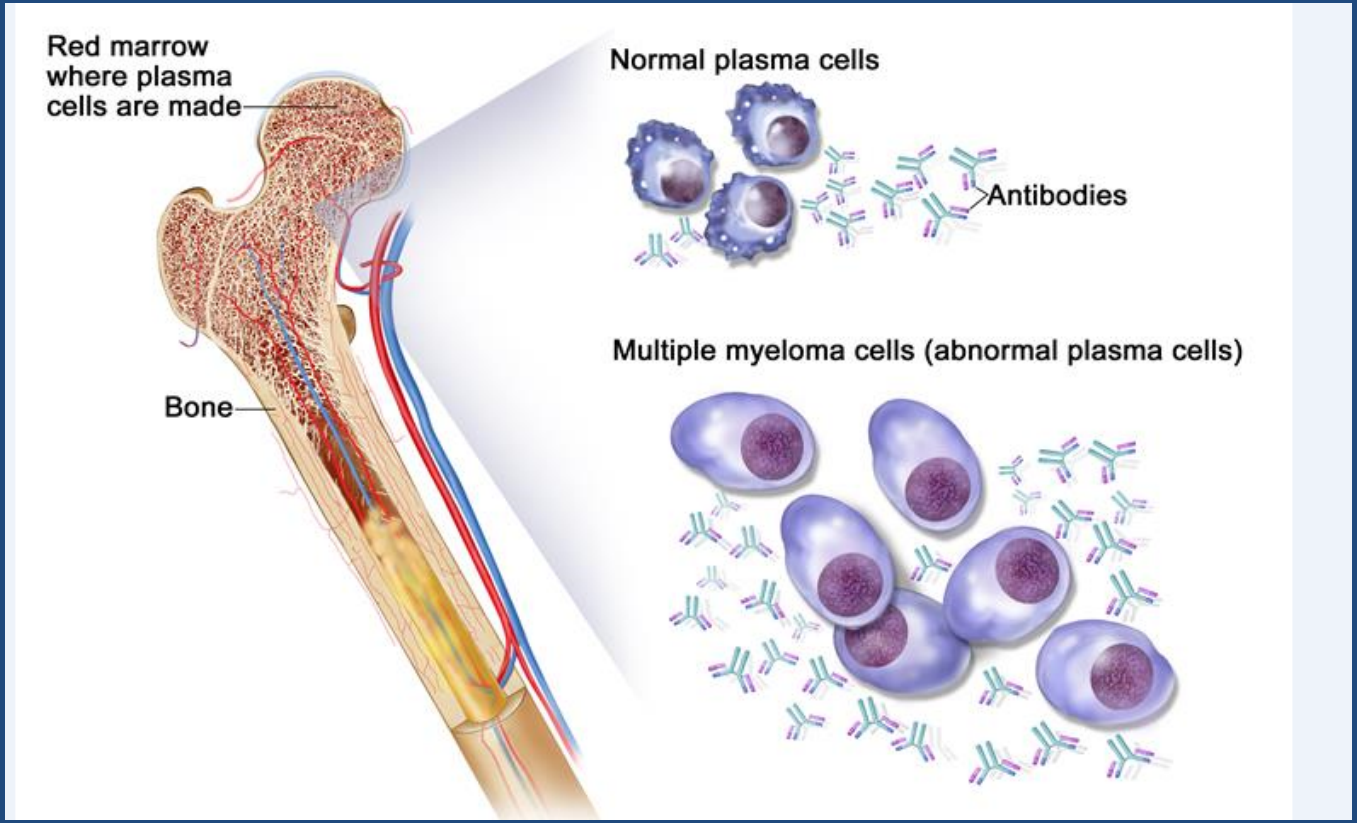
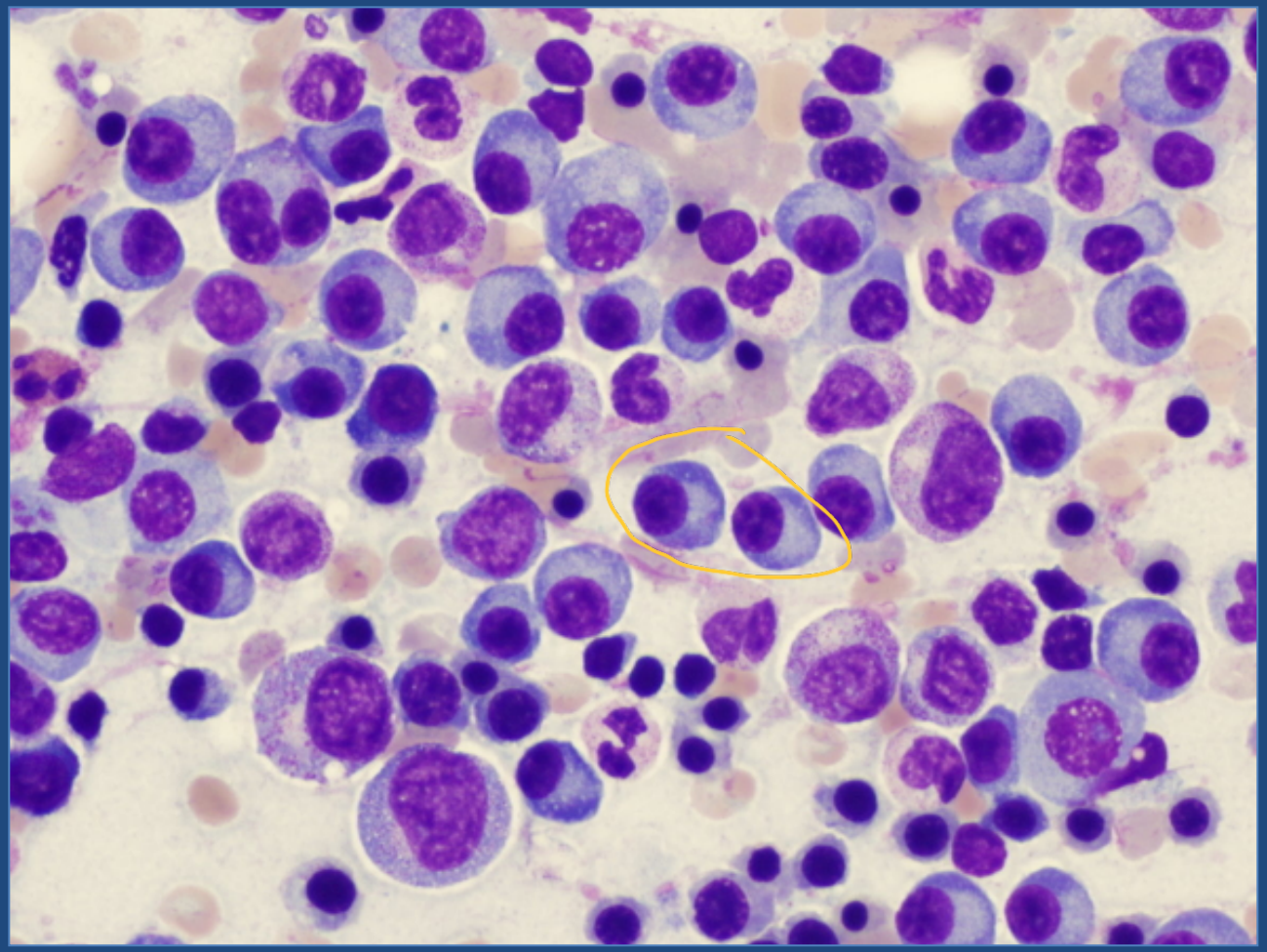
Multiple myeloma

Edited by:
Layla
Nazzal.

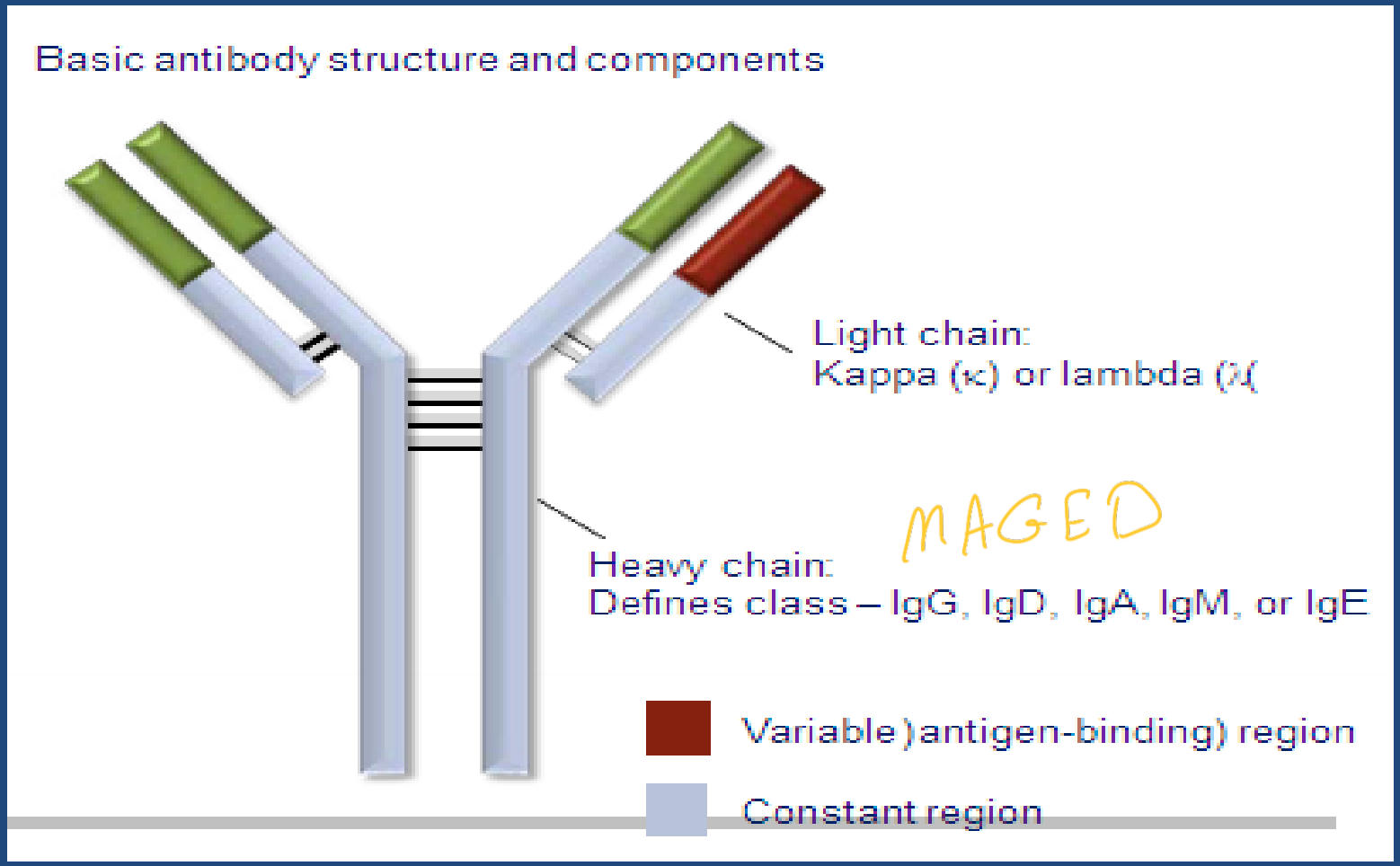
- Multiple myeloma (MM) is characterized by the neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin.



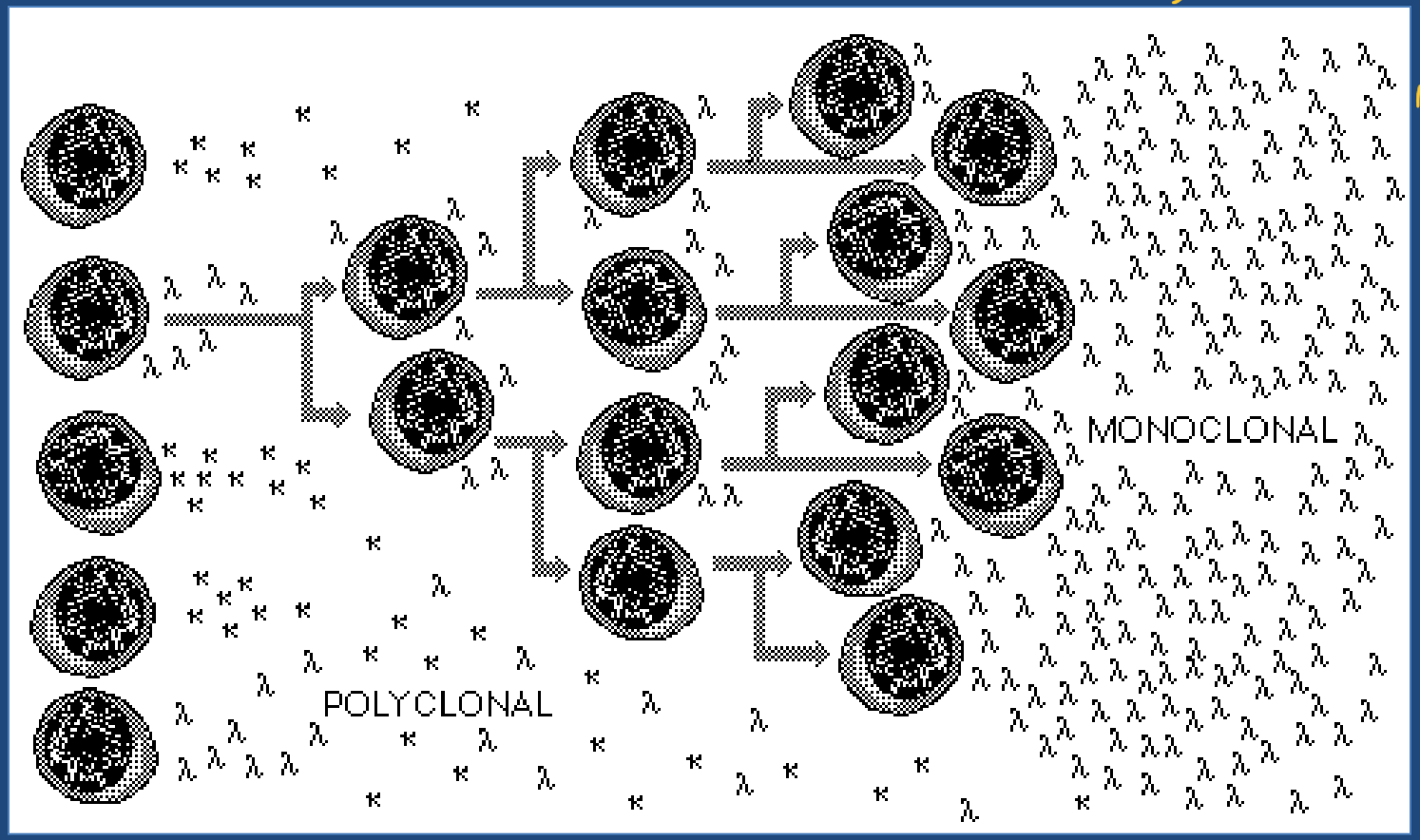
Plasma Cells



Immunoglobulins



Monoclonal Proliferation

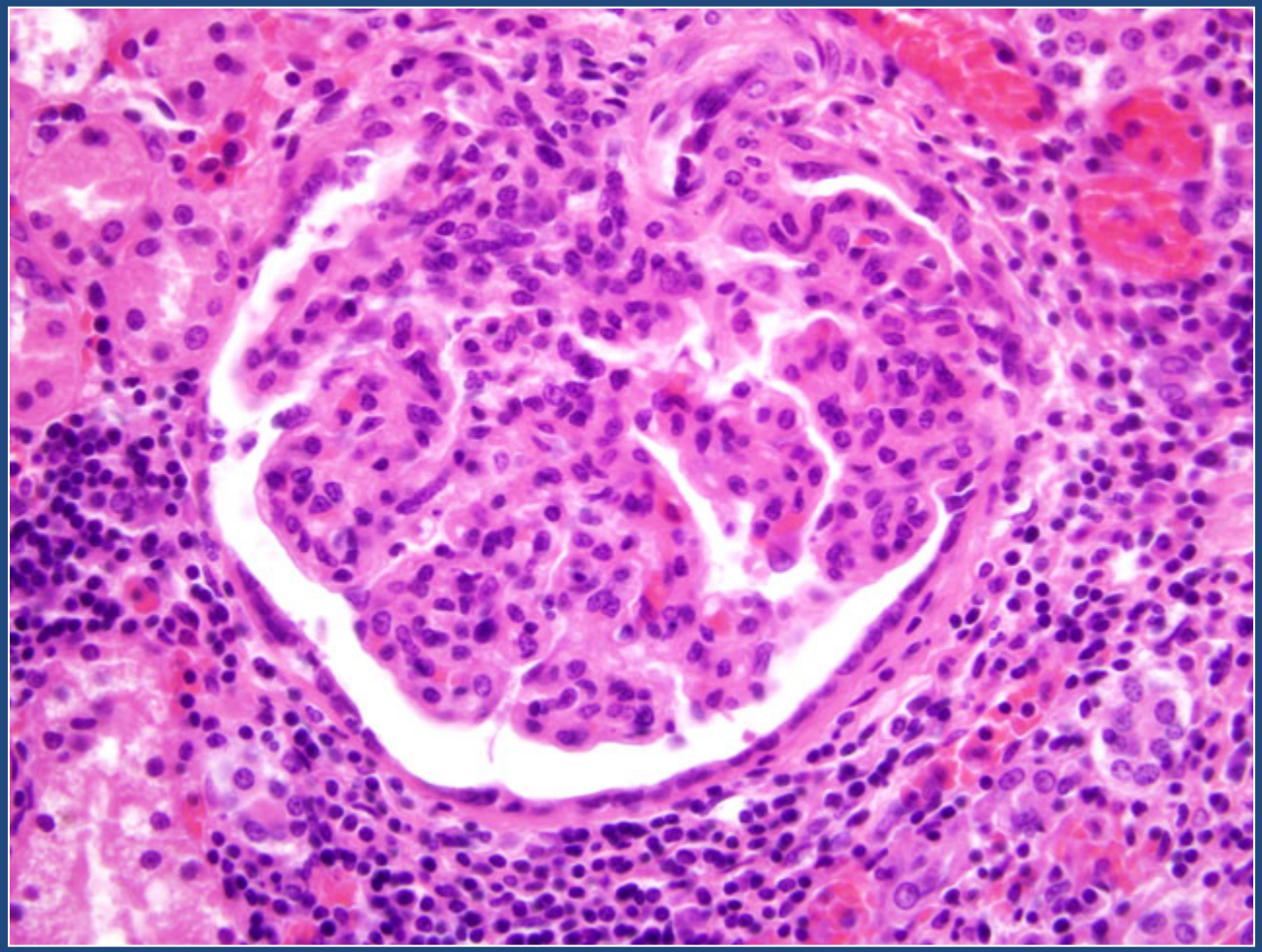


no antigenic diversity

↓

↑ risk of infection

Plasma Cell Disorders



When should we suspect MM?

Typical ♂ Elderly with bone pain (back pain) and unexplained anemia.

- Bone pain:
  - Lytic lesions discovered on routine skeletal films or other imaging modalities
- Increased total serum protein
- Unexplained anemia
- Hypercalcemia, which is either symptomatic or discovered incidentally
- Unexplained acute renal failure AkI

"CRAB" → Bone pain
- C → hypercalcemia
- R → Renal failure
- A → Anemia

Could be due to direct deposition of Igs in kidneys causing injury.

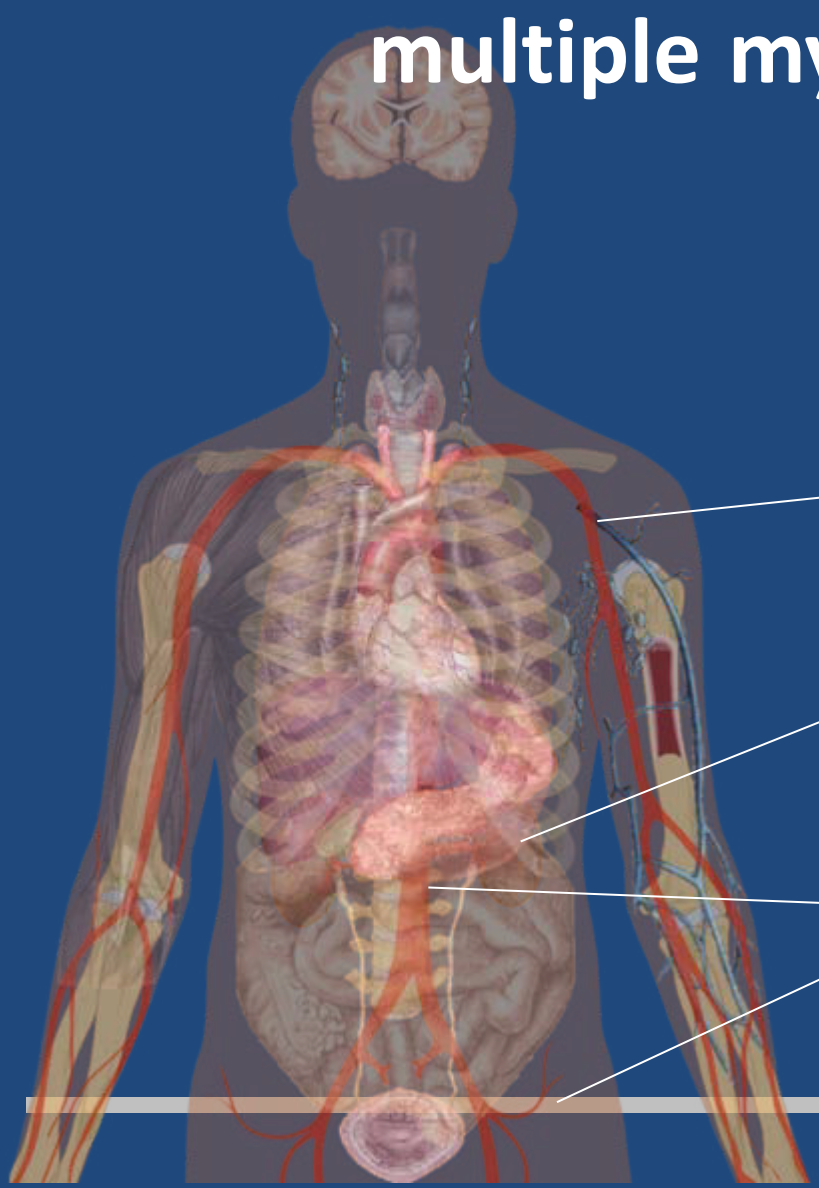
Could be due to the hypercalcemia that resulted from MM.

Normal serum protein = 6 - 8 g/dL

Common symptoms of multiple myeloma

C R A B

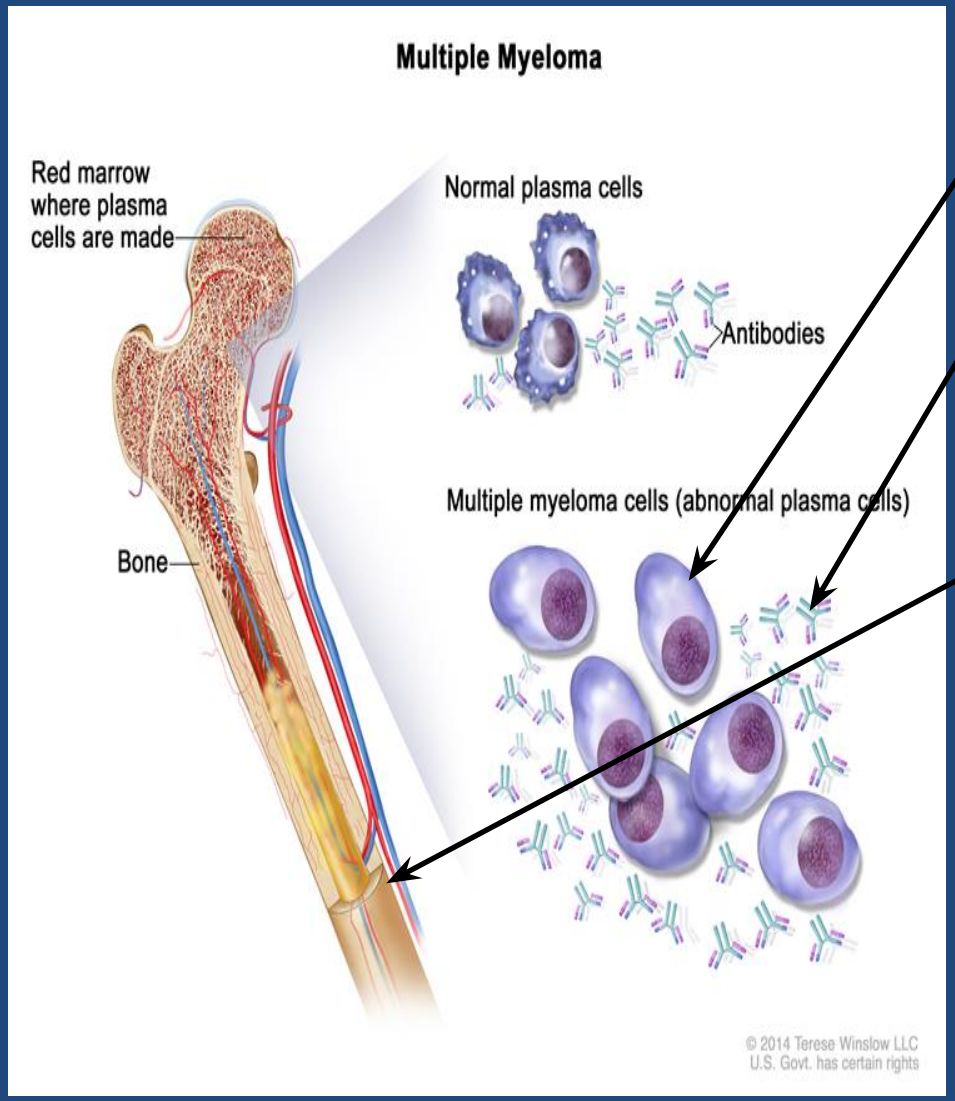
+ Recurrent infections



System affected	Symptoms[1]	Common cause(s)[1]
Blood	Fatigue, dizziness SOB, pallor.	Anemia, therapy
	Recurrent infections	Low uninvolved Ig, therapy
Kidneys	Nausea and vomiting	Renal failure, hypercalcemia
	Confusion and CNS symptoms	Renal failure, hypercalcemia
Bone/ spine	Bone pain	Pathologic fracture, cord compression
	Peripheral neuropathy	Nerve compression, amyloidosis, POEMS*, immune-mediated effects, therapy

- **CLINICAL PRESENTATION:**
  - Anemia : bone marrow replacement, dilutional or kidney damage.
  - Bone pain :
  - Elevated creatinine : light chain cast nephropathy (also called myeloma kidney) , hypercalcemia and amyloidosis
  - Fatigue/generalized weakness .
  - Hypercalcemia .
  - Weight loss .
- Extramedullary plasmacytoma. : plasma cell neoplasm of soft tissue without bone.

Workup for plasma cell disorders



Plasma cells: BMPC, plasmacytoma .biopsy, congo-red

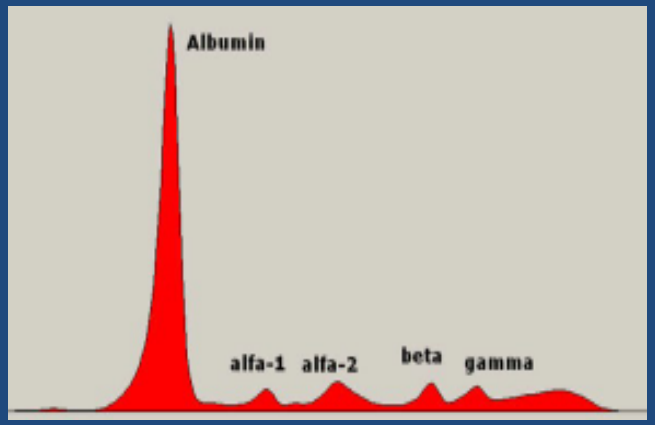
Secretions: SPEP, UPEP, SFLC, Ig levels

Calcium
Renal
Anemia
Bone → CBC, diff, BF, KFT, LFT

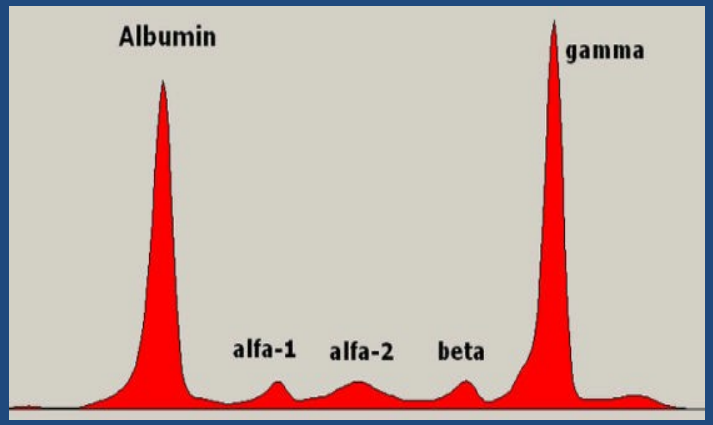
SKS, MRI, PET/CT .scan, BMD

.**Prognosis**: B2MG, albumin, LDH, ESR cytogentics, FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 ,amplification], PCLI

- **Monoclonal proteins:**



Normal SPEP

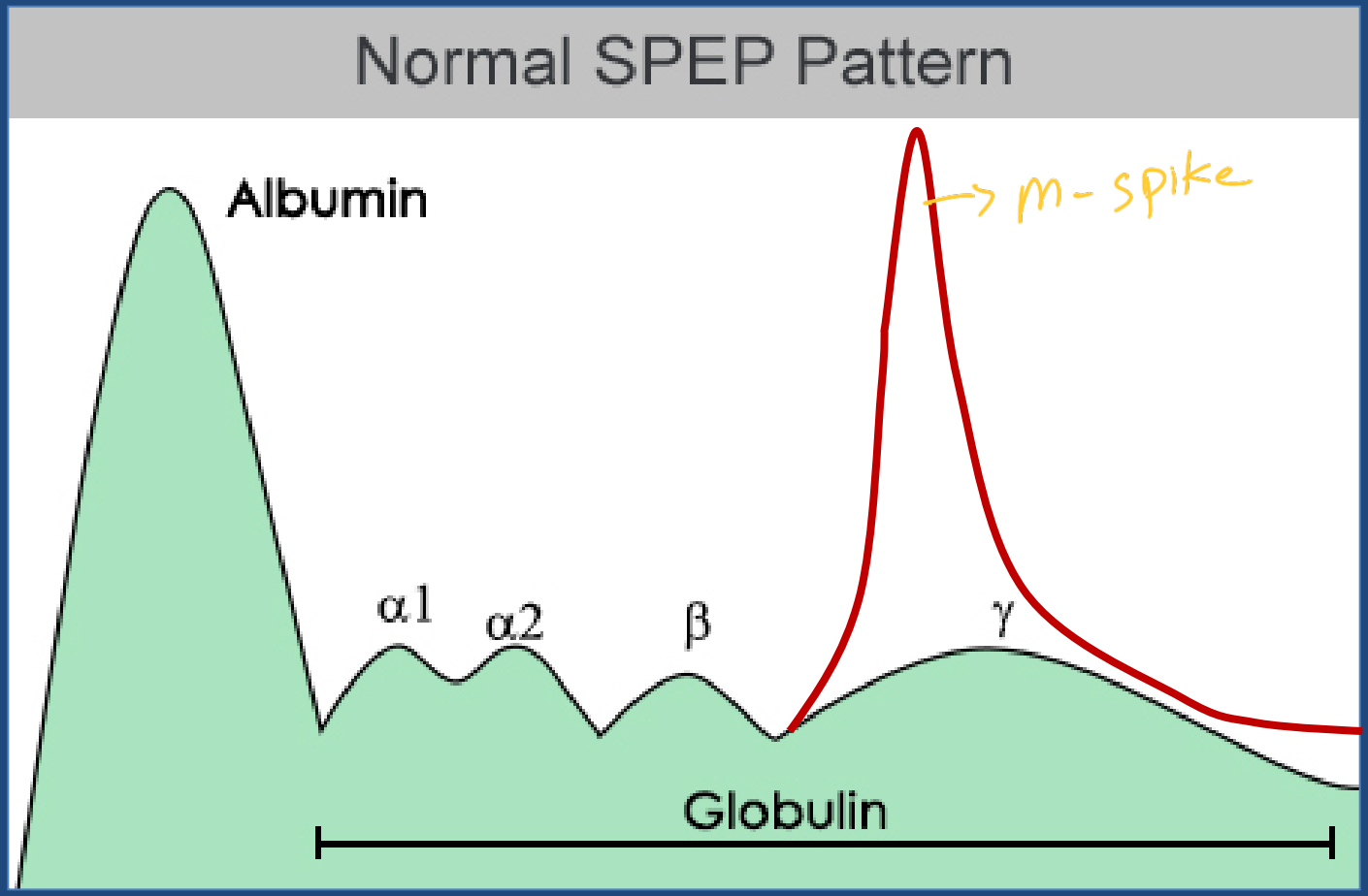


Abnormal SPEP showing
M-spike of myeloma (arrow)

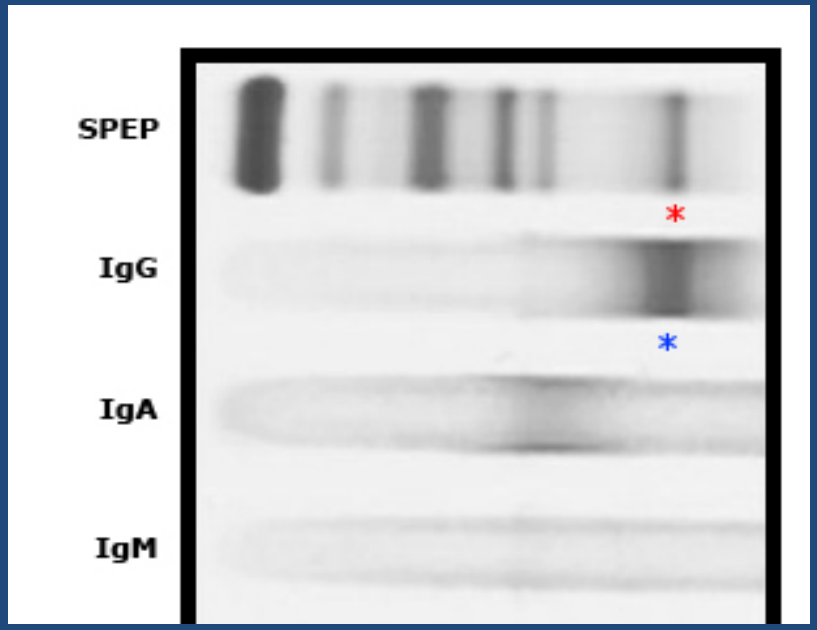
.Serum protein immunofixation
.Serum free light chain assay
Urine monoclonal protein studies (urine protein electrophoresis and urine .immunofixation)

.Light chain myeloma
.Non secretory myeloma

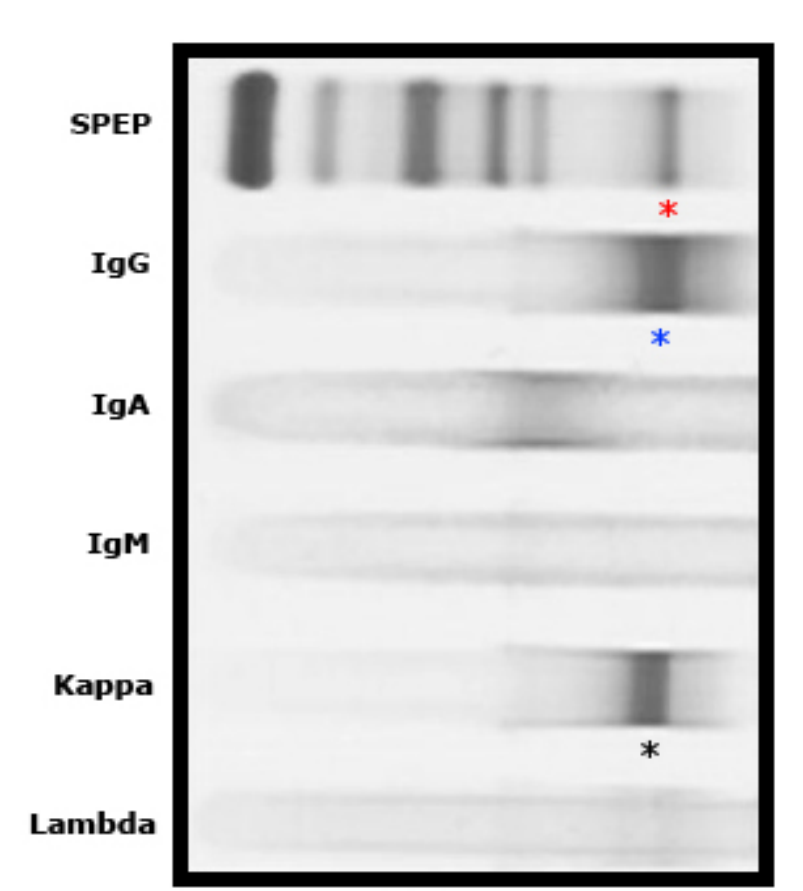
~~Normal SPEP~~



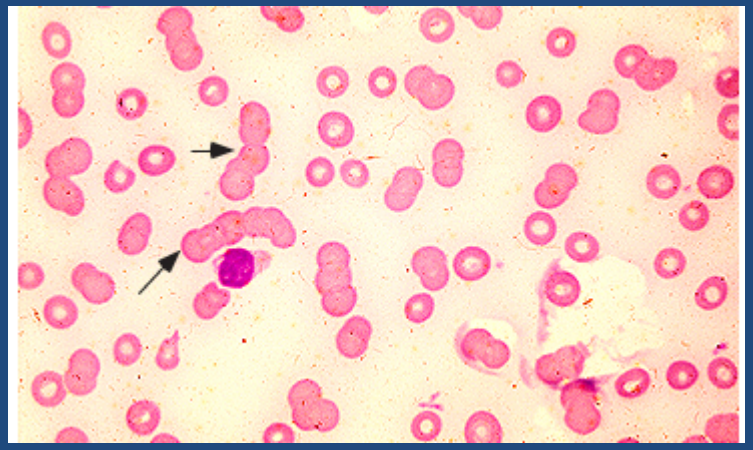
Immunofixation



Immunofixation → helps in identification of the type of secreted Igs.



- Other laboratory features:
- High ESR.
- Rouleaux formation: red cells take on the appearance of a stack of coins in diluted suspensions of blood



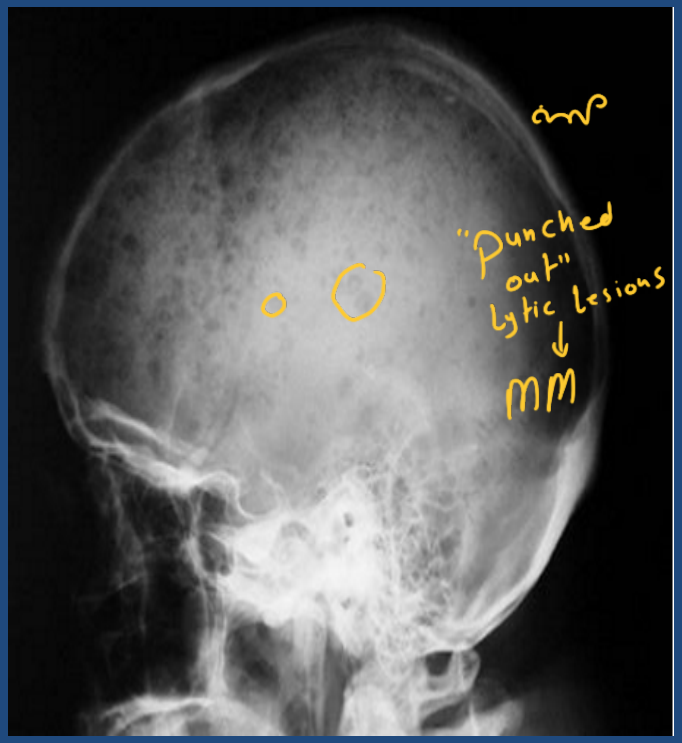
Immunoglobulins change the charge between RBCs.

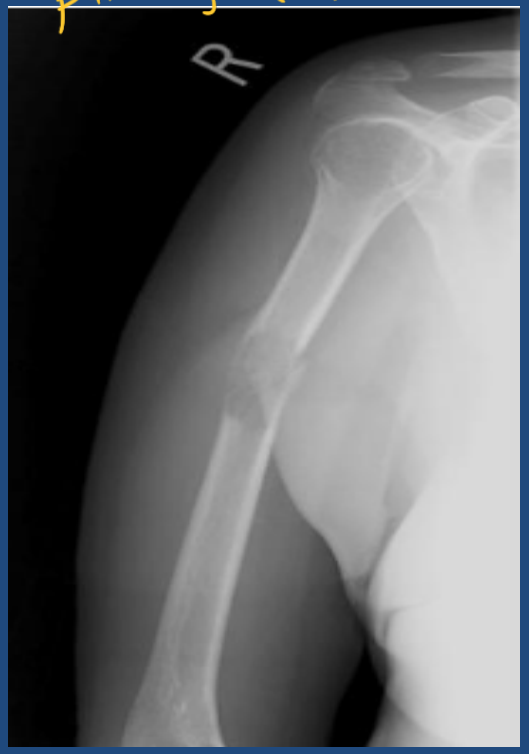
- Urine dipstick examinations primarily detect albumin, not light chains, which can be detected by sulfosalicylic acid or a 24-hour urine collection including electrophoresis and immunofixation.

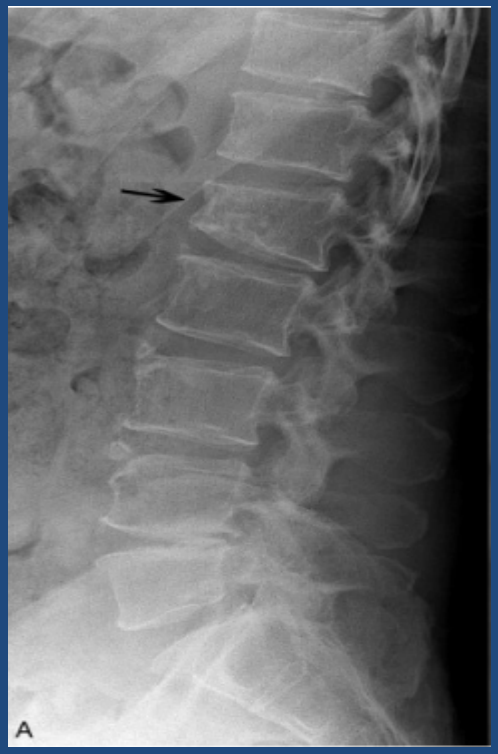
.Light chain myeloma

.Non secretory myeloma

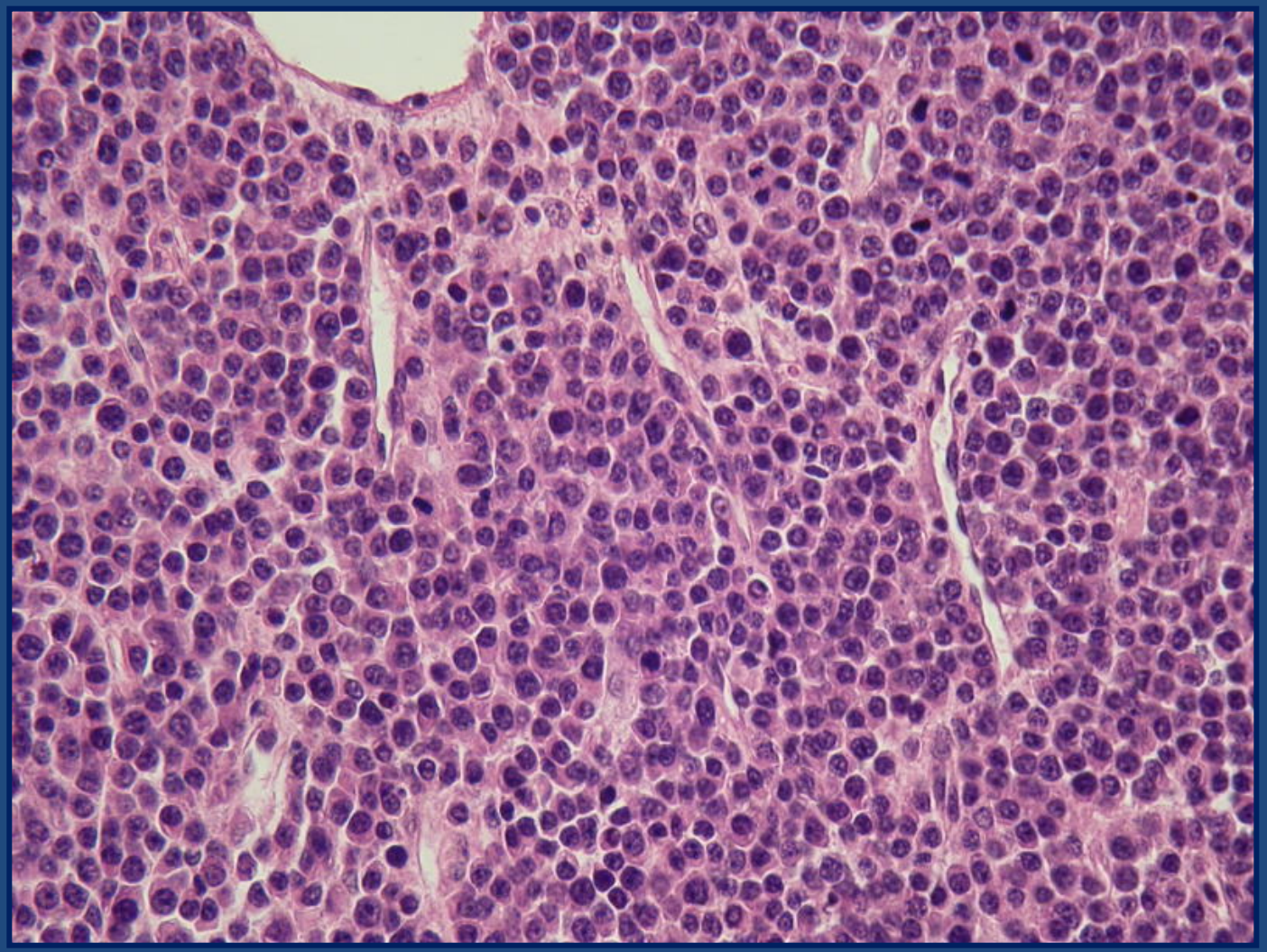
Bone disease



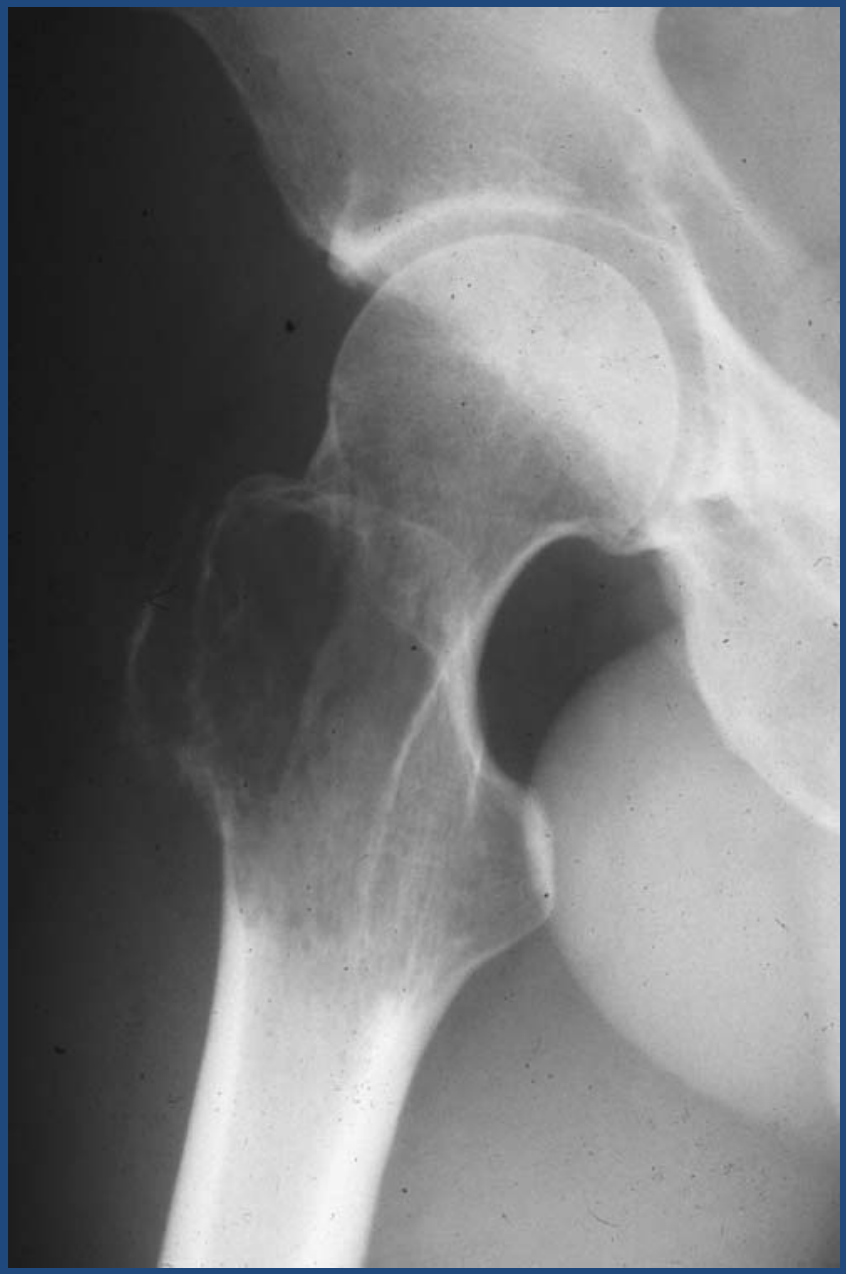




Plasmacytoma



Plasmacytoma



Differential diagnosis

V. imp

	Monoclonal gammopathy of undetermined significance (MGUS)	Asymptomatic (smoldering) myeloma	Symptomatic myeloma
Serum monoclonal protein	< 3g/dl	>3g/dl And/or	Presence of serum and/or urinary monoclonal protein
Clonal BM plasma cells	<10% (12 6-7% which is too much!)	≥10-60%	≥10%
End-organ damage	Absent	Absent	Present; Can be attributed to the underlying plasma cell proliferative disorder (CRAB symptoms)

C: Serum Calcium ≥11.5 mg/dL

R: Renal insufficiency: serum creatinine >2 mg/dL

A: Anemia: Hb <10 g/dL or 2 g/dL below normal

B: Bone lesions: lytic or osteopenic, or pathologic fractures

Diagnostic Criteria: MM

Multiple myeloma (all 3 criteria must be met)
• Presence of a serum or urinary **monoclonal protein**
• Presence of **clonal plasma cells** in the bone marrow or a plasmacytoma
• Presence of end organ damage felt related to the plasma cell dyscrasia, such as:
- Increased calcium concentration
- Renal failure
- Anemia
- Lytic bone lesions

Oh - cancerous condition, where the body makes an abnormal protein called M-protein

* Here, plasma cells make an abnormal type of Antibody called para protein (M-protein), this para protein does not do anything useful in the body.

MGUS: Diagnostic Criteria

(Monoclonal gammopathy of unknown significance)

- A monoclonal paraprotein band < 3 g/dL
- Plasma cells < 10% on bone marrow examination
- No evidence of end organ damage:
  - Hypercalcemia
  - Renal insufficiency
  - Anemia
  - Bone lesions

CRAB

- No evidence of another B-cell proliferative disorder.

MGUS Transformation

- MGUS occurs in over 3% of the general Caucasian population over the age of 50
- MGUS transformed into multiple myeloma or similar lymphoproliferative disorder at the rate of about 1-2% a year 1%
  - At 10 years: 17%
  - At 20 years: 34%
  - At 25 years: 39%

Diagnostic Criteria
Smoldering (asymptomatic) myeloma

Smoldering

(SMM, both criteria must be met)

- Serum monoclonal protein ≥3 g/dL and/or ≥10 % to <60% bone marrow clonal plasma cells
- No end organ damage related to plasma cell dyscrasia

New International Staging System		
		Median Survival
Stage	Criteria	months
I	Serum B_2-microglobulin <3.5 mg/L	62
	Serum albumin <3.5 g/dL	
II	Not stage I or III*	44
III	Serum B_2-microglobulin >5.5 mg/L	29

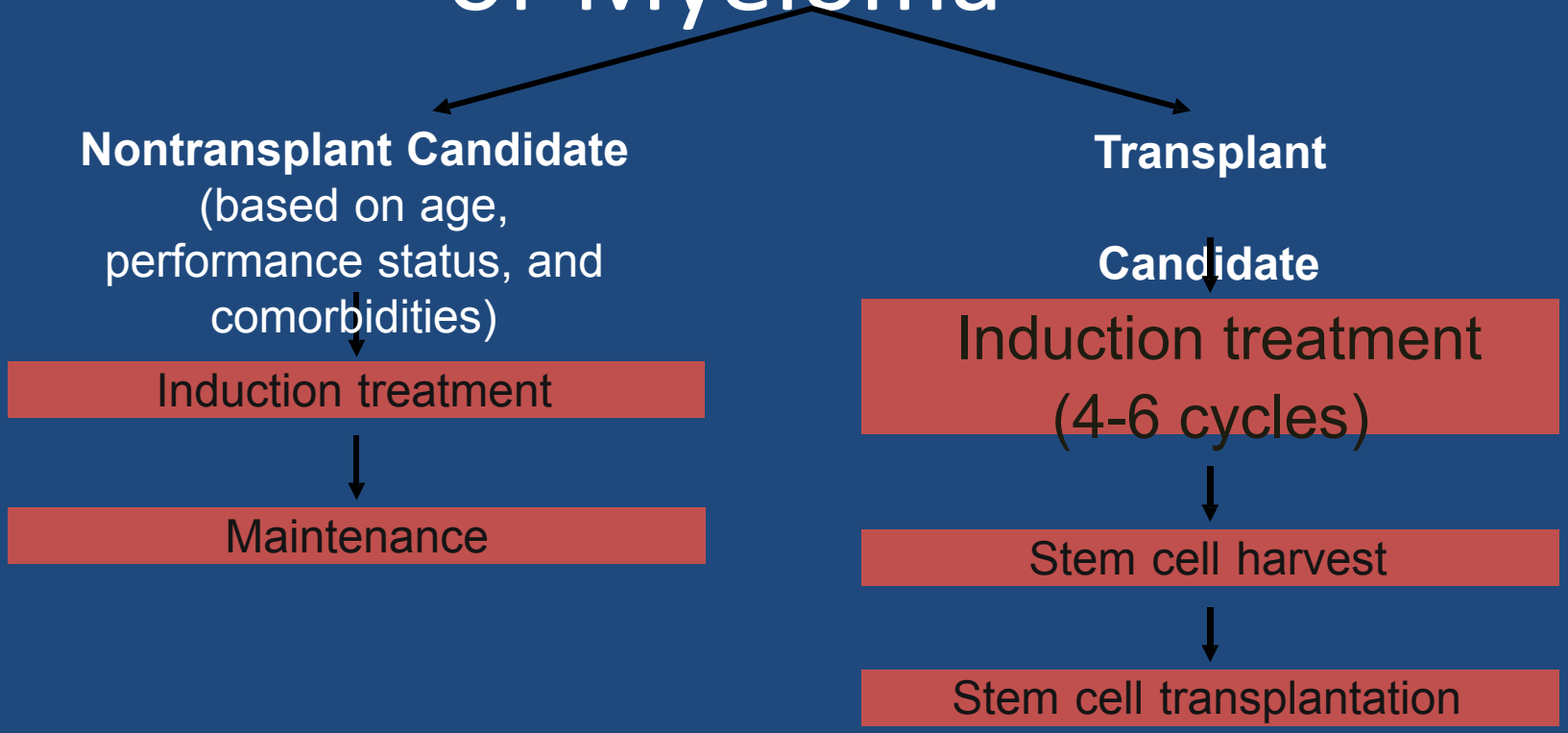
Cytogenetics

Often complex abnormalities:

- Hyperdiploidy (esp. odd number chromosomes)
- Translocations involving heavy chain gene e.g. t(4;14), t(14;16), t(14;20)
- Deletions 17p
- Amplification 1q, deletion 1p
- Del 13q
  - Originally seen as poor prognosis
  - Probably fellow traveller

Red= bad prognosis

Initial Approach to Treatment of Myeloma

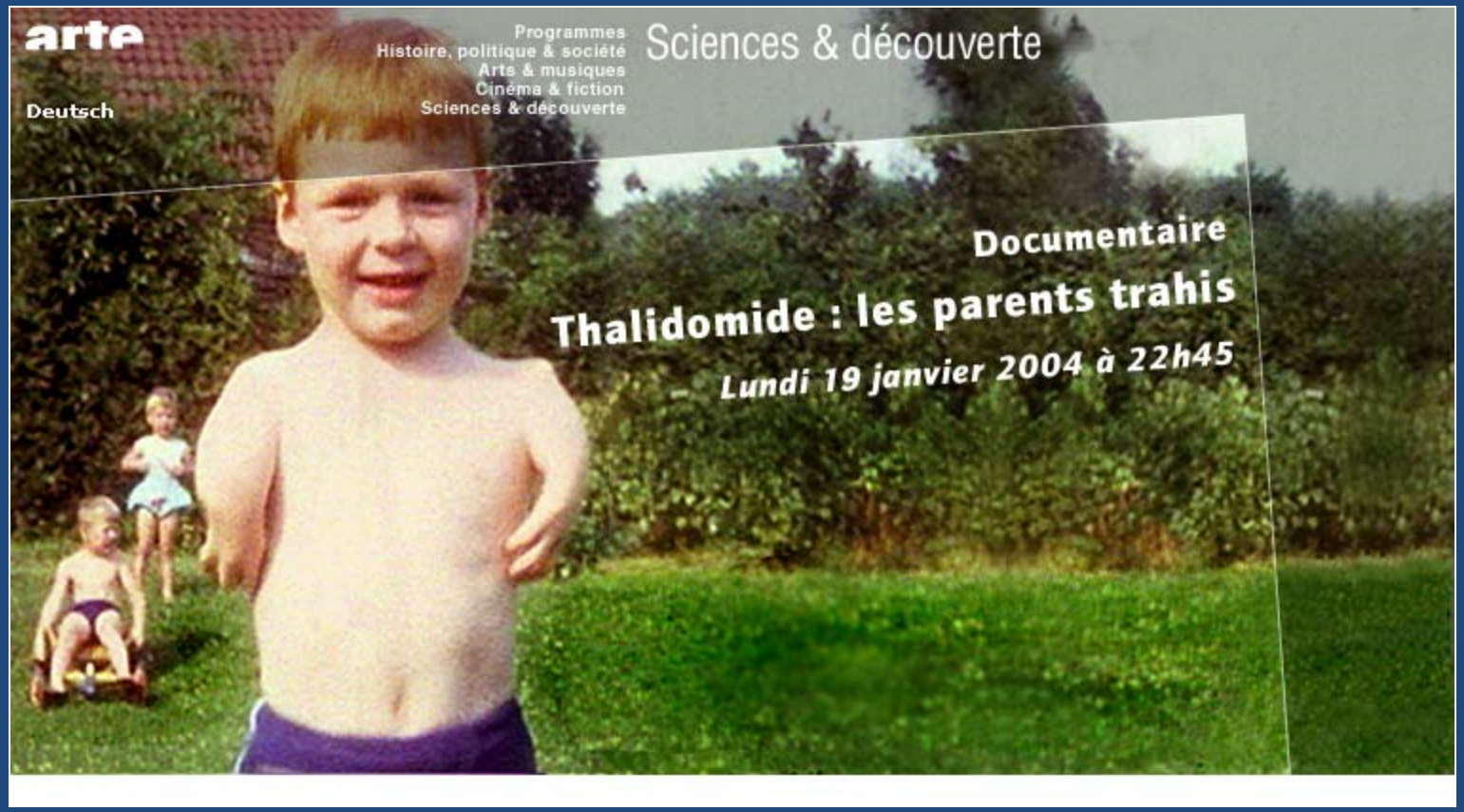


- Treatment:
  - Chemotherapy.
  - Steroids.
  - Novel agents: Bortezomib, tahlidomide, lenalidomide, carfilzomib ..etc.
- Bone health.
  - Bisphosphonates.
  - Vitamin D.

Thalidomide

- Was released into the market in 1957 in West Germany
- Primarily prescribed as a sedative or hypnotic
- Claimed to cure “anxiety, insomnia and tension
- Malformation of the limbs (phocomelia).

Phocomelia


arte
Deutsch
Programmes
Histoire, politique & société
Arts & musiques
Cinéma & fiction
Sciences & découverte
Sciences & découverte
Documentaire
Thalidomide : les parents trahis
Lundi 19 janvier 2004 à 22h45

Thalidomide

- Dermatologic:
  - Rash/desquamation (21% to 30%)
- Endocrine & metabolic: **hypocalcemia** (72%)
- Gastrointestinal:
  - **Constipation (3%-55%)**
  - Nausea (4% to 28%)
  - Anorexia (3% to 28%)
- Cardiovascular:
  - Edema (57%),
  - Hypotension (16%)
  - **Thrombosis/embolism (23%)**

Guidelines 2013

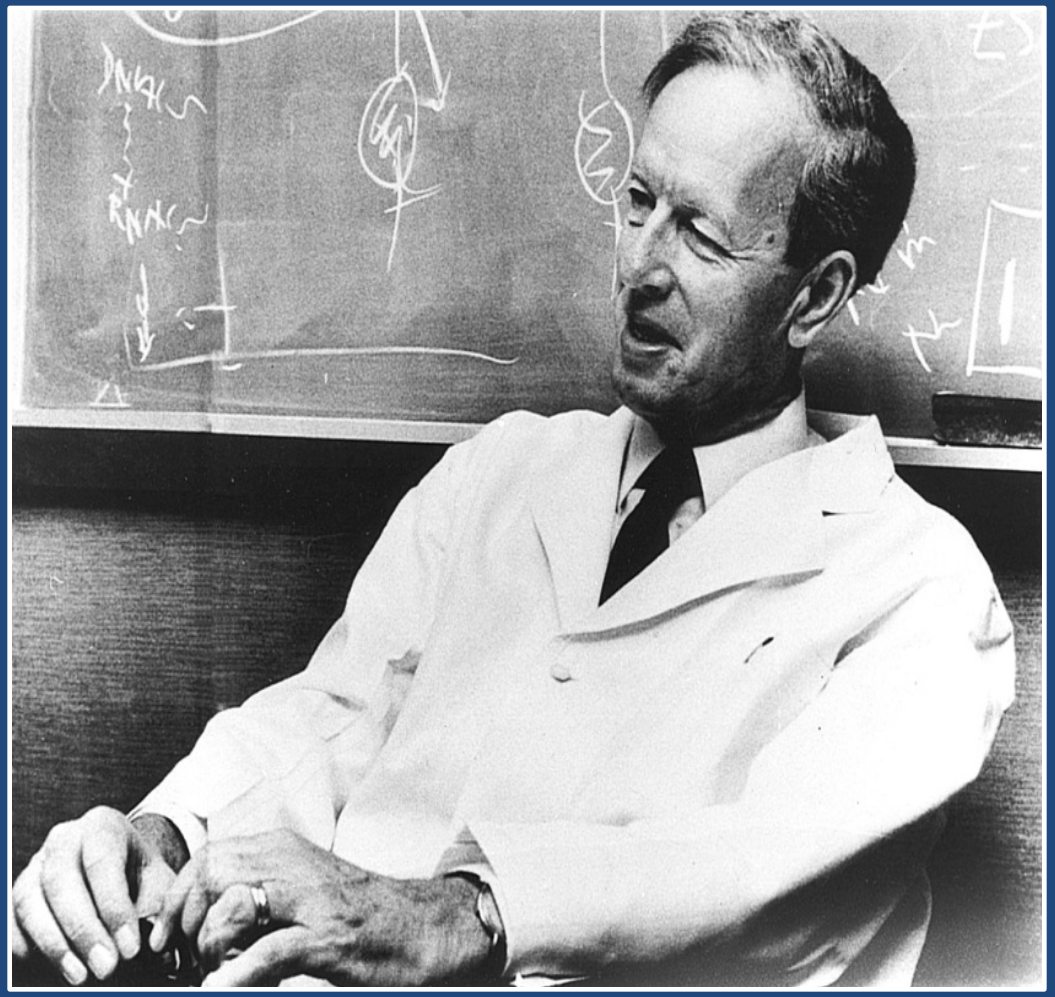
Thalidomide and Thrombosis

Recommendation 2.3

Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.

Lyman et al. JCO May 2013

Jan G. Waldenström, MD

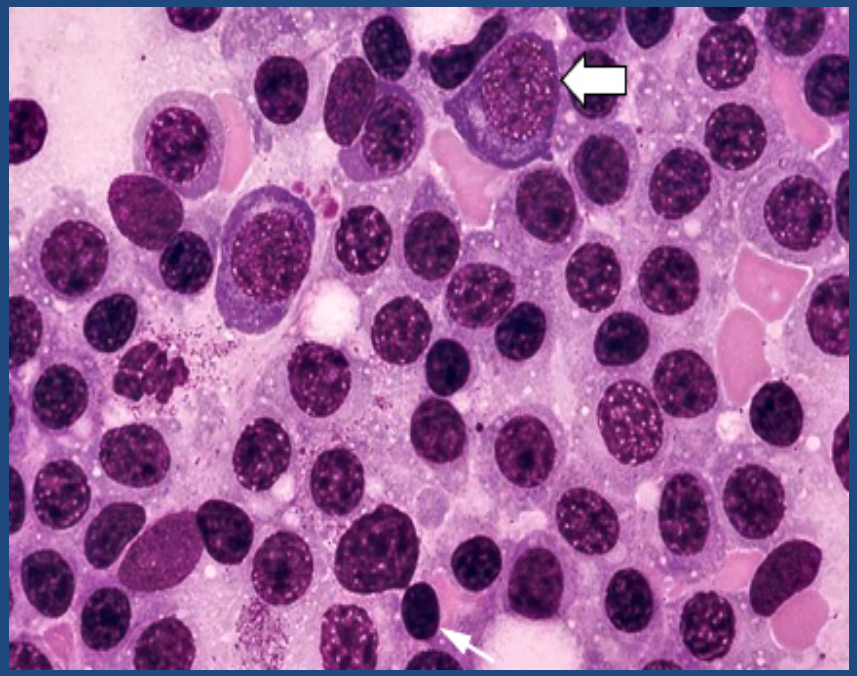


Waldenström J Acta Medica Scandinaviva 1944

Waldenström Macroglobulinemia

”A disease with two problems“

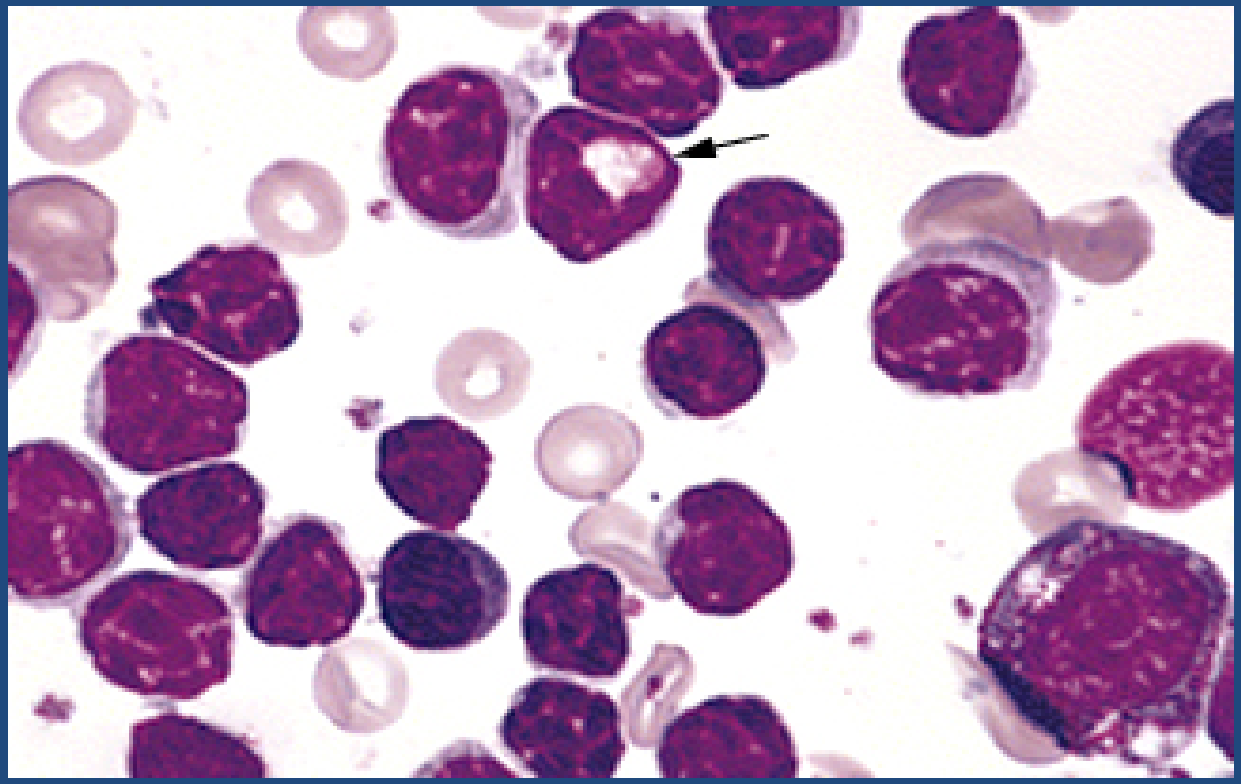
Waldenstrom



Lymphoplasmacytic infiltrate

Waldenström Macroglobulinemia

”A disease with two problems“



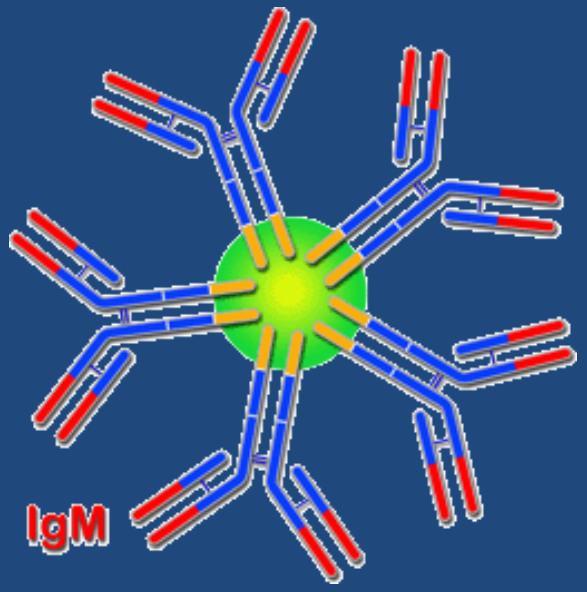
Dutcher bodies

Lymphoplasmacytic infiltrate

- Immunophenotype:
  - Surface IgM+, CD19+, CD20+, CD79a+
  - CD5−, CD10−, CD23−.
- Exclude CLL and mantle cell lymphoma

Waldenström Macroglobulinemia

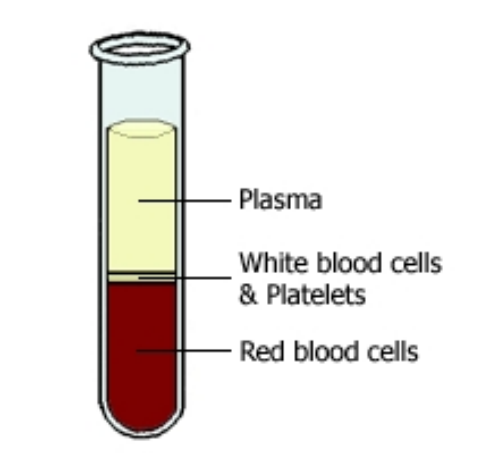
”A disease with two problems“

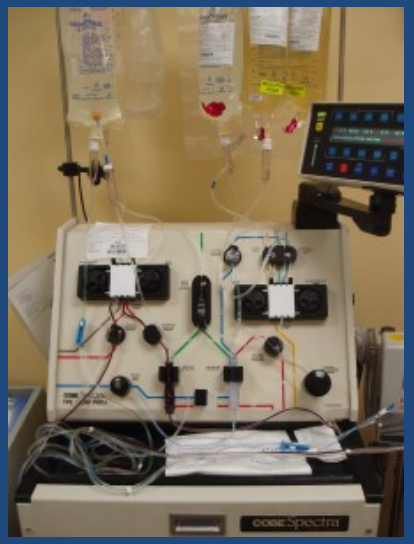


Monoclonal IgM protein

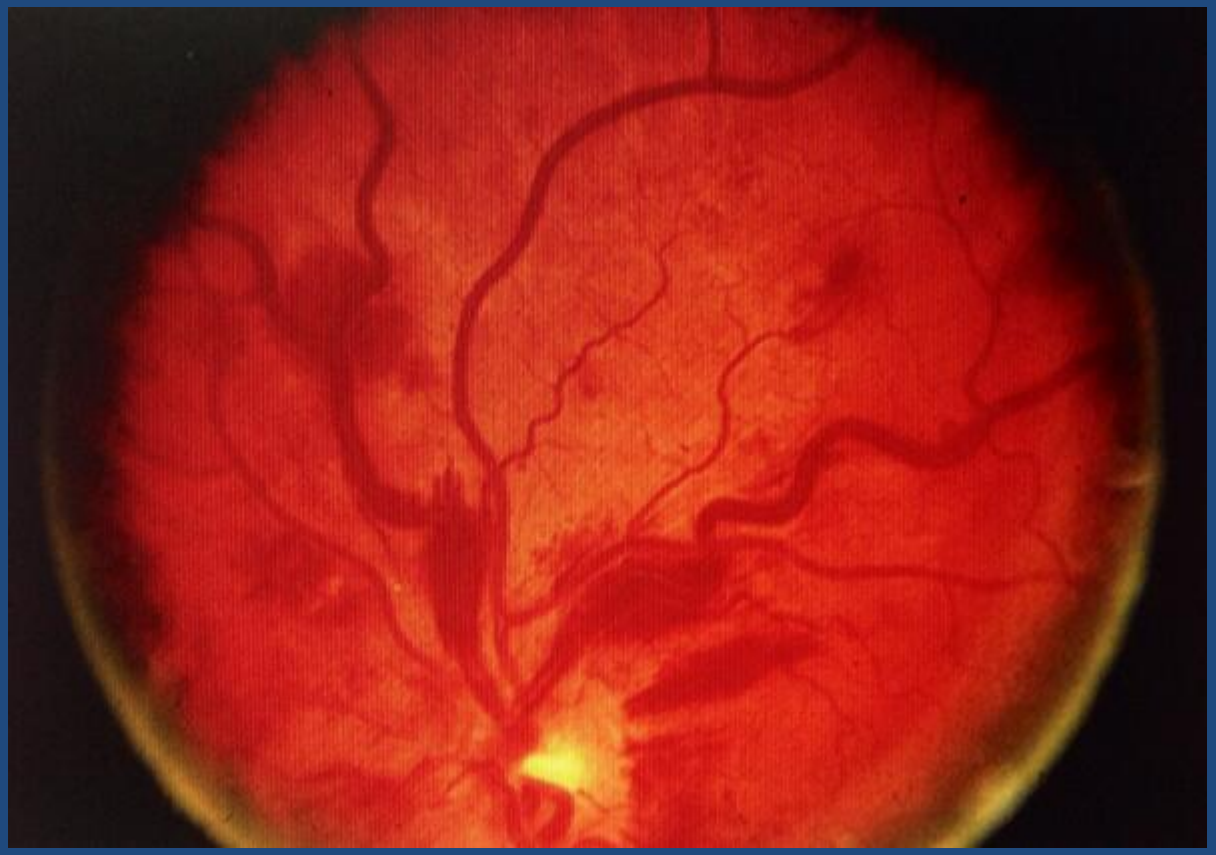
Plasma Viscosity

- Plasma viscosity can be measured in some labs
  - Normal plasma 1.4-1.8 x water
  - Normal blood ~3 x water

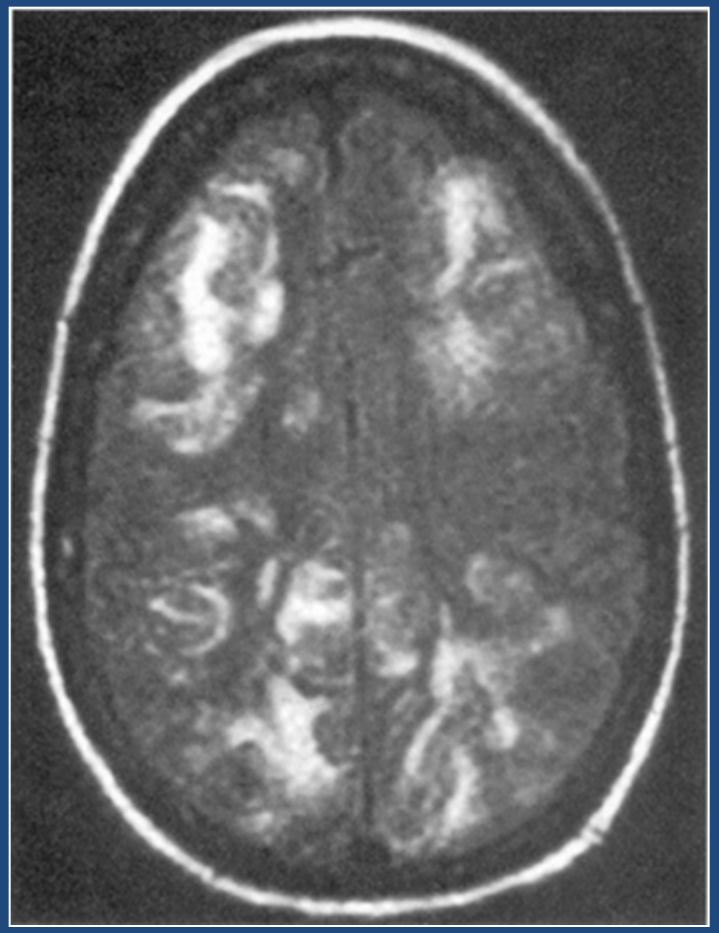




WM: Hyperviscosity



WM: Hyperviscosity



WM: Presenting symptoms

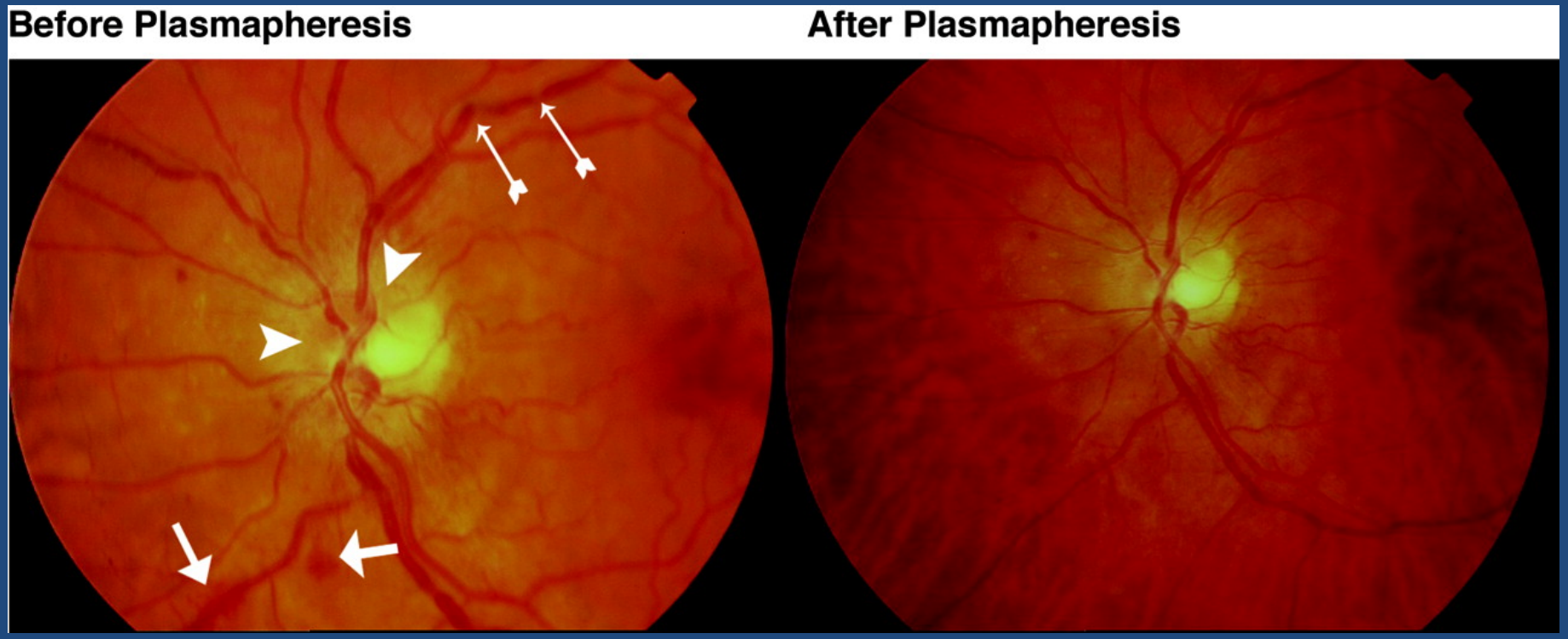
- 217 patients with serum monoclonal IgM protein ≥ 3 g/dl and > 20% bone marrow involvement -
  - Asymptomatic (27%)
  - Anemia (38%),
  - Hyperviscosity (31%),
  - B symptoms (23%),
  - Bleeding (23%)
  - Neurological symptoms (22%)

Plasmapheresis for WM

- Symptoms of hyperviscosity:
  - Visual deterioration
  - Neurological symptoms
  - Bleeding

- Rarely seen with IgM <4g/dL.

Efficacy of Plasmapheresis



Before plasmapheresis - optic disc edema (arrowheads), central retinal hemorrhages .(bold arrows), and venous “sausaging” (thin arrows)

Multiple myeloma: MM

3 criteria to diagnose MM

1. ↑ serum monoclonal protein
2. ↑ Bone marrow plasma cells
3. CRAB symptoms

* **Clinical picture**

- CRAB
  - C → Hypercalcemia
  - R → AKI
  - A → Anemia
  - B → Bone pain
- Recurrent infections

Investigations

- Roulex formation in BF
- ↑ serum protein
- M-spike on SPEP
- "punched out" Lytic lesions on x-ray.
- t(4,14), Deletion 17p

MGUS	Smoldering myeloma	MM (Monoclonal antibodies)
- < 3 g/dL	- > 3 g/dL	
- < 10% plasma cells	- 10-60%	
- No CRAB	- N CRAB	CRAB or part of it present.