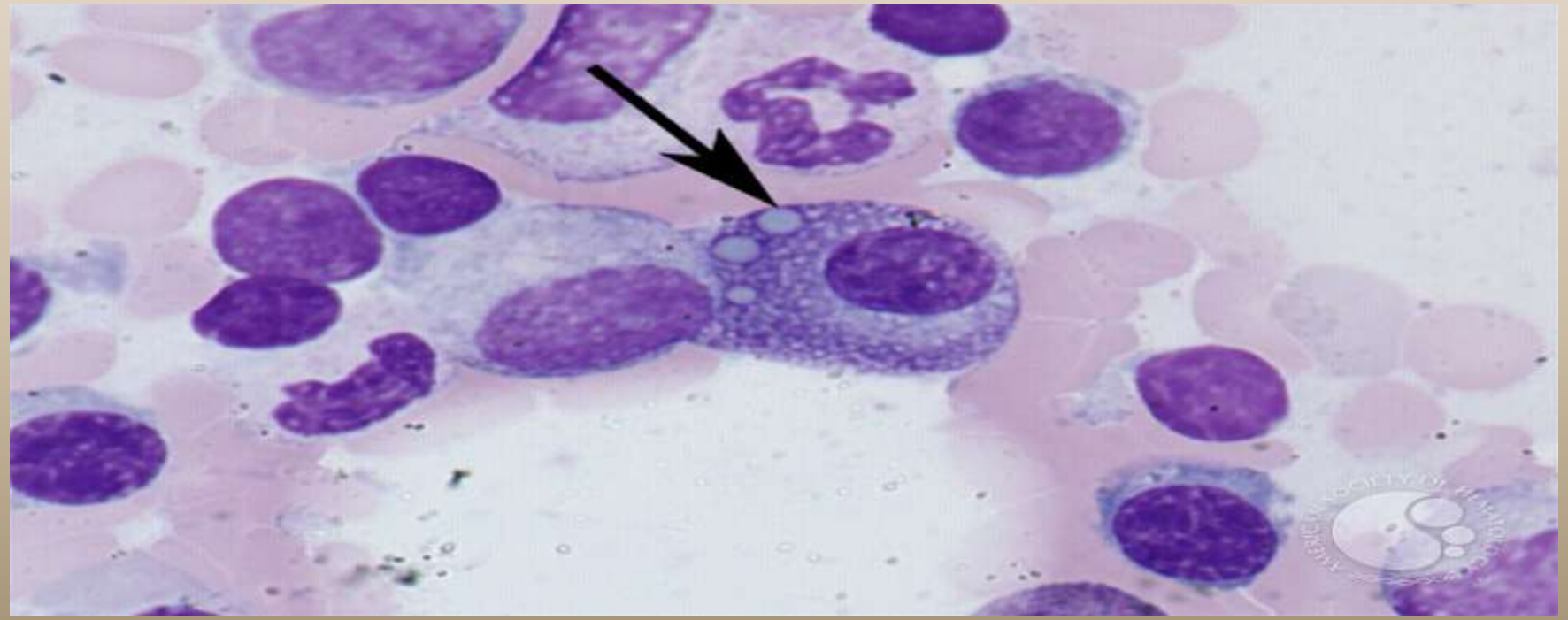


MORPHOLOGY :

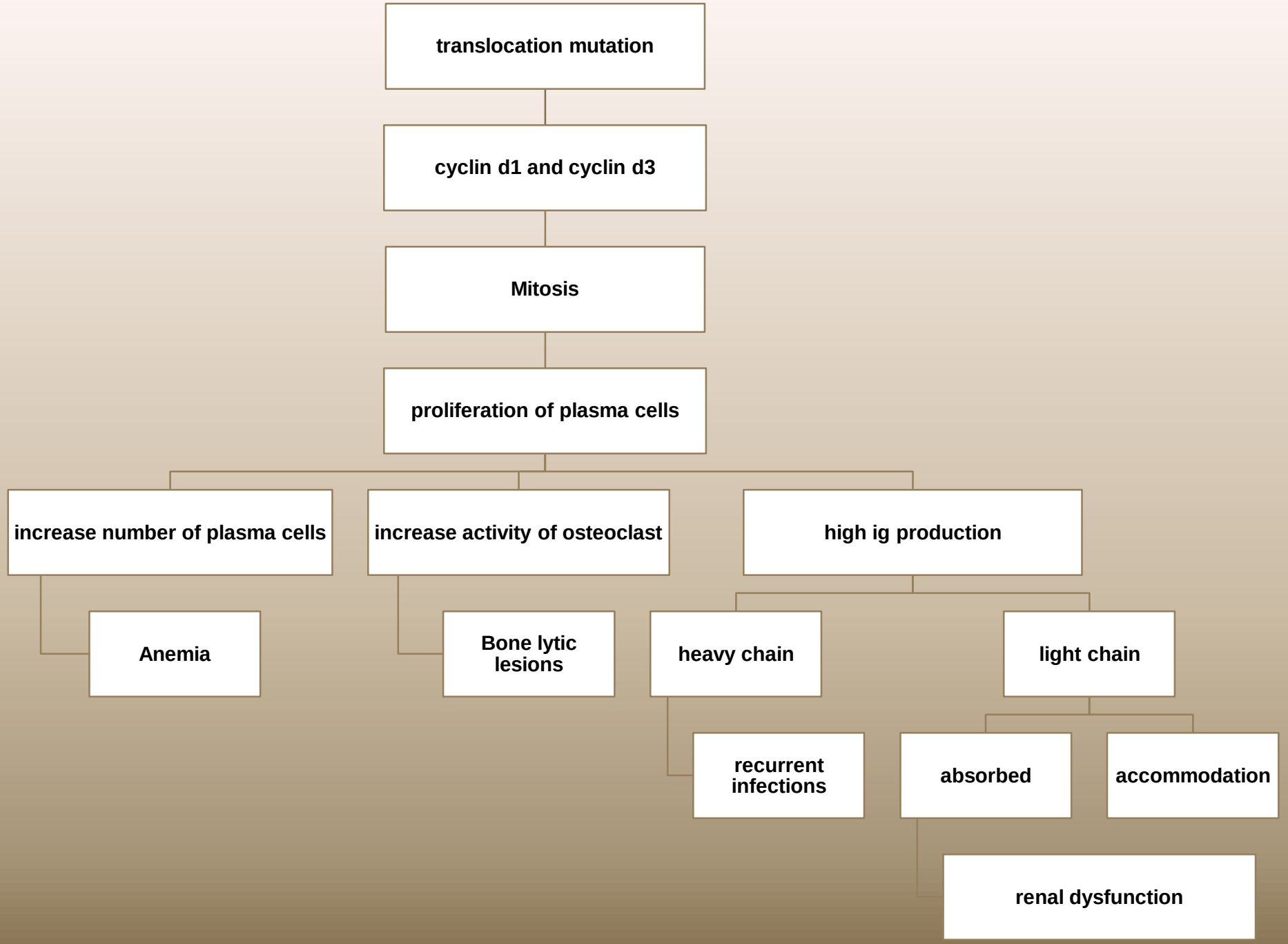
1- By bone aspiration, plasma cells must be increased to **10%** of the cellularity.

2- **Mott cells** are plasma cells that have spherical inclusions packed with Ig in their cytoplasm, Inclusions: **Russell bodies.**

RUSSELL BODIES :

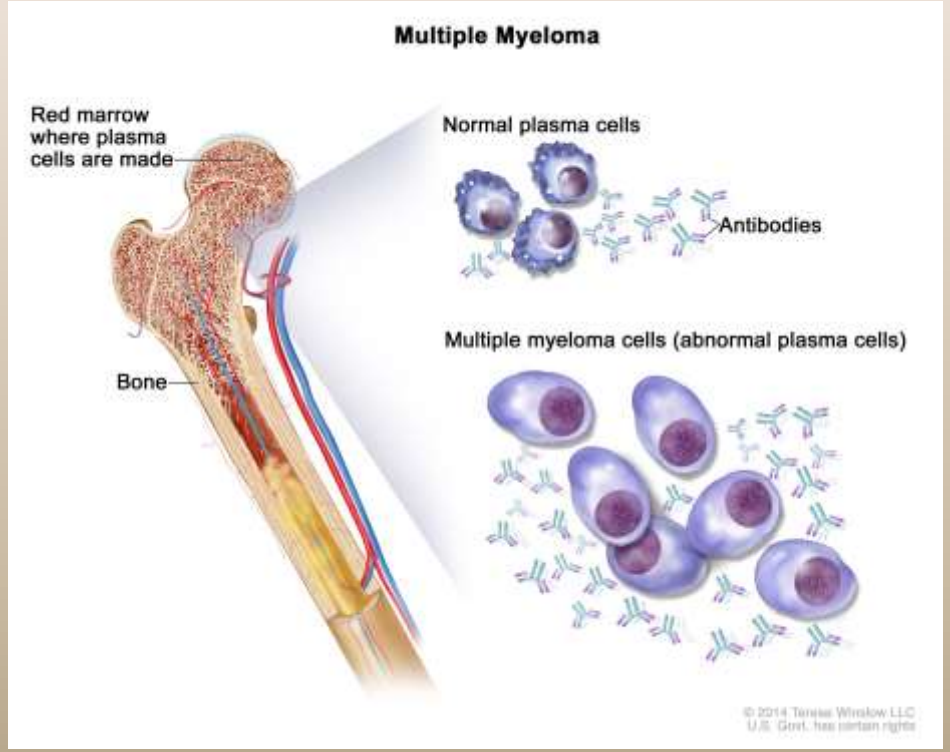


PATHOGENESIS


translocation mutation
cyclin d1 and cyclin d3
Mitosis
proliferation of plasma cells
increase number of plasma cells
increase activity of osteoclast
high ig production
Anemia
Bone lytic lesions
heavy chain
light chain
recurrent infections
absorbed
accommodation
renal dysfunction

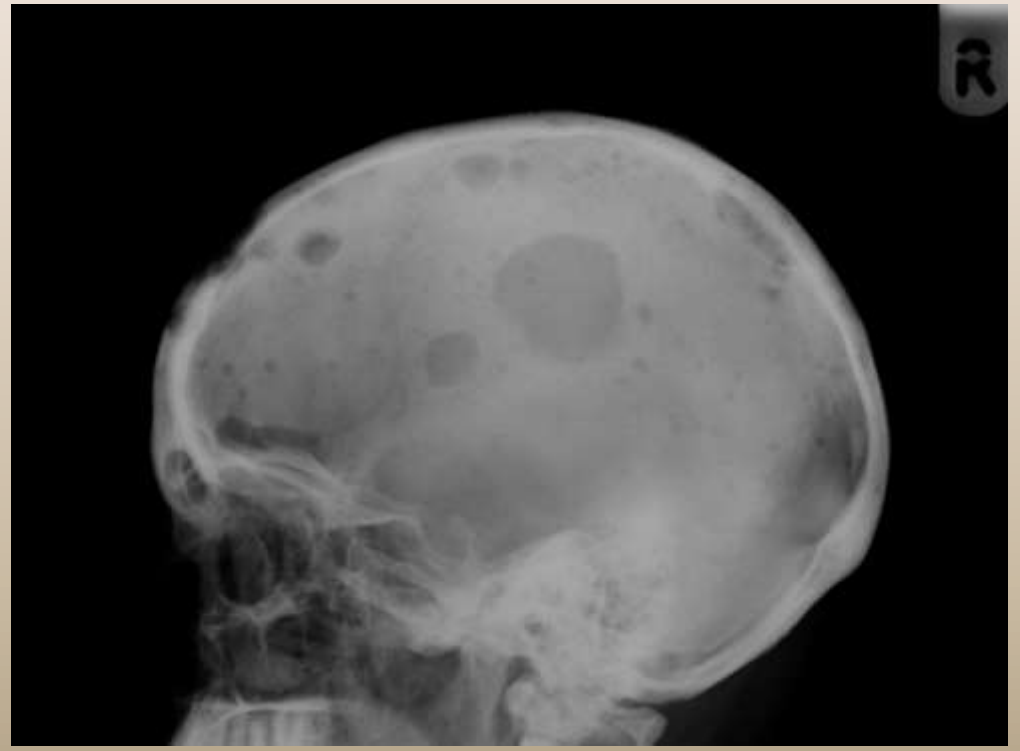
Increase numbers of plasma cells !

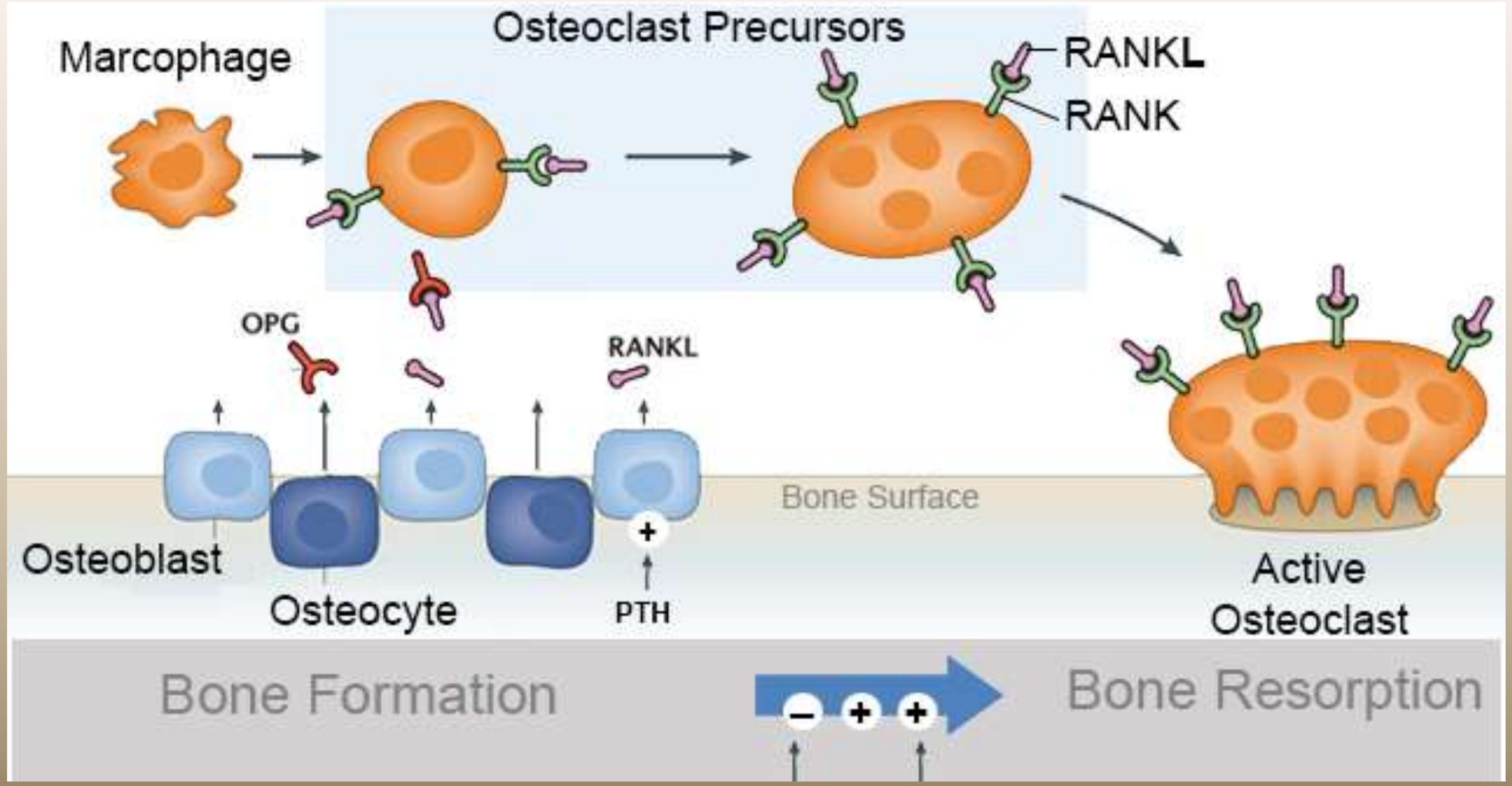
mainly because of the shifting of the myeloid progenitors to the lymphoid progenitors. plasma cells will increase in the bone marrow, leading to a decrease in the number of RBCs, platelets, and WBCs (**pancytopenia**). This will cause **ANAEMIA** and increase in bleeding time .



Increase activity of osteoclast !

The malignant plasma cells produce cytokines, which dysregulate the RANK receptors to bind to RANK. This will activate osteoclasts and inhibit osteoblasts the net result is **bone resorption**, which is called bone lytic lesions that appear as punched-out lesions




Marcophage
Osteoclast Precursors
RANKL
RANK
OPG
RANKL
Osteoblast
Osteocyte
PTH
Bone Surface
Active
Osteoclast
Bone Formation
Bone Resorption

The increasing of the IG production !

1- The light chains will deposit and accumulate as BENCE JONES protein in the renal tubules and obstruct them, and this is called **light chains cast nephropathy** or **myeloma kidney** . **BENCE JONES** proteins may get reabsorbed, causing **amyloidosis**, which also affects the kidneys and participates in its dysfunction

2- the **heavy** chains will reduce the diversity of other types of IGs that work against other antigens leading to **infections**. E.g. : pyelonephritis, pneumonia

CLINICAL FEATURES

1. Bone pain that results from bone lytic lesions (especially in the lower back, chest, and jaw), pathologic fractures, and loss of height secondary to collapse of vertebrae.

As a result of the bone destruction, hypercalcemia is also present approximately in 25% of patients. IT CAN BE ASYMPTOMATIC OR SYMPTOMATIC (EXTREME THIRST, ABDOMINAL PAIN, ANOREXIA, NAUSEA, POLYUREA, CONSTIPATION)

2. Renal failure—due to four reasons

A- myeloma nephrosis (immunoglobulin precipitation in renal tubules)

B- NSAIDs -used for bone pain.

C- hyperuricemia.

D- hypercalcemia (phosphate kidney stones).

cont…

3. Recurrent infections (especially of the lung or urinary tract)—most common cause of death, due to lack of normal immunoglobulins

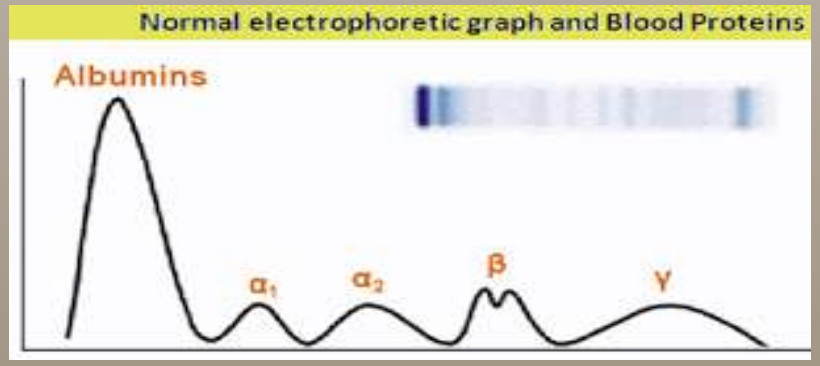
4. Tiredness weakness and shortness of breath caused by **anemia** which present in most patients due to two reasons

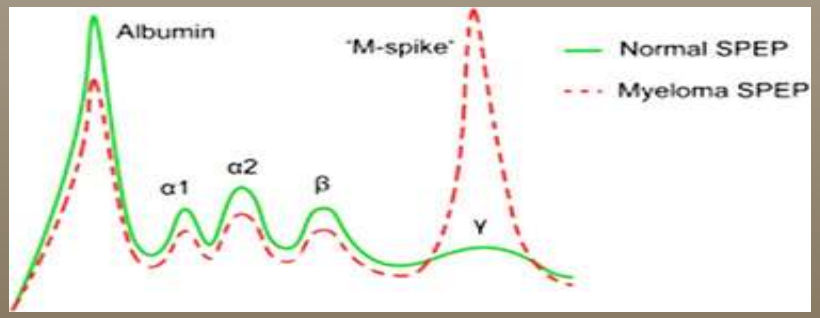
- bone marrow infiltration
- kidney failure causes decrease in erythropoietin secretion

DIAGNOSIS:

1. Serum and urine protein electrophoresis (SPEP/UPEP)—reveals monoclonal protein spike (M-spike) due to a malignant clone of plasma cells synthesizing a single Ig (usually IgG, although specific subtype can be determined via immunofixation)

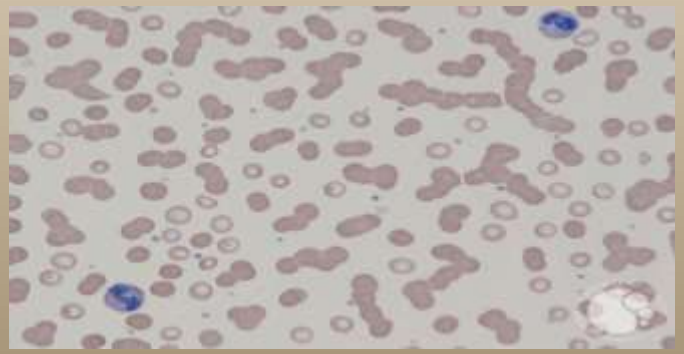
2. Bone marrow biopsy (required for diagnosis)—reveals >%10 abnormal plasma cells





3.CBC: Pancytopenia(normocytic normochromic anemia, thrombocytopenia and leukopenia)

4. Blood smear: normocytic anemia with RBCs in rouleaux formation (RBC resemble a stack of poker chips as a result of clumping caused by hyperglobulinemia) *increased serum immunoglobulin so they attached to cell blood membrane then connecting with other blood cell membrane make the blood cell stack with each other, so the RBCs appear as stacked coins.



DIAGNOSIS OF COMPLICATIONS

Electrolytes: hypercalcemia and hyperuricemia

Kidney function test: high creatinine

Urinalysis: reveals large amounts of free light chains called Bence Jones protein

Low dose CT,PET/CT ,or MRI :reveal lytic bone lesions

CRITERIA OF DIAGNOSIS:

Both criteria must be found:

1) **plasma cells** >10% of bone marrow
2) **Any of the following** (myeloma defining events):
    a) Evidence of end organ damage(CRAB):
        - hypercalcemia
        - renal failure
        - Anemia
        - bone lesions ≥ 1 lesions
    b) any of these biomarkers for cancer: *Plasma cells>60% *Serum light chains ≥100mg/dl *Greater than one focal lesions on MRI

MANAGEMENT:

- **high dose Systemic chemotherapy-** preferred initial treatment (alkylating agents) for patients who are not transplanting.
- **Autologous hematopoietic cell transplantation (HCT)** - which is the preferred treatment for multiple myeloma - For the younger patient - dramatically improve survival and decrease mortality.
- **Palliative care** " For the elderly ".
- **Radiation therapy** – if no response to chemotherapy & if disabling pain is present.

MANAGEMENT OF COMPLICATIONS:

Complications	Management options
Bone disease	Bisphosphonates Vitamin D and calcium supplement
Renal disease	High fluid intake
Peripheral neuropathy	Consider pain management with gabapentin or opioid medications
Hematological complications: Anemia	Blood transfusion Erythropoietin (EPO)

TREATMENT

of 1ry amyloidosis in multiple myeloma

1-treat the myeloma

2-TNF inhibitors ,HSCT, **Hemodialysis** if renal failure is present

THANK YOU

REFERENCES

AMBOSS :Articles (56), multiple myeloma
STEP UP TO MEDICINE : hematological dis and neoplasms P(383-384)
DAVIDSON :p976 , p977