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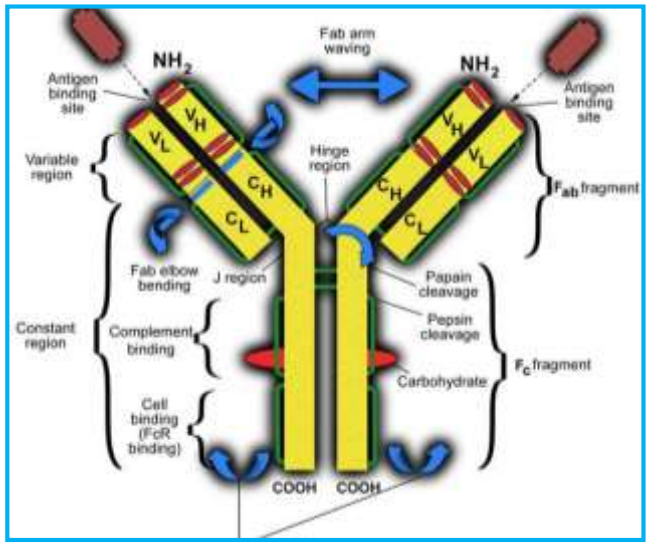
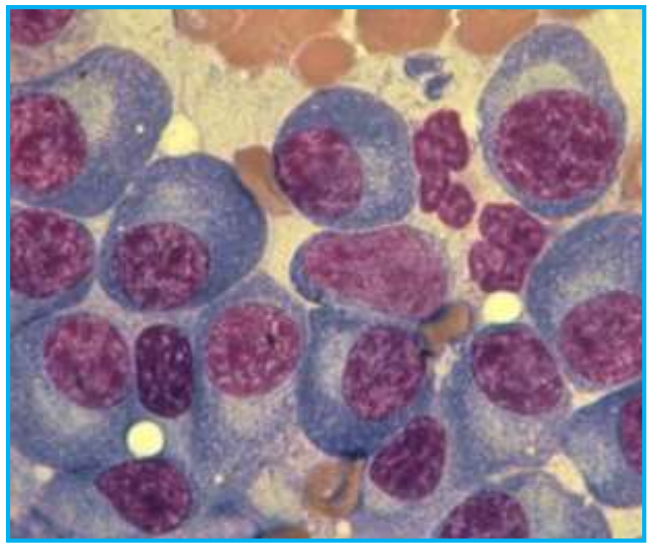
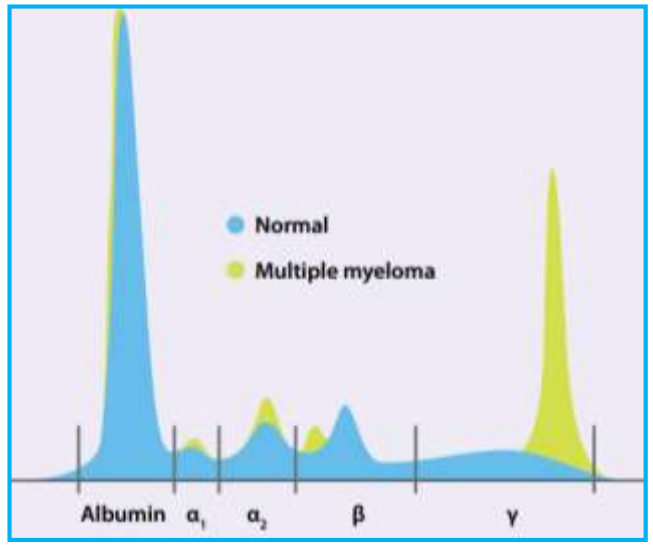
MEDICAL SCHOOL

MED-601 MGUS & Multiple Myeloma







UNIVERSITY of NICOSIA | MEDICAL SCHOOL

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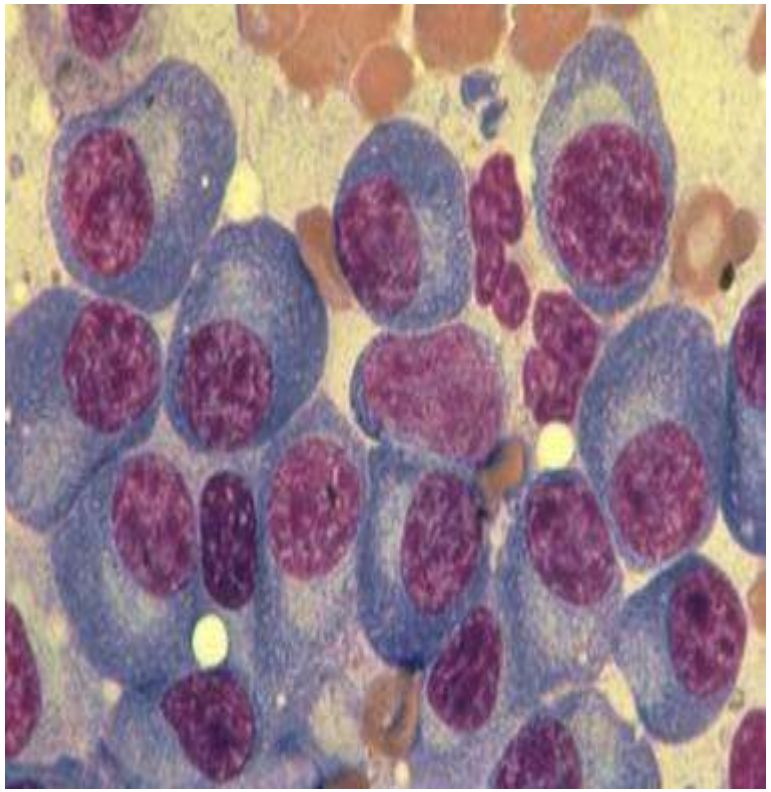
MED-601

DECEMBER 2019

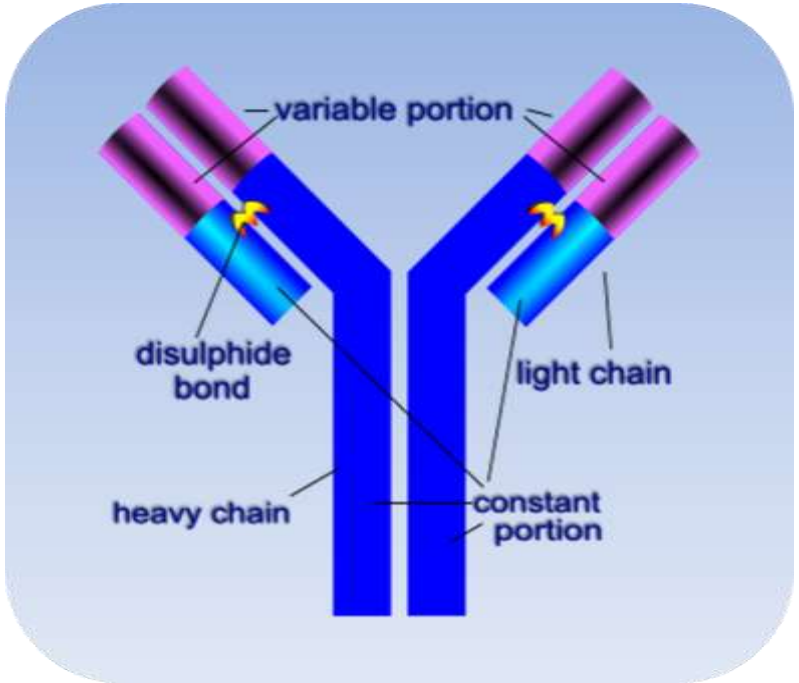
Learning Objectives

- 1. Recall and understand the **structure and function of the immunoglobulins**
- 2. Define the term **paraproteinaemia**
- 3. Distinguish myeloma from **benign paraproteinaemia**
- 4. Define **MGUS** and **smoldering Multiple Myeloma**
- 5. Understand the pathology and clinical manifestations of **Multiple Myeloma**
- 6. Describe the biochemical and **haematological abnormalities** common in myeloma and their significance
- 7. Outline the **investigation and staging** for myeloma.
- 8. Outline the **diagnosis** of multiple myeloma based on guidelines for myeloma
- 9.Be aware of the **complications** of myeloma
- 10. Discuss the **management** of myeloma
- 11. Define **solitary plasmacytoma**.
- 12. Define Lymphoplasmacytic lymphoma / **Macroglobulinemia Waldenström's** and describe the clinical manifestation



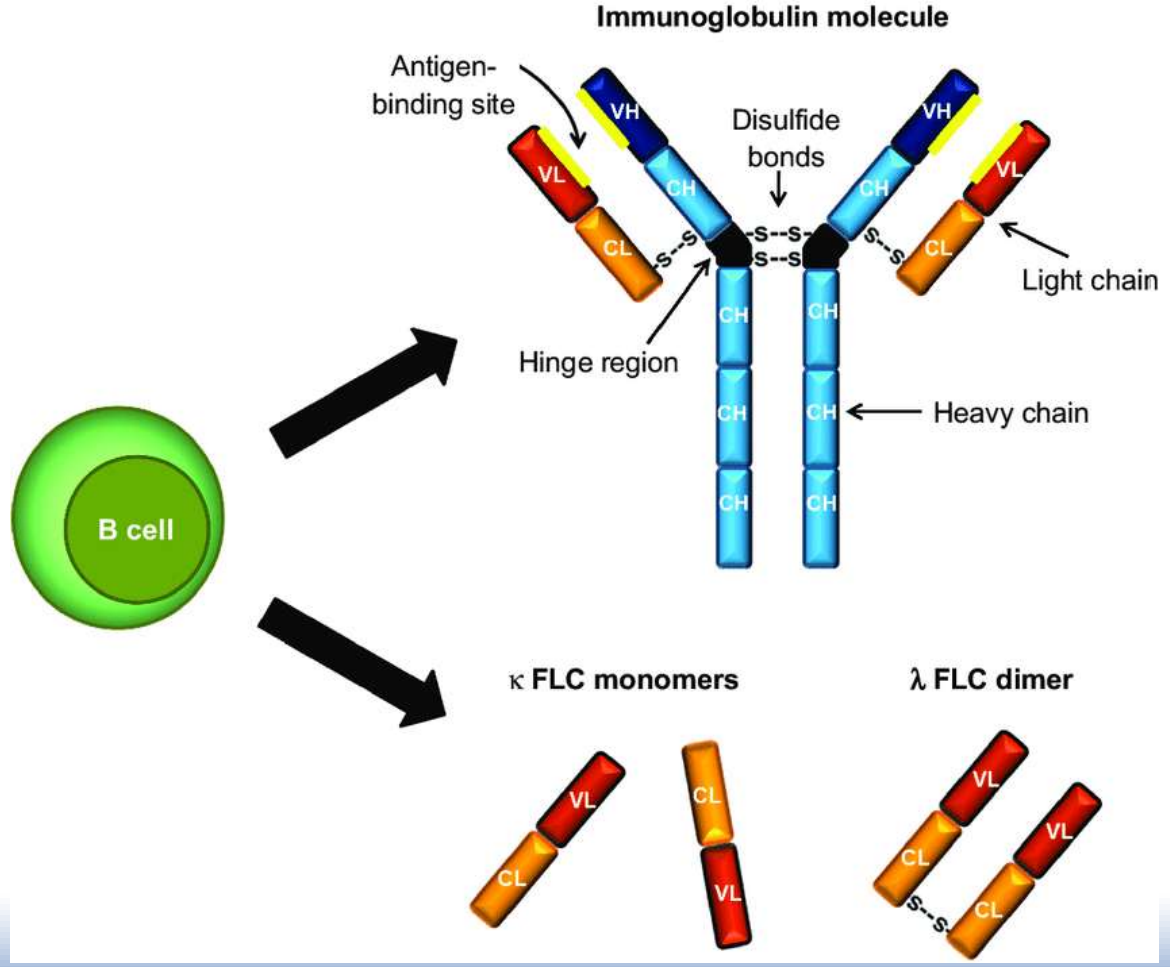
Immunoglobulins / Ig

- Are proteins produced by **plasma cells**
- Plasma cells are **activated B lymphocytes** after they was bound to an antigen
- **5 types of Immunoglobulins:** **IgG, IgM, IgA, IgD** and **IgE**
- made of **two heavy chains & 2 light chains**
- Both have **one constant** and **one variable region** which react with the antigen and give to the **Immunoglobulins the specificity**
- The main role is the **defence** against **foreign organisms**



Normal polyclonal & pathological monoclonal B cells

Normal polyclonal

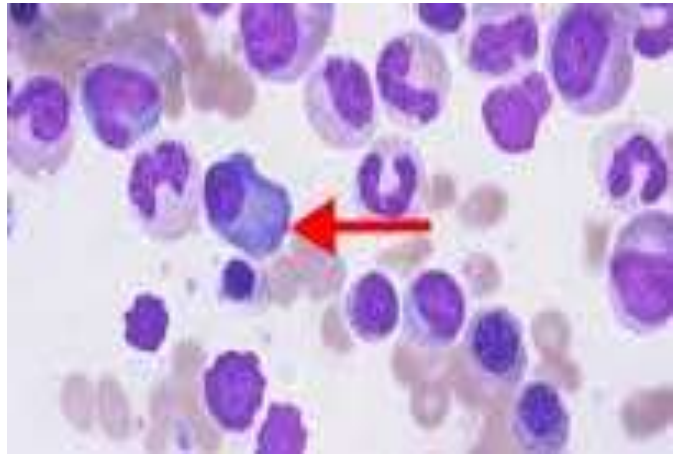


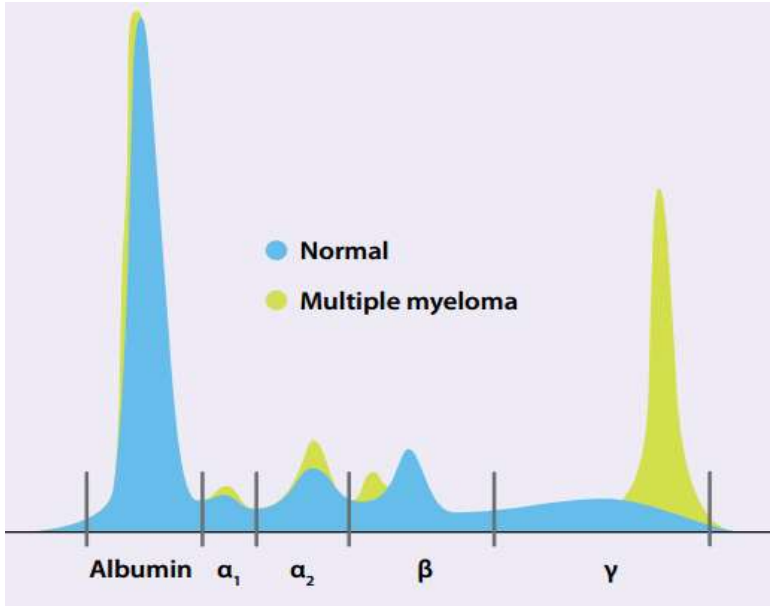
Pathological Monoclonal

- **Paraproteinemia** is the **monoclonal protein** produced from a monoclonal population of plasma cells that secrete **only kappa** or **only lambda** light chain immunoglobulins
- **Bence Jones** proteins are the **monoclonal free light chains** secreted in the urine in case of myeloma.

Paraproteinaemia

- A **single plasma** cell proliferate ➔ **a clone of plasma cells** secreting the **same immunoglobulin** with only **kappa or only lambda chain**
  ➔ **monoclonal protein= M protein=Paraprotein**

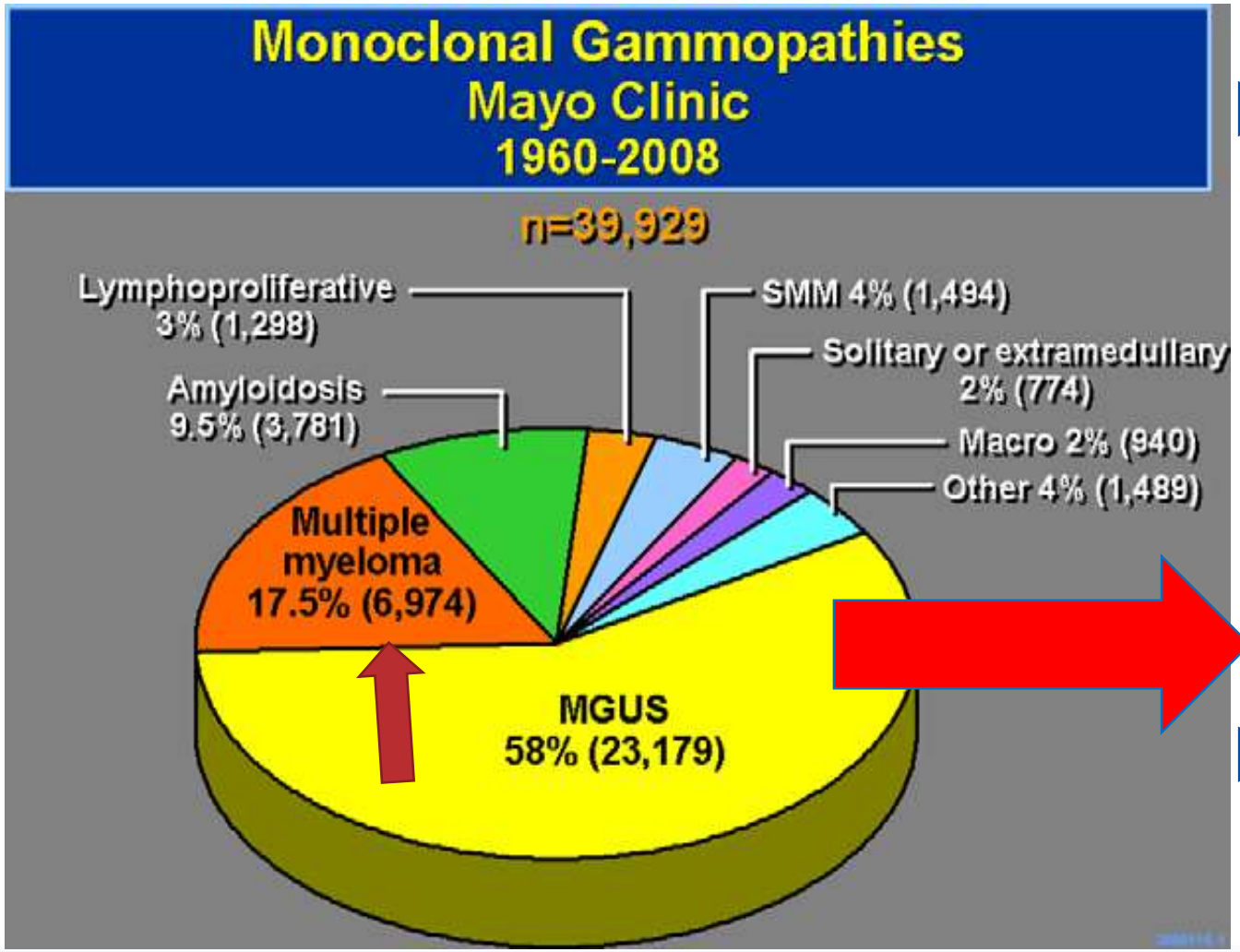




Protein Electrophoresis

- **This Monoclonal protein** appear in **serum protein electrophoresis as a monoclonal band in gamma region**

Monoclonal Gammopathies

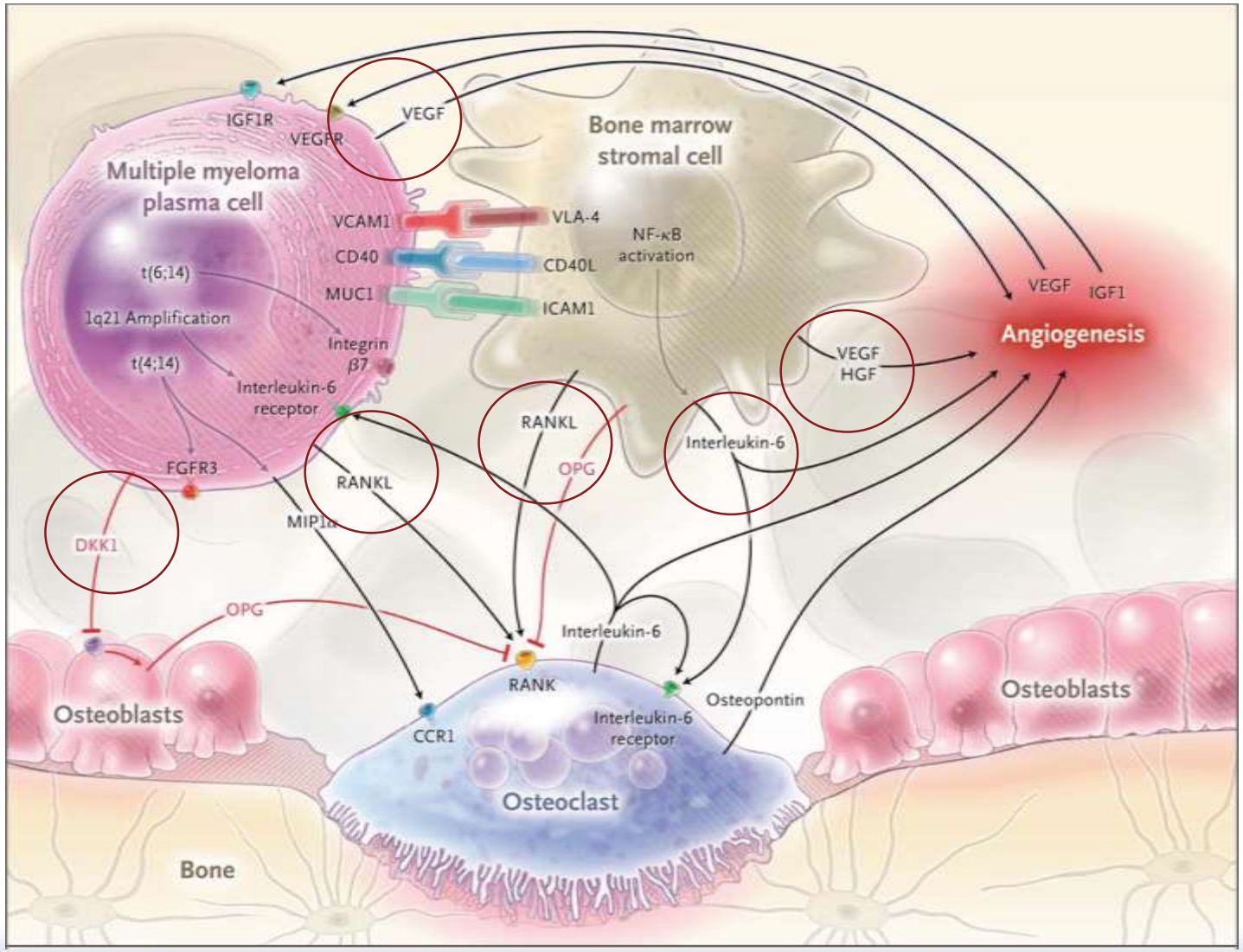


- **Systemic non neoplastic diseases**
  - Autoimmune diseases
  - Hepatopathies
  - Chronic Inflammations
  - Immunodeficiencies (HIV, after transplantations)
- **Malignancies**

SMM:smoldering MM
Macro: Macroglobulinemia Waldenström's

Madan S and Greipp P. Blood Rev, 2009

Pathophysiology in Multiple Myeloma



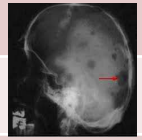
- **Myeloma plasma cell**
- **Bone marrow Stromal cells**
- **Osteoclasts**
  - ↑**osteoclastic activity** with the increase in production of RANKL and decrease in production of osteoprotegerin
- **Osteoblasts**
  - ↓**Osteoblastic activity after the secretion of** dickkopf homolog 1 DDK1
- **Angiogenesis**
  - ↑**IL-6**
  - ↑**VEGF vascular endothelial growth factor**

Palumbo A, et al, NEJM 2011

Myeloma stages

1) **Myeloma cells** derive from plasma blasts (immature plasma cells)
2) **MGUS**: Monoclonal gammopathy of **undetermined** significance with an **annual rate** of **progression of 1%**
3) **Smoldering Myeloma** → Intramedullary phase is dependent on **marrow microenvironment and IL-6**
4) **Extramedullary Myeloma** → Myeloma cells become **independent** of bone marrow microenvironment
5) **Plasma cell leukaemia** → **Myeloma cells in peripheral blood**
6) **Active Myeloma** → **angiogenesis** and **bone destruction**

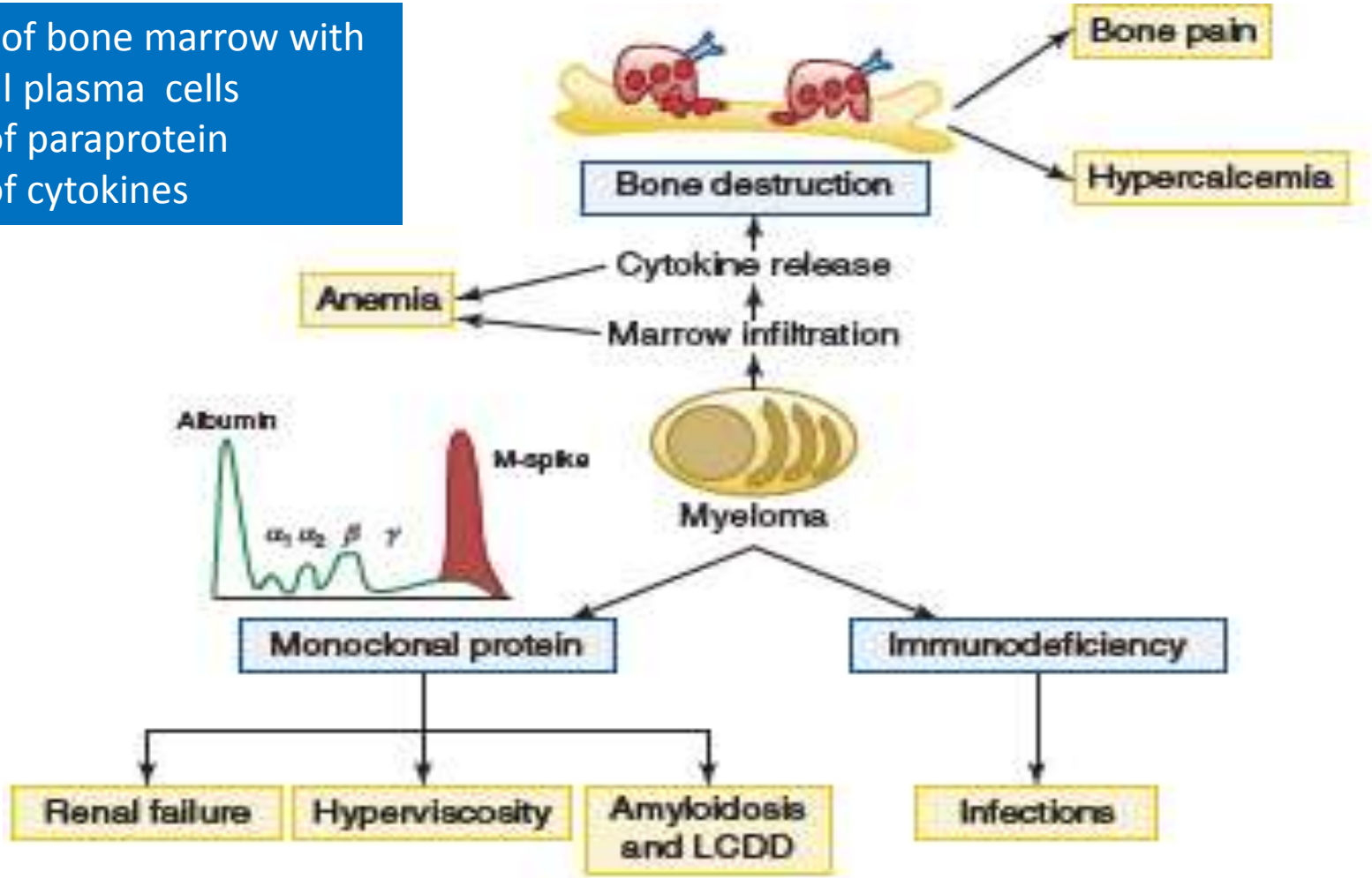
Clinical & laboratory features of Monoclonal gammopathy

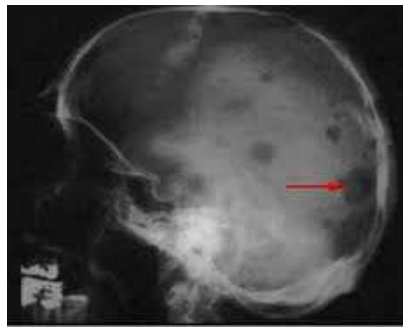
	MGUS	Smoldering Myeloma	Symptomatic Myeloma	Criteria for Dg of Multiple Myeloma *
Bone Marrow (BM) plasma cells 	<10%	≥ 10%	≥ 10%	**1. Monoclonal Plasma ≥ 10% Extramedullary plasmacytoma**
Monoclonal Paraprotein	< 30g/L	≥ 30g/L	≥ 30g	**2. Monoclonal Paraprotein**
Normal Immunoglobulins	Normal	Reduced	reduced	**3. Any one of the following**
Free light chains ratio	Normal/abnormal	Abnormal	Abnormal	• Ca > 11mg/dl • Creatinine > 2g/dL • Hb < 10g/dl • ≥ 1 osteolytic lesion
Clinical features	None	None	**C** Hyper**C**alcaemia	
			Renal failure	
			Anaemia 	**Any one or more of the**
			Bone lesions 	• Clonal BM plasma > 60% • Free light chain ratio>100 • > 1 focal bone lesion
Progression to symptomatic myeloma	1% per year	10% per year		

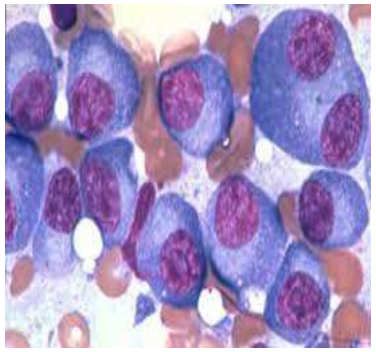
* International Myeloma Working Group updated criteria Lancet Oncol 2014

Multiple Myeloma - Clinical manifestation

1. Infiltration of bone marrow with monoclonal plasma cells
2. Secretion of paraprotein
3. Secretion of cytokines





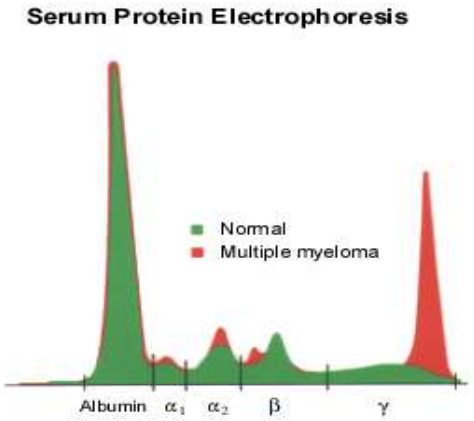


Amyloidosis

LCDD: Light chain deposition disease

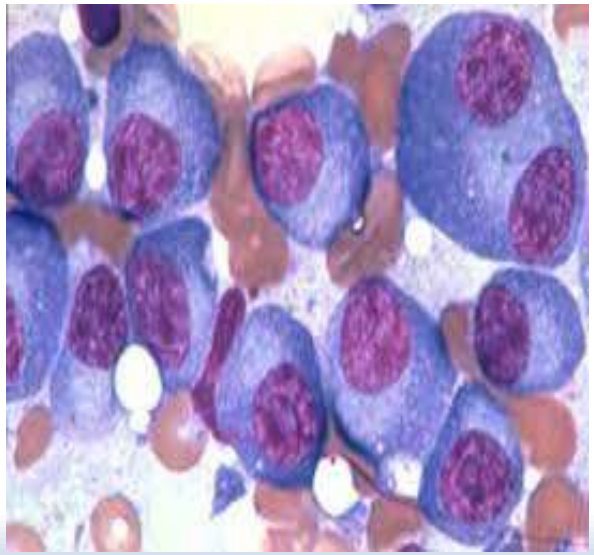
Multiple Myeloma - Clinical manifestation

- Patient usually presents with
  - **Bone pain,** pathologic **fractures** and **anaemia**



Hallmarks of MM:

- Punched out **osteolytic lesions** seen on x-ray.
- **M – spike** in protein electrophoresis.
- Clinical **tetrad CRAB:**
  - **C:** Hyper - Calcaemia, due to activation of osteoclasts that leads to bone lesions with increased risk for pathologic fractures
  - **R:** Renal failure,
  - **A:** Anaemia
  - **B:** Bone lesions



- **Other symptoms:**
  - **Amyloidosis:** in 5% of the patients carpal tunnel, macroglossia
  - **Hyperviscosity syndrome** in 2% with visual failure

Multiple Myeloma- Laboratory investigation

▶1. Paraprotein :

- IgG> 30g/dL➔ in 60% of the cases
- IgA> 20g/dL ➔ in 20% of the cases
- Bence Jones > 10g/24hours ➔ 20%

▶2. Free light chain in serum and urine

- $\frac{\kappa}{\lambda}$= 0.6 (0.26- 1.65)

▶3. Immunoparesis= Immunodeficiency

- Reduce the level of normal Immunoglobulins

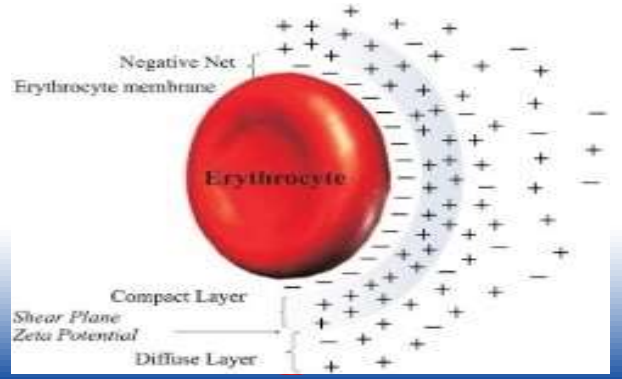
▶4.Bense Jones in urine in 40% of the patients: Monoclonal free light chains n urine➔ renal failure

▶5.Roulaux formation in RBC

▶6. Increased ESR: Erythrocyte sedimentation rate

Fibrinogen Vs Zeta potential

The zeta potential is the normal, **negative force** that exists between red cells and pushes them apart from each other.



Multiple Myeloma- Laboratory investigation -2

- **7. immunophenotyping:** Malignant plasma cells **: CD38+, CD138+, CD45**
- **8. MRI of the spine:**
  - **Osteolytic areas** without osteoblastic areas in 68% of the cases
  - **Generalized osteoporosis** in 20% of the cases
- **9.Serum calcium increased** in 45% of the cases
- **10.Creatinine** is increased in 20% of the cases
- **11. Low albumin** is a prognostic factor for evaluation of international score
- **12. Increased β2 microglobulin** is a prognostic factor
- **13.Aneploidy and translocation** involving **heavy** chain of immunoglobulin in chromosome **14**

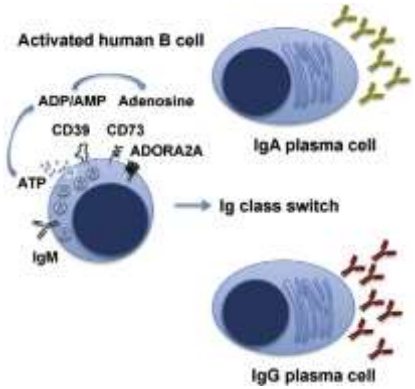
Multiple Myeloma - Staging

Salmon and Durie staging

Stage I:
- Haemoglobin > 10 g/dL
- Serum calcium value normal or =12 mg/dL
- Normal bone structure or solitary plasmacytoma
- Low M-component production rate:
  - IgG <50 g/L; IgA <30 g/L; Bence Jones <4 g/24 hr

Stage II:
- Neither stage I nor stage III

Stage III: One or more of the following:
- Haemoglobin <8.5g/dl
- Advanced lytic bone lesions
- High M-component production rate:
  - IgG >70 g/L; IgA >50 g/L; Bence Jones >12g/24h



- **A:** creatinine < 2mg/dL
- **B:** creatinine > 2mg/dL

Revised International Staging System

Stage I:
- Serum beta-2 microglobulin < 3.5 mg/L
- and serum albumin ≥ 3.5 g/dL
- No high risk chromosomal abnormalities
- Normal LDH

Stage II:
- Neither stage I nor stage III

Stage III:
- Serum beta-2 microglobulin ≥ 5.5 mg/L
- One or both of
  - High risk Chromosomal Abnormalities
  - High LDH

High Risk Chromosomal abnormalities (FISH)
: Del 17p t(4;14) t(14;16)

Multiple Myeloma - Complications

- **1. Hypercalcaemia**
- **2. Acute renal failure** due Bence Jones proteins eliminated with urine ➔ renal tubule are distended with hyaline protein
- **3. Anaemia**
- **4. Bone lesions / fractures**
- **5. Amyloidosis**= extracellular deposition of abnormal protein (AL amyloid) in different organs:
  - Tongue, Skin, Nerves, Connective tissue
  - Heart, kidneys, liver, spleen

Deposits of amyloid in tongue and lips

1. Supportive treatment

- **Renal failure:**
  - **Hydration** to dilute the pathologic protein
  - **Treatment for hypercalcaemia** → bisphosphonates
    - pamidronate
    - zoledronic acid
  - **Treatment for hyperuricaemia** → allopurinol, rasburicase
- **Anaemia:**
  - Transfusions
  - Erythropoietin
- **Infections:**
  - Prophylactic **iv Immunoglobulins**
  - Oral broad –spectrum **antibiotics and antifungal**

2. Specific treatment

- The **prognosis** and the **life expectancy** of the patient with myeloma **has improved** in the last 10-15 years with the introduction of **new drugs**.

- **Intensive chemotherapy** with **Autologous bone marrow** transplantation is given in patients **< 70 years old**
  - **VTD:** Velcade, Thalidomide and dexamethasone
  - **VCD:** Velcade, Cyclophosphamide, dexamethasone

- Non intensive therapy is given in patients **> 70 years old** that are not eligible for transplantation
  - **MPT:** melphalan, prednisone, thalidomide
  - **VMP**: Velcade, melphalan , thalidomide

Mode of action of Specific treatment

Immunomodulators

►Thalidomide

►Lenalidomide=Revlimid

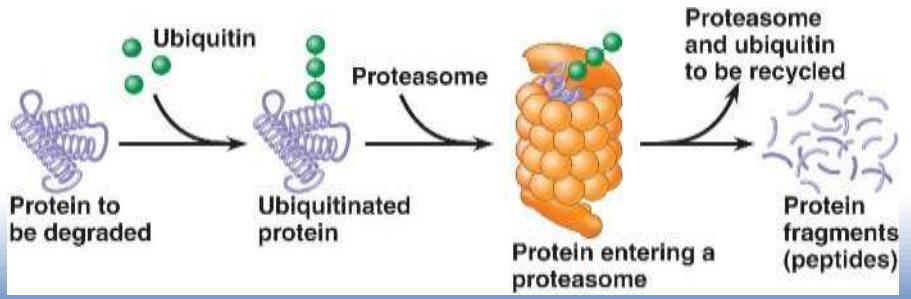
- **Activate** the CD4 and CD8 lymphocytes and NK cells
- **Enhance NK cells proliferation**
- **Inhibit angiogenesis** by reducing levels of VGF

Proteasome Inhibitors

►Bortezomib/Velcade

►Carfilzomib /Kyprolis

- **Inhibit proteasomes**, cellular complexes that break down proteins➔**prevent degradation** of **proapoptotic factors** such as:
  -**the p53 protein** tumor suppression
  -**the I-KB** that is the inhibitor of NF-KB that is responsible for proliferation of myeloma cells

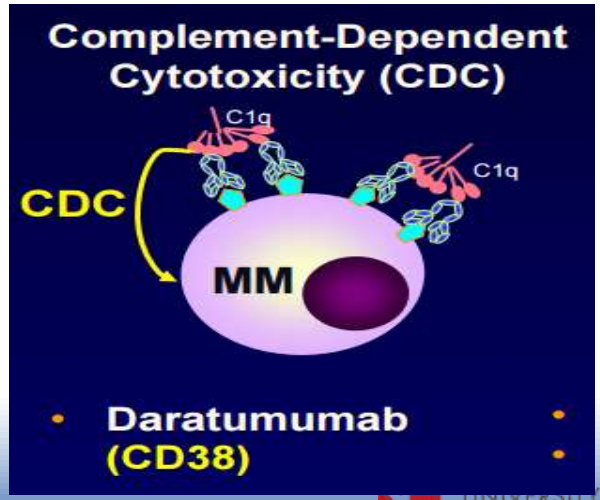


Monoclonal Antibodies

► Daratumumab/Darzalex

- It is and **anti-CD38** antibody
- Kills all cells with this specific **cluster of differentiation** on its membrane

➔Mainly **plasma cells**



Treatment Algorithm

Asymptomatic (smoldering) MM

" wait and see"

Symptomatic

- C elevated calcium
- R renal dysfunction
- A Anaemia
- B Bone lesions

Suitable for intensive treatment and ABMT **Autologous Bone marrow transplantation**

< 70 years old

Non suitable for intensive treatment and ABMT **Autologous Bone marrow transplantation**

> 70 years old

1) Several courses of chemotherapy
2) And after ABMT

Melphalan, Thalidomide Dexamethazone

PLATEAU➔ stop treatment
Maintenance thalidomide or lenalidomide

If < 50 years Allotransplant

2^{nd} Autologous BMT ??
Further chemotherapy

RELAPSE (increasing paraprotein)

Further chemotherapy

Solidary plasmacytoma

- Are isolated plasma tumours
- Appear as **masses** with malignant monoclonal **plasma cells**
- Can be localised in **bones** or in **soft tissue** as in mucosa of respiratory or Gastrointestinal tract and …. everywhere
- Monoclonal gammopathy disappears after treatment with localised , involve field ➔ **Radiotherapy**
- Can **relapse as Multiple Myeloma**

Case Nr. 1

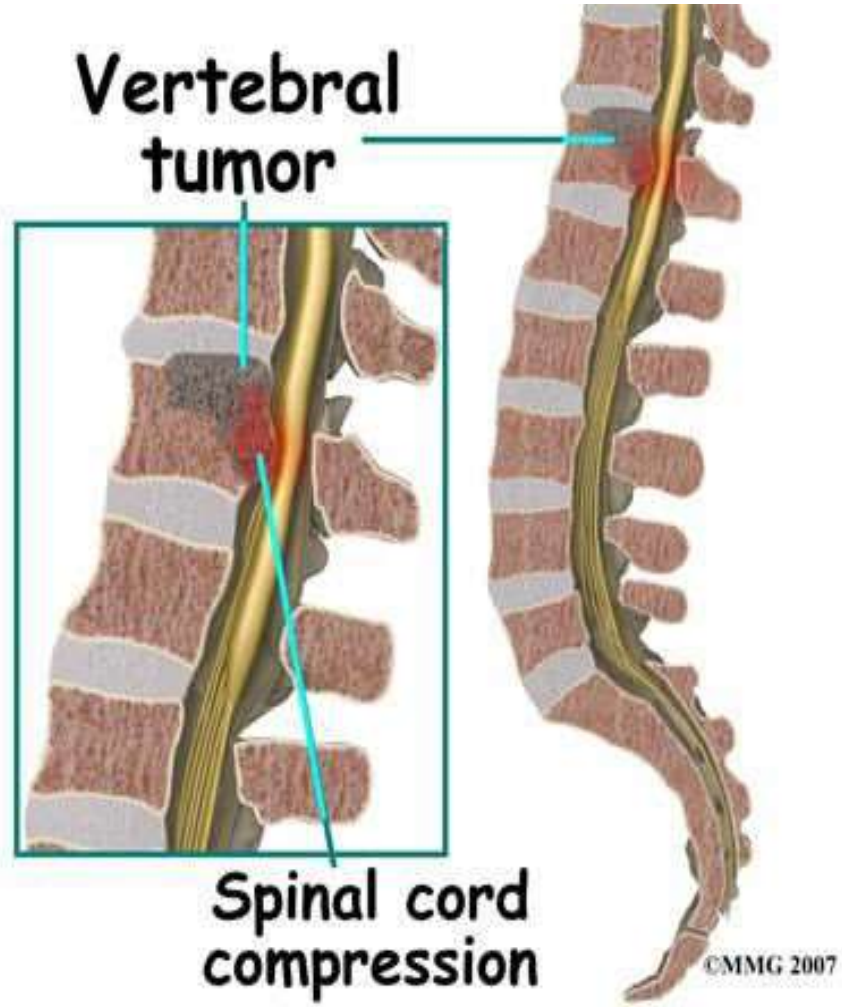
- A 58 year old lady fit and well, presents with back pain for 7 months
- The last 2 weeks the patient presented with additional difficulties in walking and numbness in her right leg
- She has not opened her bowels for 3 days and she has also difficulty in passing urine

What do you think could be the cause of patients symptoms?

Spinal cord compression

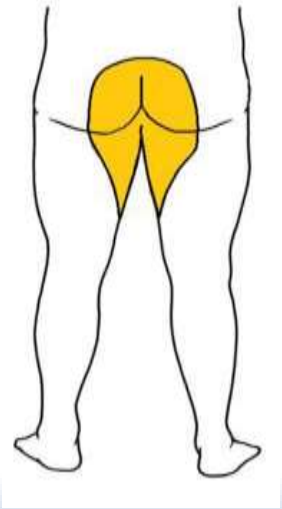
Spinal Cord Compression

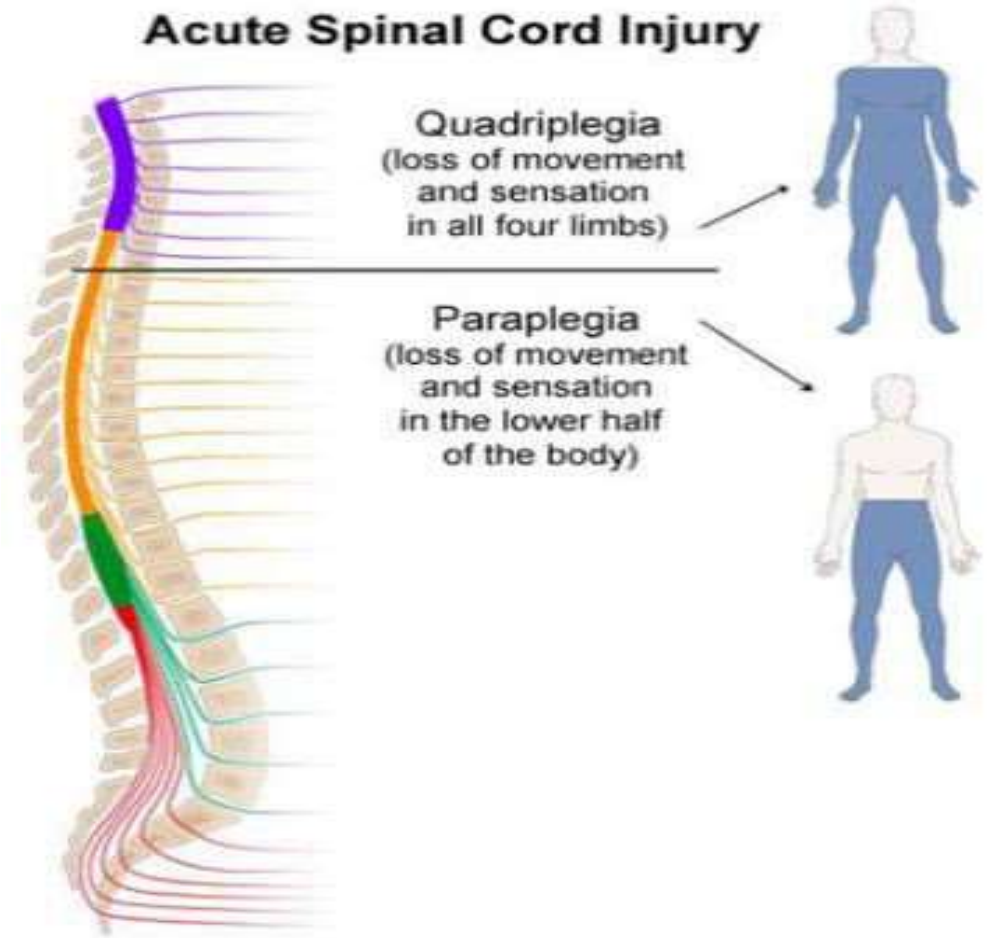
- **Causes :**
  - Myeloma and plasmacytoma
  - lymphoma,
  - metastatic solid tumor in spine
    - Lung, breast and prostate cancer
  - Compression vertebral fracture
- **More than 20%** of the patients do not have history of cancer
- **Delayed diagnosis** can result in permanent paralysis



Acute spinal cord injury - Symptoms

- Back pain
- Paresthesia
- Sphincter disturbance
- Neurological symptoms based on the lesion's level:
  - The higher the injury on the spinal cord, the more dysfunction can occur.
    - Quadriplegia
    - Paraplegia
    - Cauda equina compression syndrome





Spinal Coord compression management

- History and careful neurological examination
- Urgent MRI
- Steroids
- Bed rest if unstable spine
- Refer to acute oncology team to asses for need:
  - **Radiotherapy**
  - **Surgery**
  - **Diagnostic investigations for malignancy**

Dexamethasone Reducing regimen

Day	Dexamethasone daily dose	Administration
1-3	16mg	16mg OM or 8mg BD (8am & 12noon)
4-6	8mg	8mg OM
7-9	4mg	4mg OM
10-12	2mg	2mg OM
13	Discontinue	

- While the patient is on steroids commence PPI (e.g. Lansoprazole) for gastric protection.
- A slower reducing regimen may be required for patients who have received previous courses of steroids.

Case Nr. 2

- A 58-year-old lady presents to her GP with **fatigue and aches** everywhere saying that she is “non-specifically unwell” the last two months
- Over last week she has developed **nose bleeds**, **blurred vision** and **headaches**
- On clinical examination she has cervical and axillary lymphadenopathy and palpable spleen

On laboratory examination:

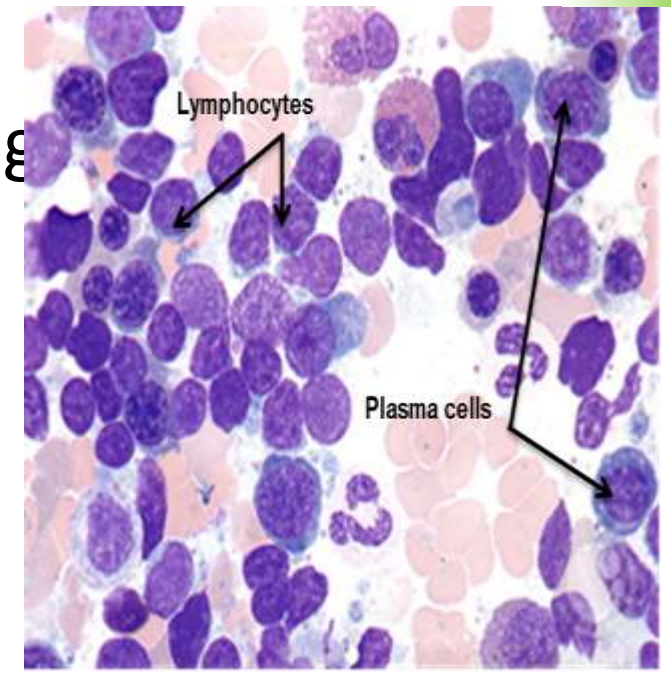
- **Hb: 8.0g/dL** (RV:12-16g/dL)
- **WBC: 3.5 X 10^9** (RV: 4.0-10.0 X 10^9)
- **Total protein: 13g/dL** (RV: 6.6 – 8.1g/dL)
- Immunoglobulins:
  - IgG: 4.4 g/L (RV: 7.0-16.0)
  - IgA: 0.7 g/L (RV:0.7 – 4.0)
  - **IgM: 76 g/L (RV: 0.4- 2.3)**
- **Protein electrophoresis**: monoclonal band in gamma zone

What is the most possible diagnosis?

Macroglobulinemia Waldenström's with Hyperviscosity syndrome

Lymphoplasmacytic Lymphoma Macroglobulinemia Waldenström's

- It is an indolent B-Cell neoplasm manifested by accumulation of clonal **immunoglobulin IgM** secreting **Lymphoplasmacytic cells**



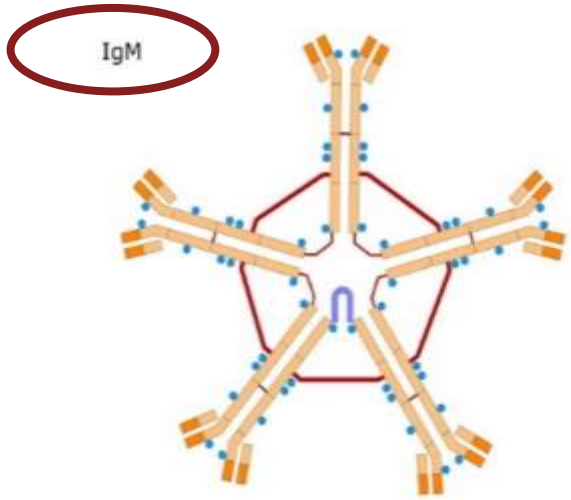
- **In the bone marrow the clone of B cells** reveals a range of differentiation
  - from small lymphocytes with large focal deposits of surface immunoglobulins
  - to lymphoplasmacytic cells and
  - to mature plasma cells that contains intracytoplasmic **IgM** and co-express of **CD38** and **CD138**

Macroglobulinemia Waldenström's

Hyperviscosity syndrome

▶ Clinical presentation

- **Mucosal bleedings**
- **Visual disturbances**
- **Nervous system symptoms**
  - Lethargy, Confusion
- Congestive heart failure



▶ Treatment:

- **plasmapheresis**

- **No hypercalcaemia**
- **No lytic lesions**
- **Involvement of**
  - **lymph nodes**
  - **and spleen**

Cryoglobulinemia type I

▶ Clinical presentation

- Raynaud phenomenon
- Acrocyanosis
- Ulcers
- Purpura
- Cold urticaria

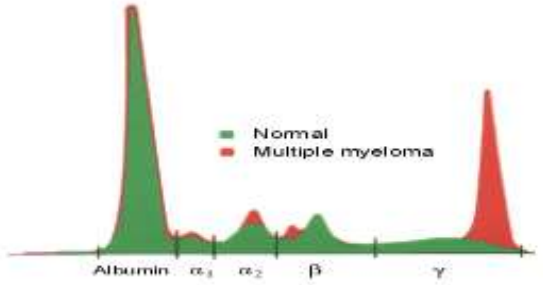
▶ Treatment:

- **Avoid exposure to cold**
- Plasmapheresis in severe cases

Case Nr 3

- A 61 year-old woman presents to your office complaining of fatigue and low energy.
- She also notes experiencing intermittent back pain that responds to ibuprofen.
- She has no significant past medical history
- Her family history is significant for his father dying of a heart attack at 60.
- Faecal occult blood test is negative
- **Laboratory studies reveal**:
  - Hb:11.8% (RV:12-47)
  - MV:86fL (RV:80-100)
  - WBC:7.000/mm3 (RV:4-10.000)
  - PLT:170.000/mm3 (RV:150-400.000)
  - Sodium:136mEg/L (RV:135-145)
  - Potassium:4.5mEg/l (RV:3.5-5.1)
  - AST:34U/L (up to 40)
  - TBIL:0.8mg/dl (up to 1)
  - Creatinine:0.7mg/dL (0.5-0.9)

Plasma Protein Electrophoresis reveals a **high peak** corresponding to **gamma-globulins.**



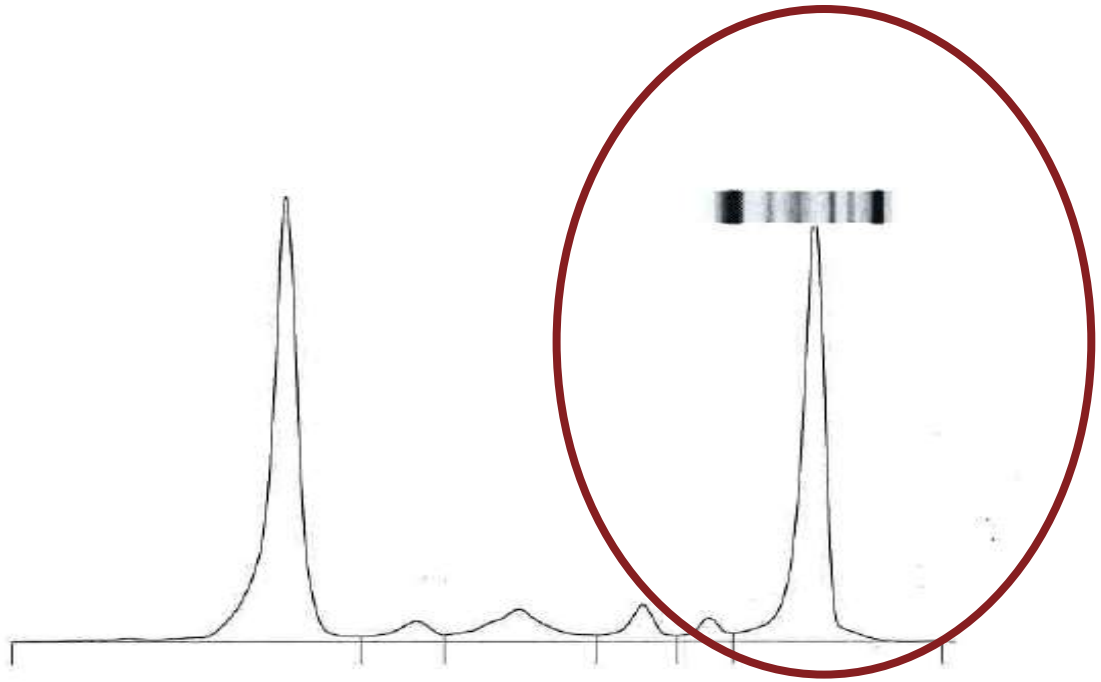
What is the most likely diagnosis ?

A. Iron deficiency
B. Aplastic anaemia
C. Plasma cell neoplasm
D. Smoldering Myeloma
E. MGUS

We don't know. We need more investigations

➔Can be anyone of the last 3 answers

Serum Protein Electrophoresis



Electrophoresis

Fractions	. %	Ref. %	g/l	Ref. g/l
Albumin	**46.5**	55.8 - 66.1	43.5 <	40.2 - 47.6
Alpha 1	**2.9**	2.9 - 4.9	2.7	2.1 - 3.5
Alpha 2	**7.3**	7.1 - 11.8	6.8	5.1 - 8.5
Beta 1	**3.9**	4.7 - 7.2	3.6 <	3.4 - 5.2
Beta 2	**2.3**	3.2 - 6.5	2.2 <	2.3 - 4.7
Gamma	**37.1**	11.1 - 18.8	34.7 >	8.0 - 13.5

What is your Differential diagnosis ?

- **MGUS**
- **Smoldering Multiple Myeloma**
- **Symptomatic Multiple Myeloma**

What test do you order next?

- Quantitative Immunoglobulins
- Kappa and lambda light chains
- Immunotyping

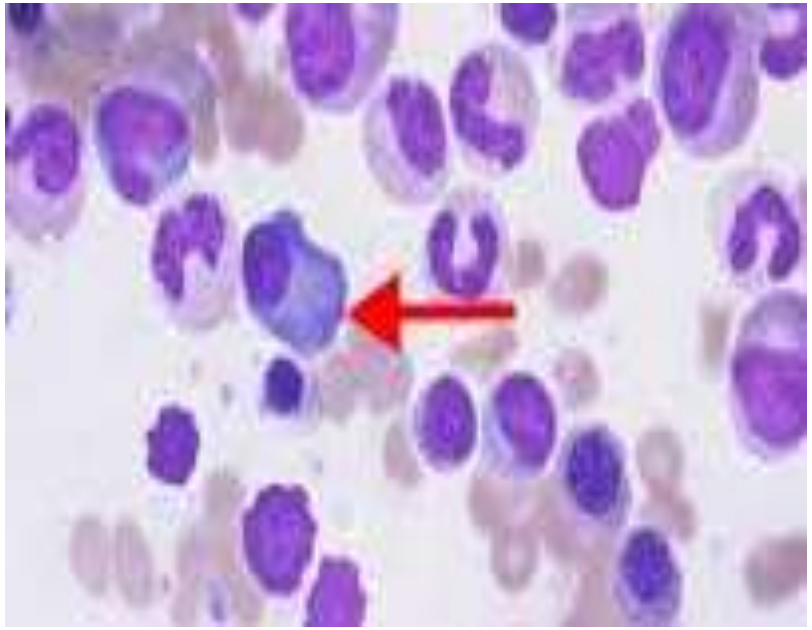
Immunoglobulins-Kappa/lambda

INVESTIGATION	RESULTS	UNIT	REF. VALUES
SER PROTEIN			
• Total protein	9.61	g/L	6.60 – 8.30
• Albumin	3.71	g/L	4.00- 4.94
• Globulin	5.90	g/L	1.30- 3.50
• A/G ratio	0.63		
IMMUNOGLOBULINS			
• IgG	42.83	g/L	7.00 – 16.00
• IgA	0.43	g/L	0.70 – 4.00
• IgM	0.28	g/L	0.40 – 2.30
FREE LIGHT CHAINS			
• Kappa	0.725	g/L	1.38 – 3.75
• Lambda	10.107	g/L	0.93 – 2.42
• κ/λ ratio	0.072		1.17 – 2.93

What test do you order next

Bone marrow karyotype

Bone Marrow and Karyotype

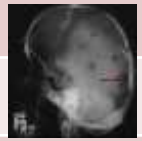


Monoclonal Plasma cells 10%
Karyotype : normal

What other tests are needed for dg

- Calcium= normal
- Creatinine= Normal
- Hb=11.8g/dl

Clinical & laboratory features of Monoclonal gammopathy

	MGUS	Smoldering Myeloma	Symptomatic Myeloma	Criteria for Dg of Multiple Myeloma *
Bone Marrow (BM) plasma cells 	<10%	≥ 10%	≥ 10%	**1. Monoclonal Plasma ≥ 10% Extramedullary plasmacytoma**
Monoclonal Paraprotein	< 30g/L	≥ 30g/L	≥ 30g	**2. Monoclonal Paraprotein**
Normal Immunoglobulins	Normal	Reduced	reduced	**3. Any one of the following**
Free light chains ratio	Normal/abnormal	Abnormal	Abnormal	• Ca > 11mg/dl • Creatinine > 2g/dL • Hb < 10g/dl • ≥ 1 osteolytic lesion
Clinical features	None	None	**C** Hyper**C**alcaemia	
			Renal failure	
			Anaemia 	**Any one or more of the**
			Bone lesions 	• Clonal BM plasma > 60% • Free light chain ratio>100 • > 1 focal bone lesion
Progression to symptomatic myeloma	1% per year	10% per year		

* International Myeloma Working Group updated criteria Lancet Oncol 2014

Which is your final diagnosis?

► Smoldering Multiple Myeloma

Case Nr 4

- **A 63-year-old woman is admitted to the hospital after fracturing her hip. She has a history of three episodes of pneumonia in the last 6 months.**
- **Laboratory studies show:** M
  - Leukocyte count: 4,500/mm^3 (RV: 4-10.000)
  - Hemoglobin 10 mg/dL (RV: > 12)
  - CV 85 μm^3 (RV:80-100)
  - Serum calcium 15 mg/dL (RV: up to 10mg/dL)
  - Serum creatinine 1.8 mg/dL (RV: 0.6-0.9 mg/dL)
  - Erythrocyte sedimentation rate (ESR) 35 mm/hour
  - Serum electrophoresis Presence of monoclonal spike
  - Urinalysis 4+ proteins, no blood

Which of the following is the most likely composition of the proteins detected in the urine?

A. Heavy chains from IgG
B. Heavy chains from IgM
C. IgG monomers
D. IgM monomers
E. Light chains from IgG
F. Light chains from IgM

SBA 1

▶ MGUS is best described as :

A. The presence of monoclonal immunoglobulin in serum with only mild bone marrow plasmacytosis

B. The presence of monoclonal serum or urine immunoglobulin with significant bone marrow plasmacytosis

C. The presence of significant bone marrow plasmacytosis in a patient with only a few symptoms of plasma cell myeloma

D. The presence of monoclonal immunoglobulin in a patient with a solidary mass composed of plasma cell

Multiple Correct Answers

- **Which of the following statements about myeloma is true?**
  - ● Can be asymptomatic
  - ● Prognosis is indicated by serum albumin level
  - ● Is associated with an increased risk of Hyperviscosity
  - ✖ Is associated with hypocalcaemia
  - ✖ Splenectomy is often indicated.

- **Which of the following statements about multiple myeloma is true?**
  - ● Is often proceeded by monoclonal gammopathy of undetermined significance?
  - ● Can cause spinal cord compression
  - ● Is more common among black population
  - ✖ Is associated with infection by EBV
  - ● Typically causes lytic bone lesions?

Brief overview:

- **Monoclonal gammopathy**: appear in electrophoresis as **a spike** and occurs NOT only in **multiple myeloma**.

- **Polyclonal gammopathy: ** Occurs in **chronic infection or inflammation**. The gamma section of the serum protein electrophoresis would be **elevated and wide**, but not a tall M-spike.

- **Monoclonal gammopathy of undetermined significance (MGUS):** Patients with MGUS may either have a **chronic infection/inflammation** or may eventually develop **multiple myeloma later**.

- **Waldenström's macroglobulinemia:**
  - Associated with **lymphoplasmacytic lymphoma**. Serum protein electrophoresis will show an **IgM monoclonal gammopathy**.
  - There is involvement of **lymph nodes, bone marrow and spleen.**
  - Unlike multiple myeloma, there **is no hypercalcemia or lytic bone lesions.**

- **Plasmacytoma:** A **solitary myeloma** that can occur within the bone or soft tissue, e.g., respiratory tract.


Thank You!

Do you have any questions?

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