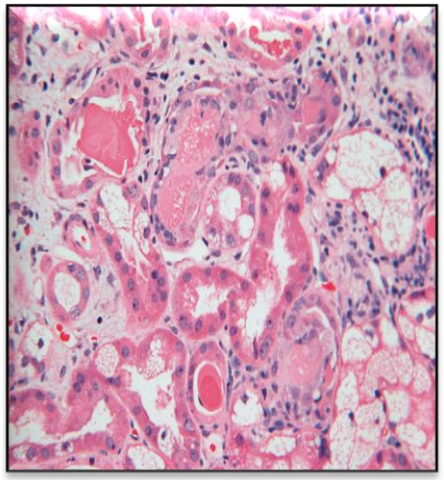
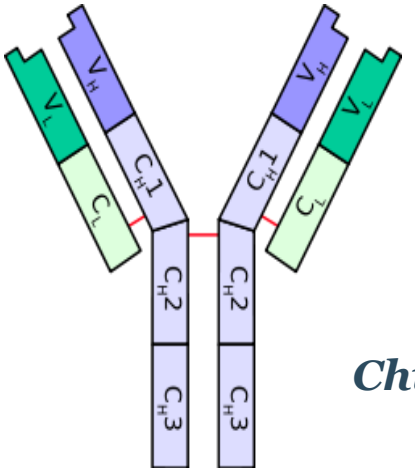
The Egyptian Society of Nephrology & Transplantation

The Kidney in Multiple Myeloma

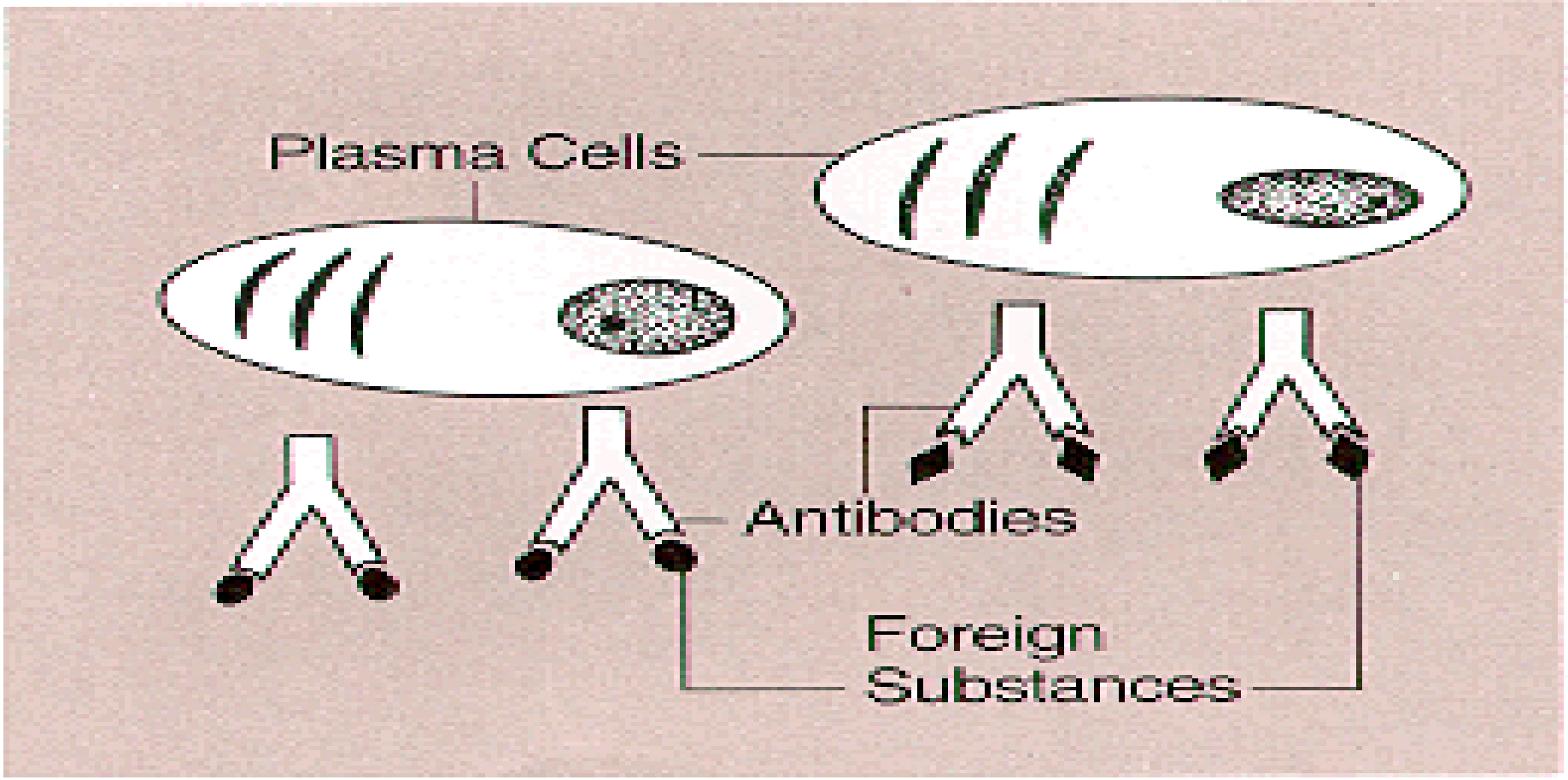




Tarek ElBaz, MD.

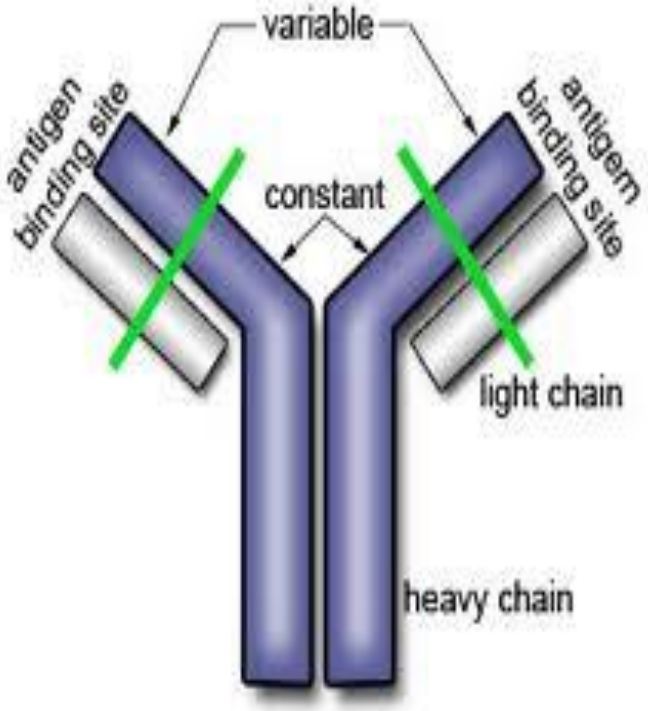
Prof. Internal Medicine
Chief, Division of Renal Medicine
Al Azhar University
President, ESNT

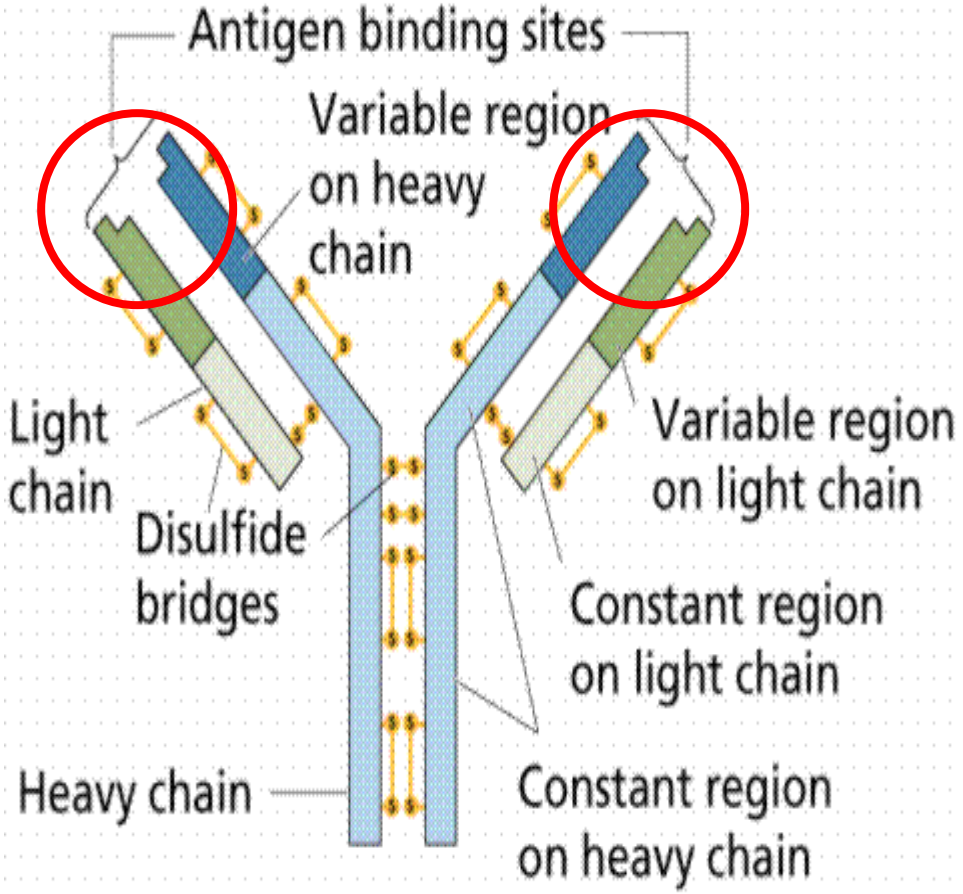
Normal Cell



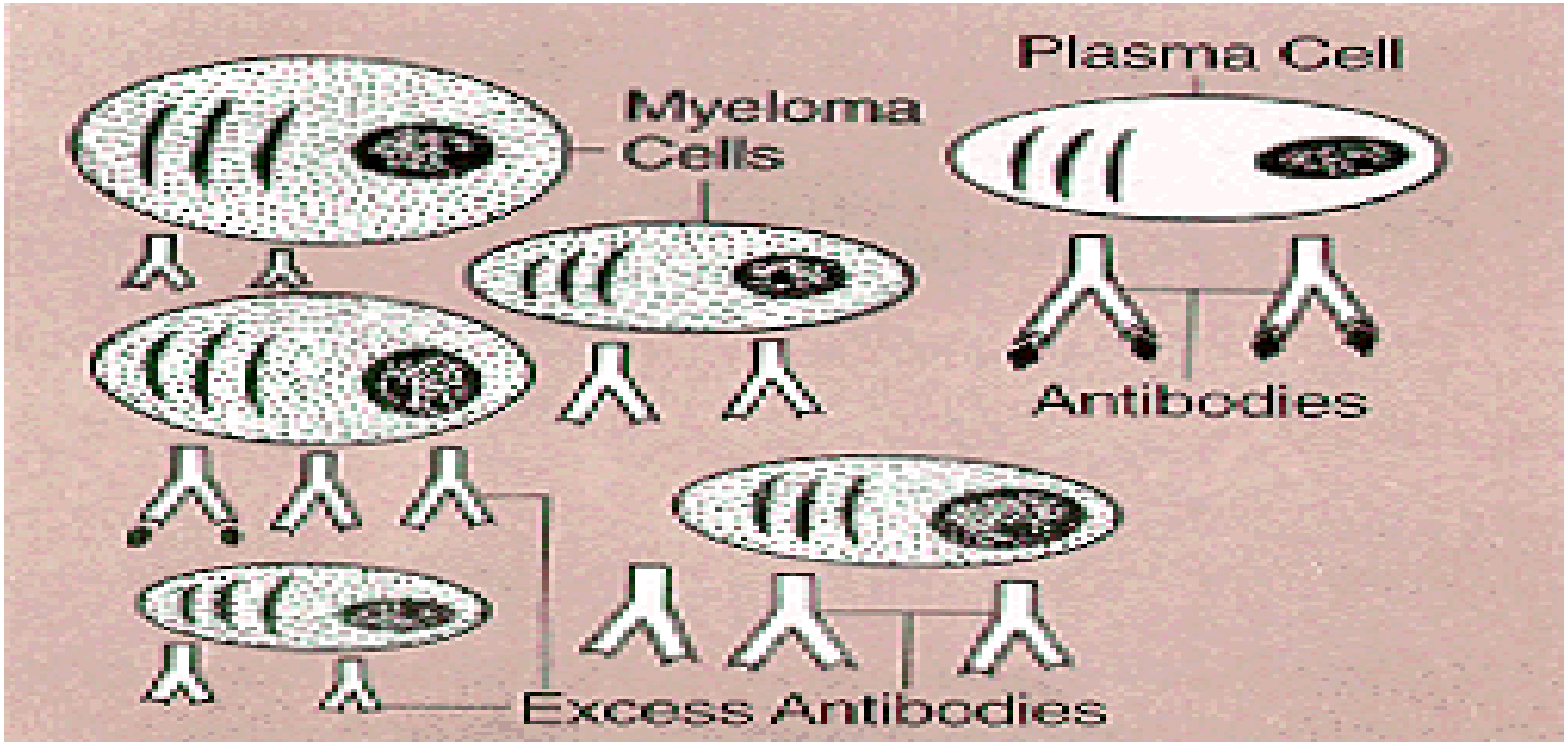
Plasma cells produce antibodies that bind to antigens, fighting infection and at times causing disease.

Antibodies


variable
antigen binding site
constant
antigen binding site
light chain
heavy chain


Antigen binding sites
Variable region on heavy chain
Light chain
Disulfide bridges
Variable region on light chain
Constant region on light chain
Heavy chain
Constant region on heavy chain

Myeloma Cells

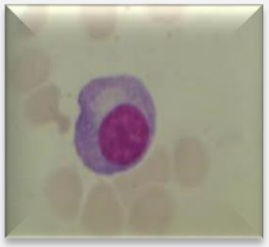


In multiple myeloma, a malignant transformation occurs producing myeloma cell.
These cells produce antibodies in excess.

Multiple Myeloma

- Definition: Malignant proliferation of plasma cells derived from a single clone

- MM is a plasma cell dyscrasia that accounts for almost 10% of all hematologic malignancies



- Etiology: radiation; mutations in oncogenes; familial causes; role of IL 6

- Incidence increases with age Males> females ; Blacks > Whites

Kyle et al. Cancer 101 : 2667–2674, 2004
Korbet & Shawartz. JASN **September 2006** vol.

Clinical Manifestations

Bone Pain:

- 70%, precipitated by movement
- Pathological fractures
- Activation of osteoclasts by OAF produced by myeloma cells

Susceptibility to infections:

- Diffuse hypogammaglob. If the M spike is excluded
- Poor antibody responses, neutrophil dysfunction
- Pneumococcus, S. aureus: Pneumonia, pyelonephrits

Rajkumar. Et al., Mayo Clin Proc 80 : 1371–1382, 2005

Clinical Manifestations

Common

- Bone pain and pathological fractures
- Anemia and bone marrow failure
- Infection due to immune-paresis and neutropenia
- Renal impairment

Less common

- Acute hypercalcemia
- Symptomatic hyperviscosity
- Neuropathy
- Amyloidosis
- Coagulopathy

Clinical Manifestations

Renal failure: 25%

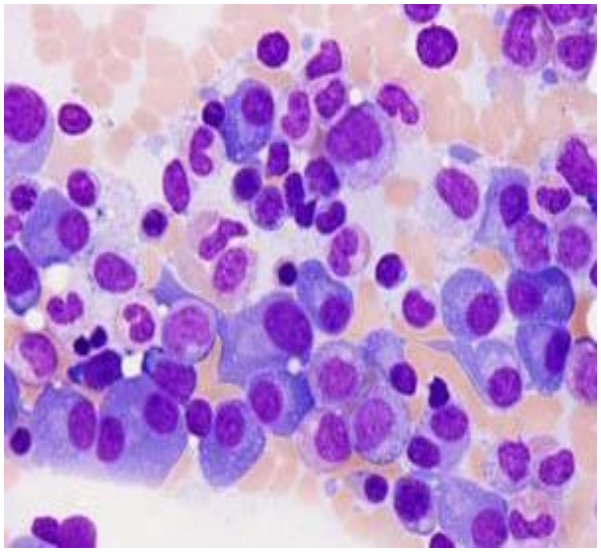
- Multiple contributory factors
- Hypercalcemia, hyperuricemia, recurrent infections
- Tubular damage produced by Light chains
- type 2 proximal RTA, non selective proteinuria

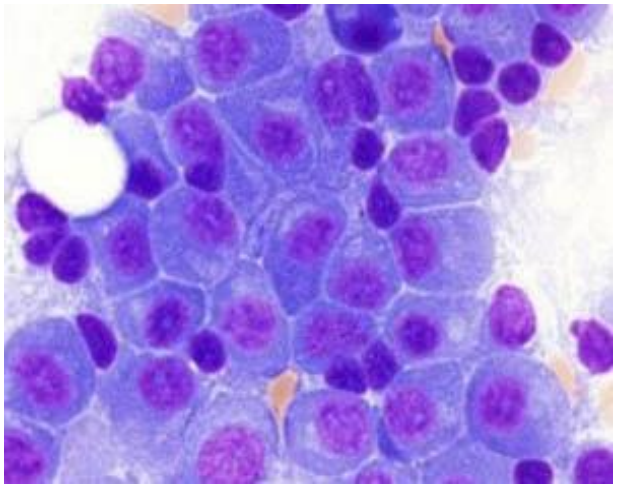
Anemia: 80%

- Normochromic/normocytic
- Myelophthisis: inhibition by cytokines produced by plasma cells.
- Leukopenia/thrombocytopenia only in advanced cases.

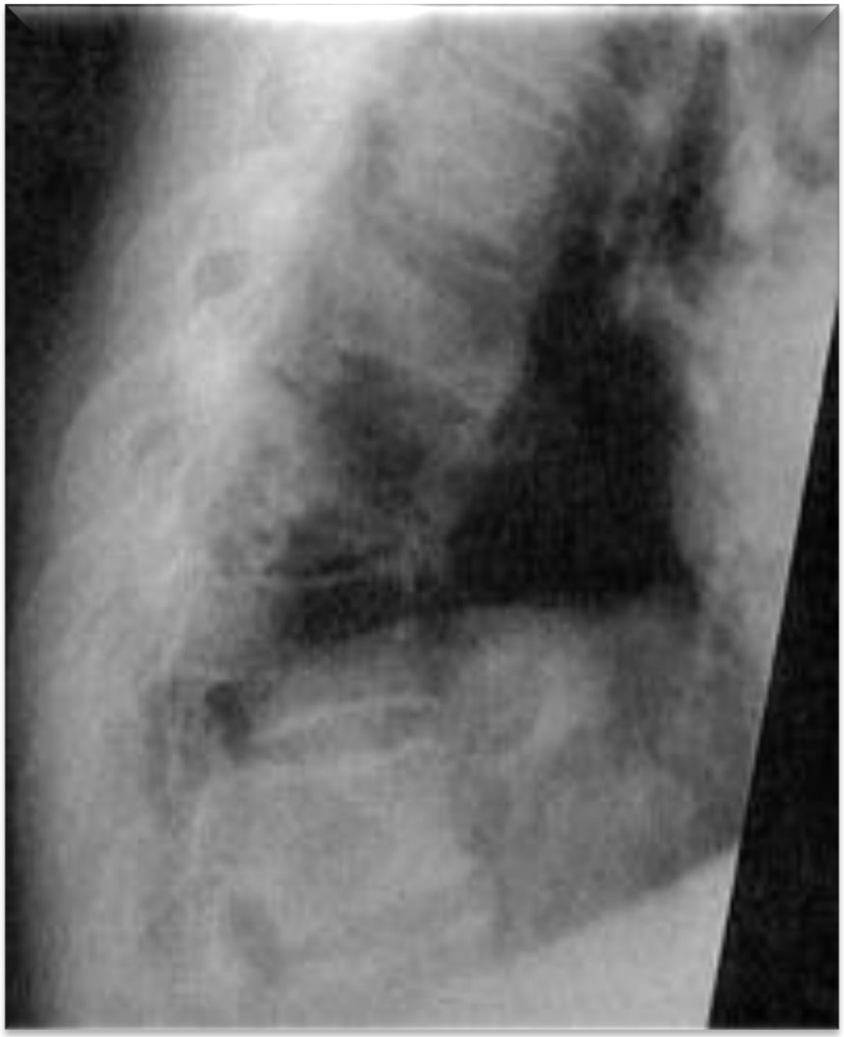
Bone Disease

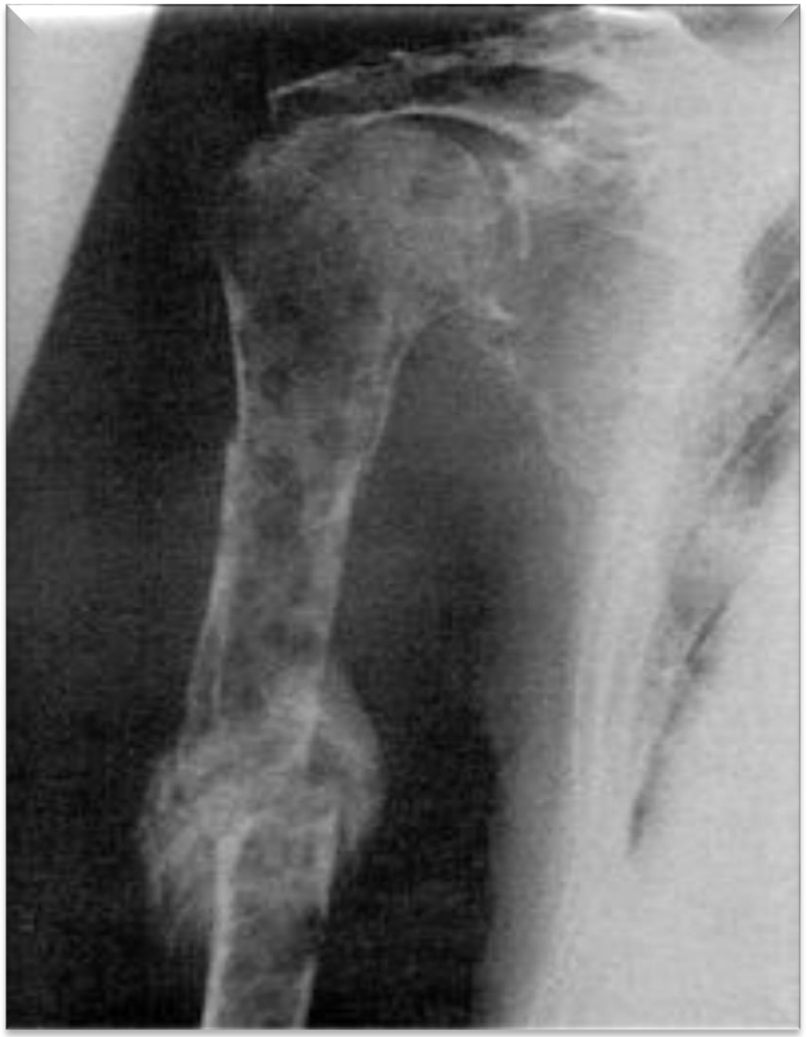
- Lytic lesions – 60%
- Osteoporosis, Fx, compression Fx – 20%
- Myeloma cells produce Cytokines that:
  - Stimulate osteoclastic activity
  - Inhibit osteoblastic Activity

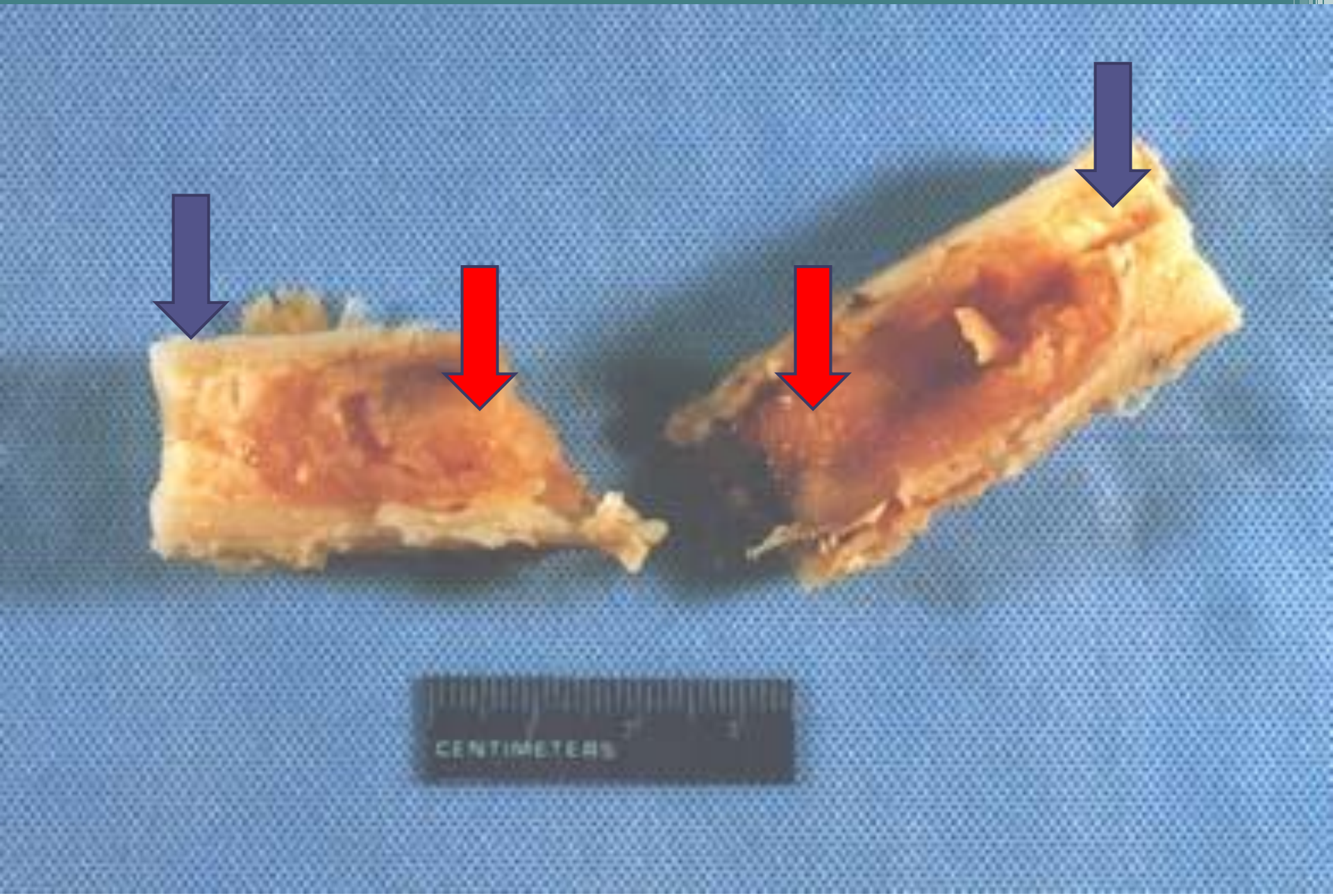




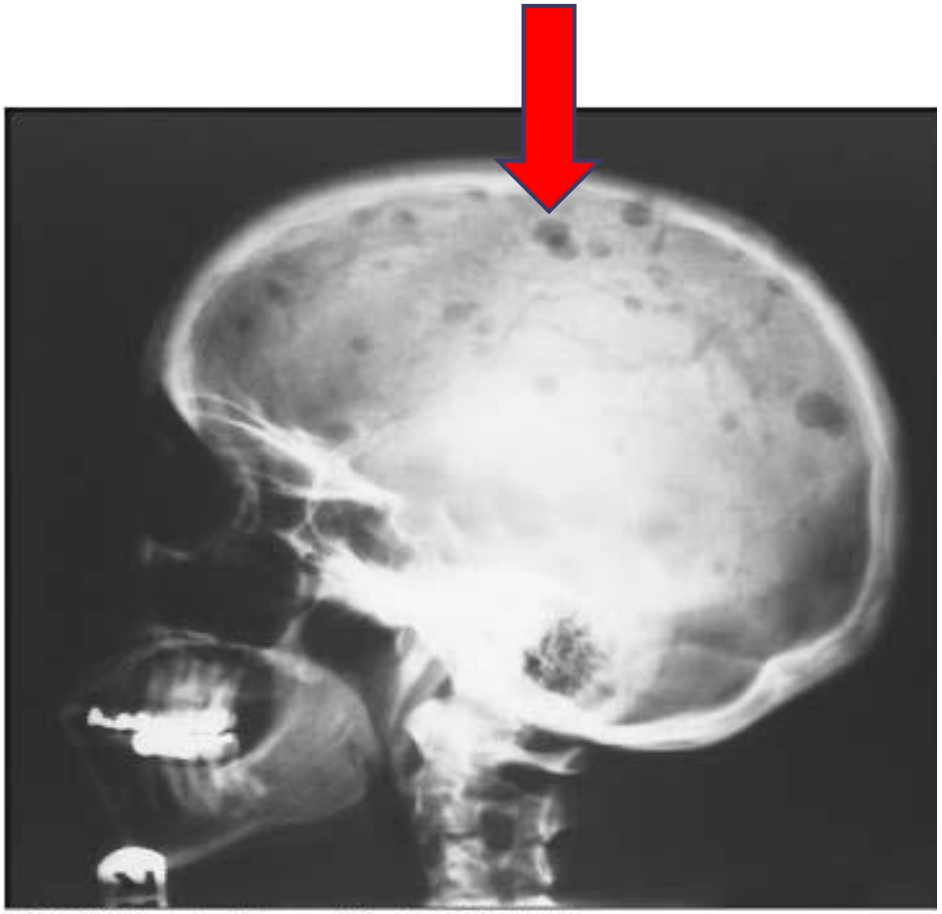
70% cellularity, increased atypical plasma cells comprising 60% of cellularity.






CENTIMETERS

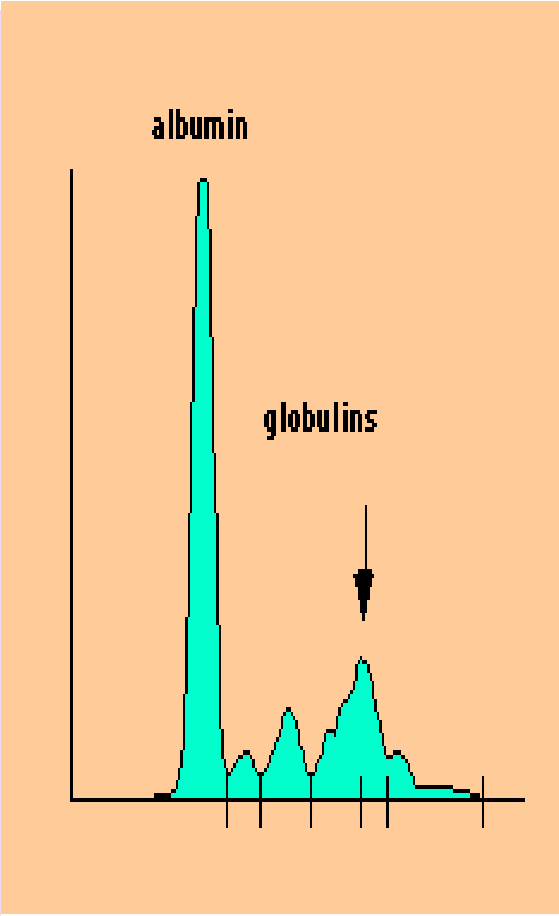
Skull infiltrations



Minimal diagnostic criteria for myeloma

- >10% Plasma cells in bone marrow or plasmacytoma on biopsy
- Clinical features of myeloma

- Plus at least one of:
  - *Serum M band (IgG >30 g/l; IgA >20 g/l)*
  - *Urine M band (Bence Jones proteinuria)*
  - *Osteolytic lesions on skeletal survey*



Myeloma and The kidney

Etiology of Renal Injury and Clinical Manifestations

	Cause	Manifestation
Prerenal		
Volume depletion	Hypercalcemia	Polyuria and polydipsia
	Gastrointestinal losses (nausea and vomiting)	Hypotension
	Sepsis	Fever
Hemodynamic	Hemodynamic from NSAIDs	Oliguria, hyperkalemia
Other	Hyperviscosity (IgA, IgG_3)	Mental state alterations
	Hyperuricemia	Tumor lysis
Renal	Proximal tubular injury from light chains, urate; distal tubular injury from casts	Fanconi syndrome Tubular proteinuria Crystalluria
	Glomerular disease (LCDD, amyloid)	Nephrotic proteinuria Hematuria, active sediment
Post Renal	Calculi	Colic

Epidemiology

- Serum creatinine > 1.5 -2.0 mg/dl
- The one-year survival is 80% in pts. with Cr < 1.5 compared to 50% in pts. with a Cr > 2.3
- Prognosis is especially poor in pts. who require dialysis

Causes of renal failure in MM

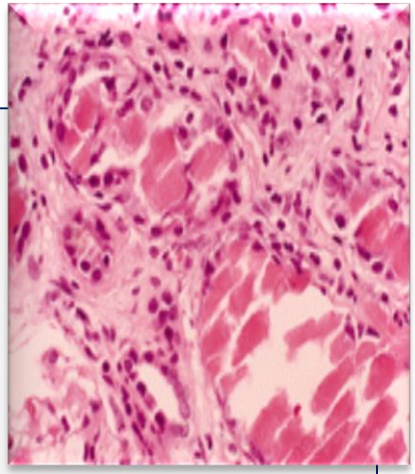
- Cast nephropathy
- Light chain deposition disease
- Primary amyloidosis
- Hypercalcemia
- Renal tubular dysfunction
- Volume depletion
- IV contrast dye, nephrotoxic medications

Renal Pathology in Patients with Multiple Myeloma

Histological Finding	Prevalence
Myeloma kidney *(Myeloma cast nephropathy)*	30%-50%
Interstitial nephritis/fibrosis without cast nephropathy	20%-30%
Amyloidosis	10%
Light chain deposition disease	5%
Acute tubular necrosis	10%
Other (urate nephropathy, tubular crystals, hypercalcemia, FSGS)	5%

Start et al., Am J Physiol. 1998;275:F246-F254.

Myeloma Kidney



Two main pathogenetic mechanisms:

- *Intracellular cast formation*
- *Direct tubular toxicity by light chains*

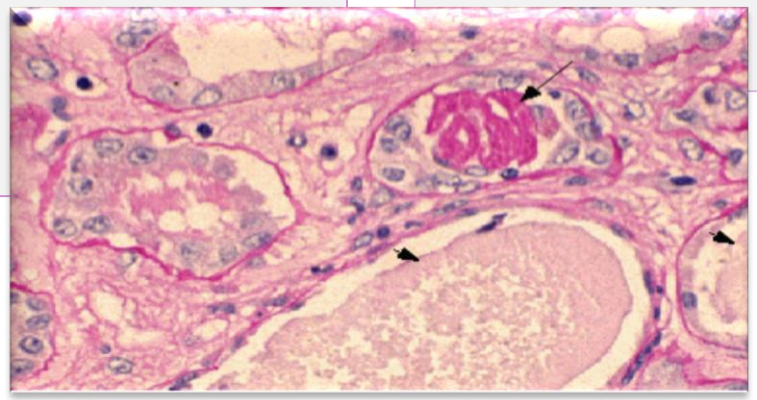
Contributing factors to presence of renal failure due to multiple myeloma:

- *High rate of light chain excretion (tumor load)*
- *Biochemical characteristics of light chain*
- *Concurrent volume depletion*

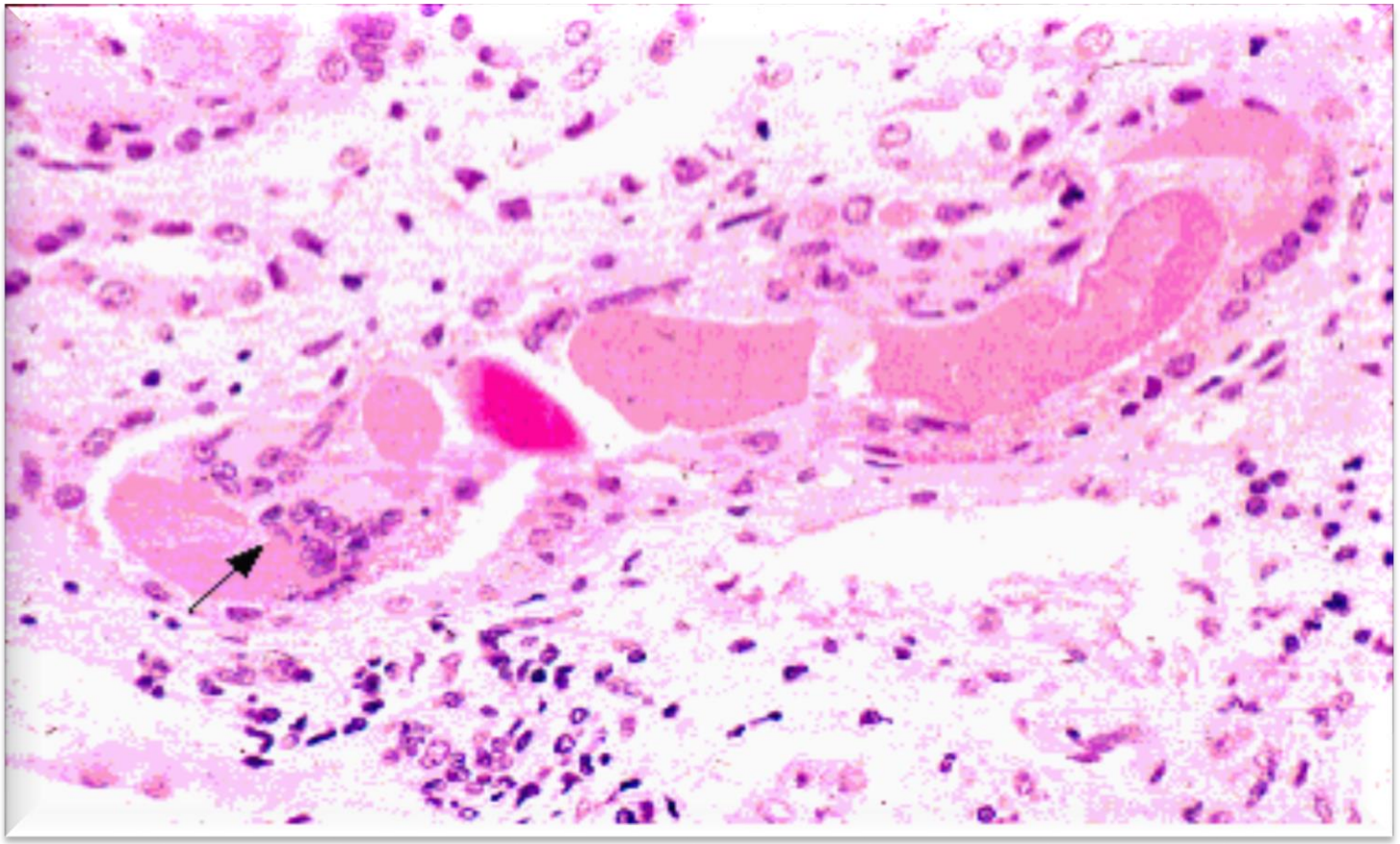
Cast Nephropathy

- Most common pathological diagnosis on renal biopsy in multiple myeloma
- Due to light chains binding with Tamm-Horsfall mucoprotein, which is secreted by tubular cells in ascending loop of Henle, forming casts

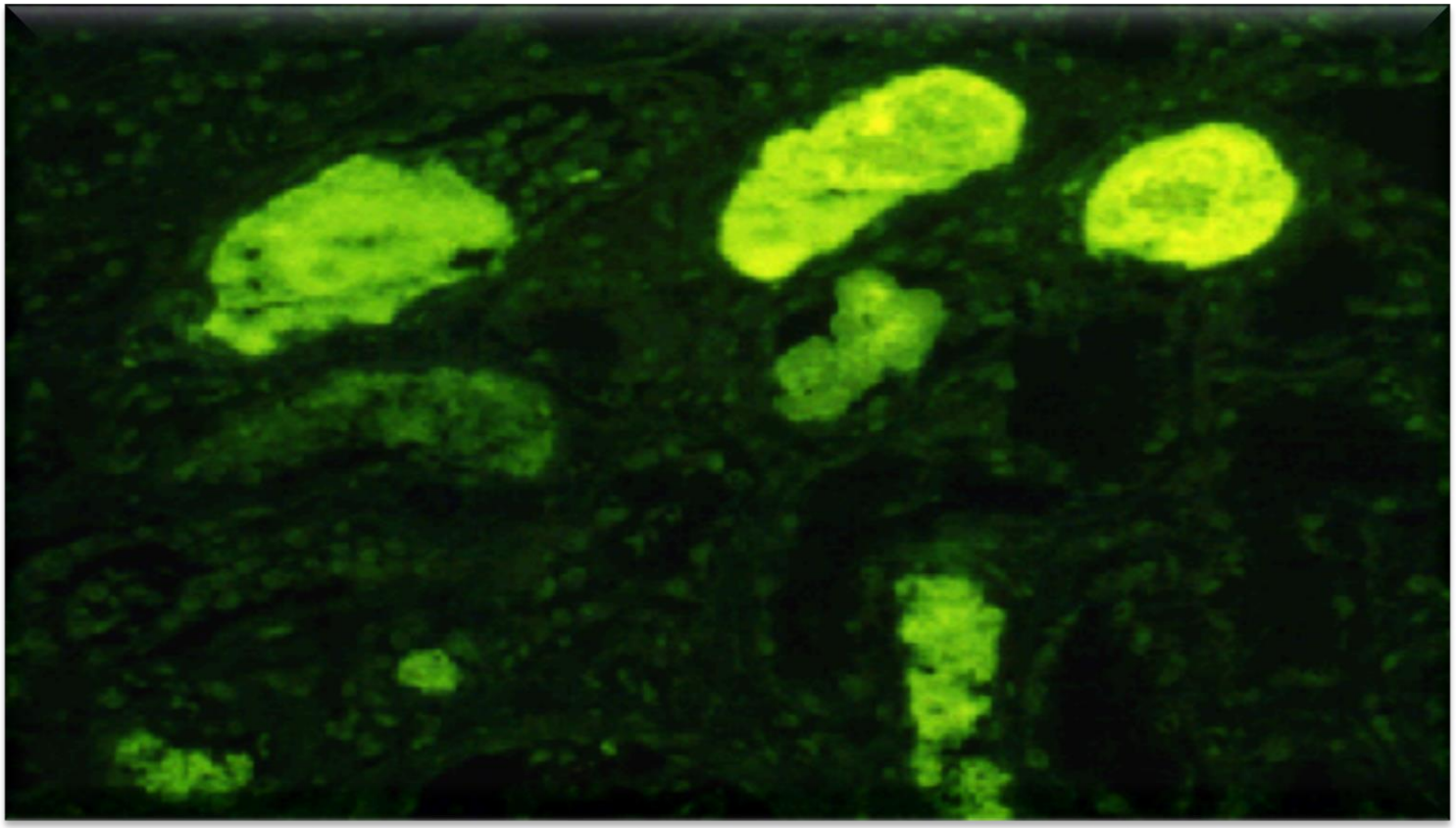
- Multinucleated giant cells surround the casts
- Dehydration worsens cast nephropathy due to decreased flow in tubules, increased concentration of light chains



Cast Nephropathy



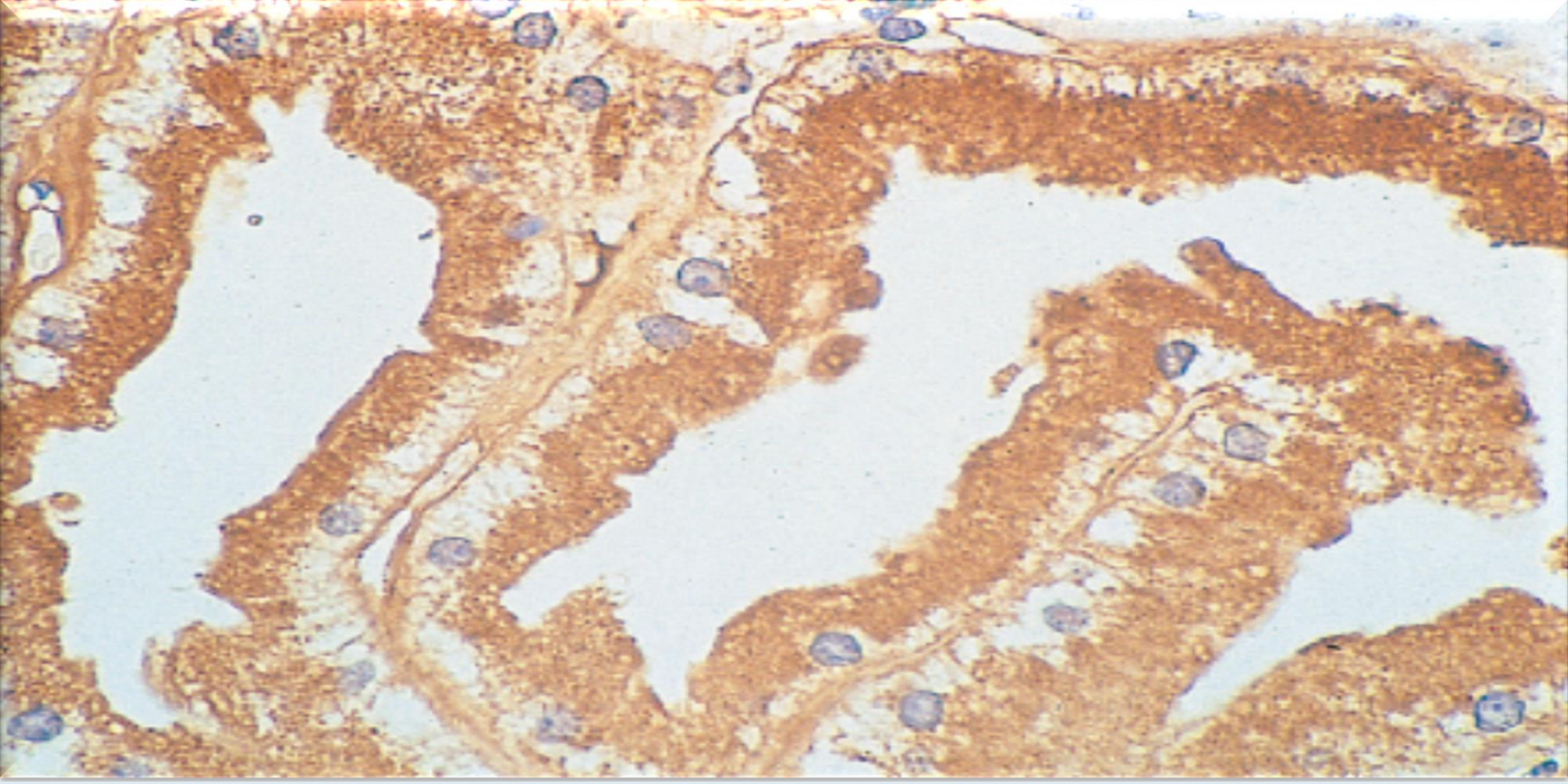
Cast Nephropathy



Light Chain Deposition Disease LCDD

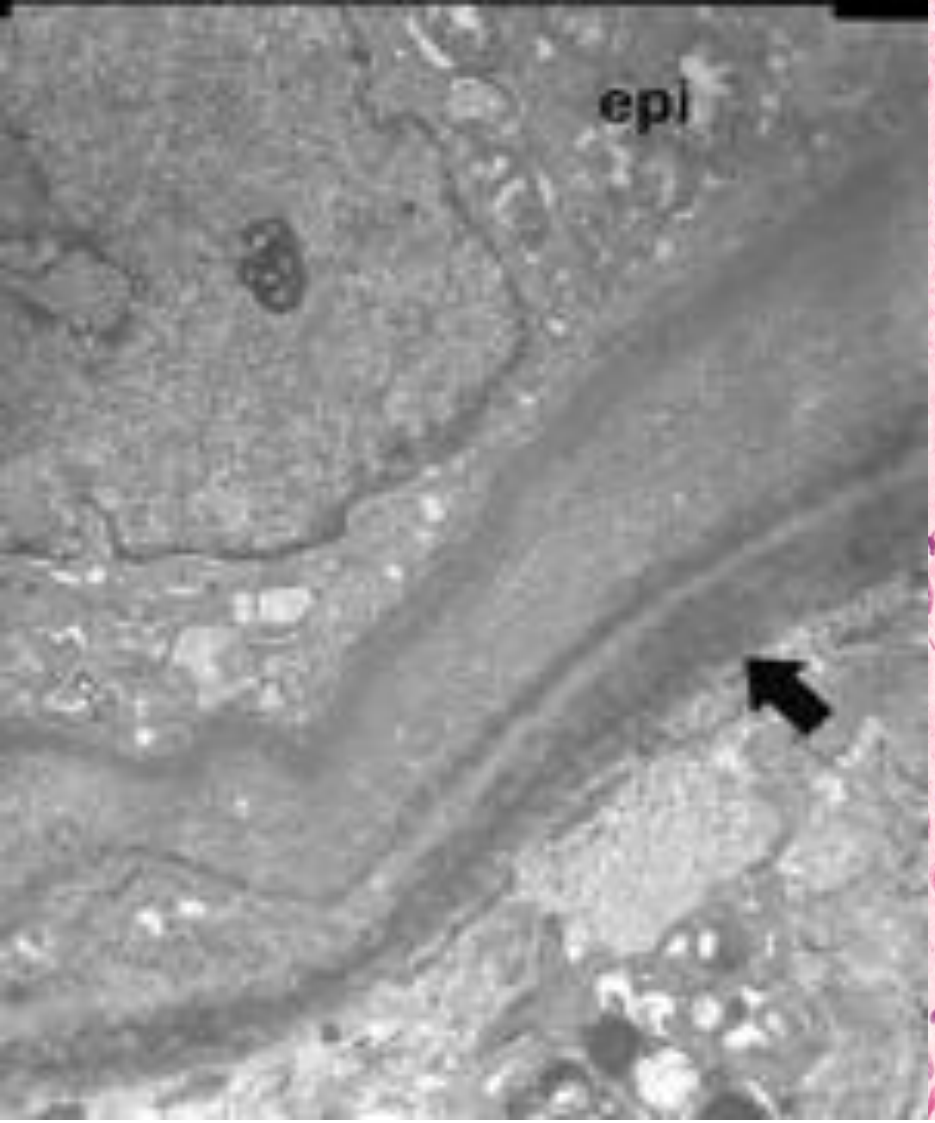
- Most commonly presents with both renal insufficiency and nephrotic syndrome
- Usually due to kappa **(κ)** immunoglobulin fragments which deposit in kidneys
- Circulating light chains are taken up and partially metabolized by macrophages, and then secreted and precipitate, causing tubular injury – and thus, proteinuria

Korbet and Schwartz. JASN September 2006 vol. 17 no. 9 2533-2545

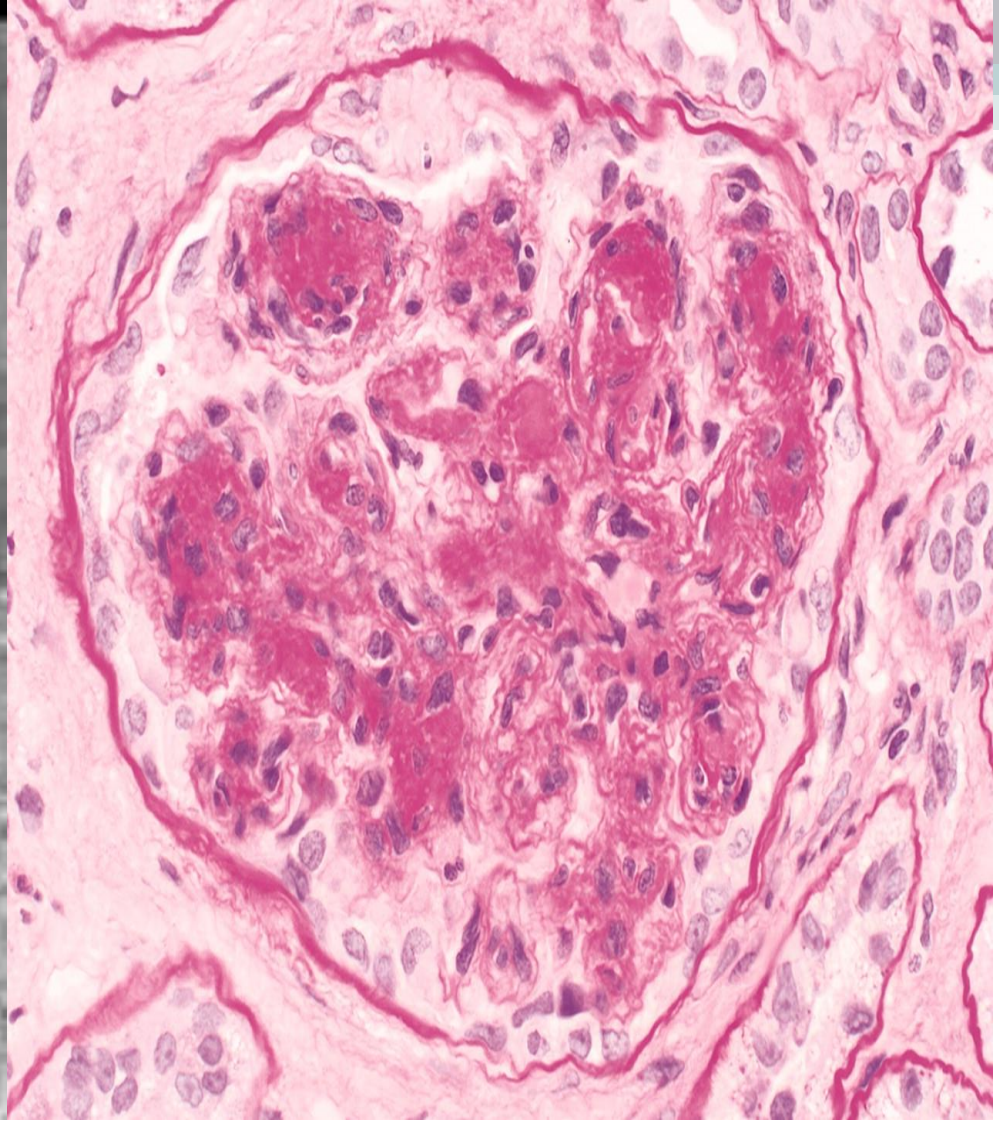


Uptake of light chains by proximal tubular cells. Renal biopsy specimen from a patient excreting κ light chains. Immunoperoxidase staining showing κ light chains along the brush border and in the cytoplasm of the PTC (brown stain).

Batuman et., Am J Physiol. 1998;275:F246-F254.



The tubular basement membranes stained with κ lg light chain (A) show bright (3+)



Monoclonal lg deposition disease (MIDD) with diffuse and nodular glomerulosclerosis.

Courtesy of Jean L. Olson, University of California San Francisco

AL-amyloidosis

- AL-amyloidosis is found in up to 30% of patients who present with multiple myeloma; conversely, multiple myeloma is present in up to 20% of patients who present with AL-amyloidosis.

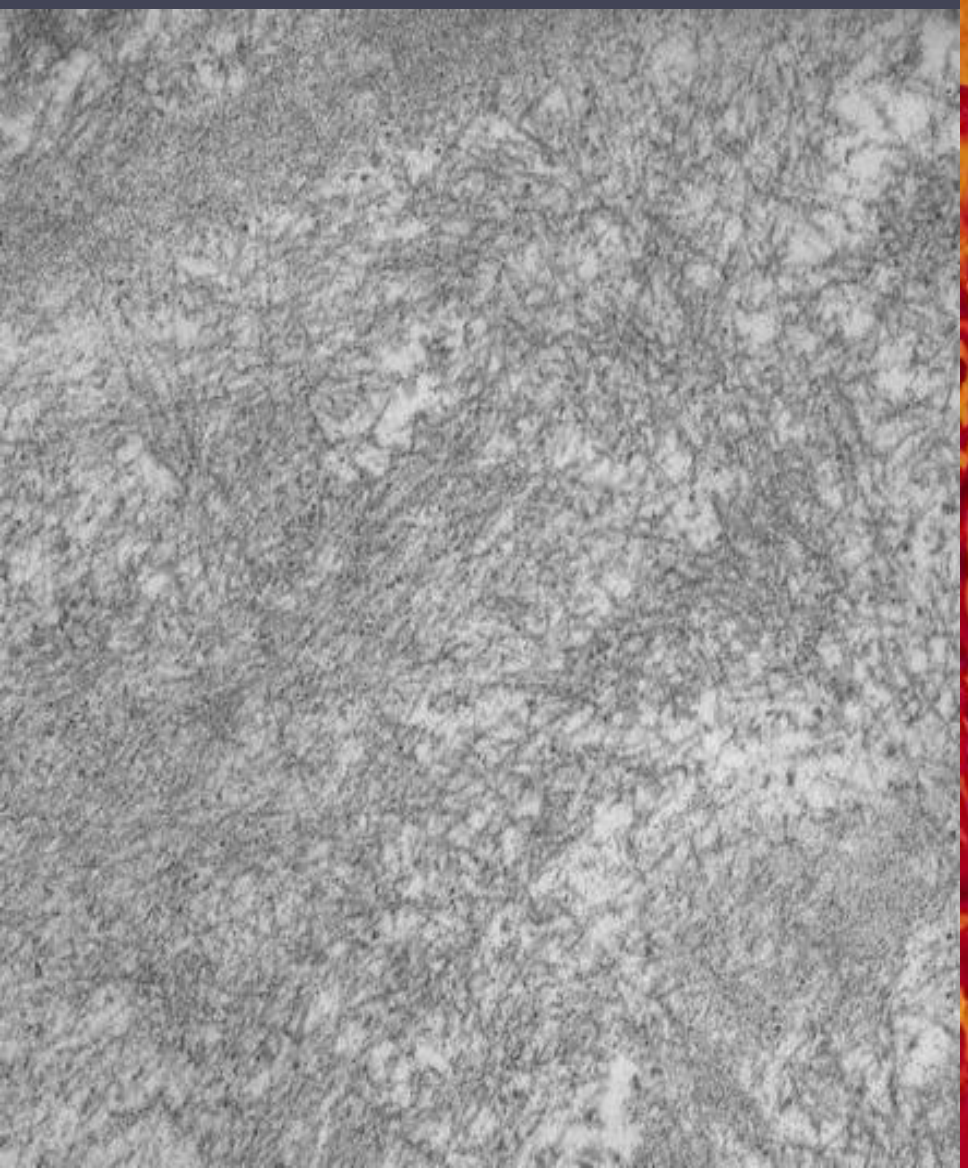
- Proteinuria is the most common renal manifestation at presentation, occurring in up to 80% of patients with the nephrotic syndrome seen in 30 to 50% of these patients.

Posi et al. Clin Nephrol 43 : 281–287, 1995

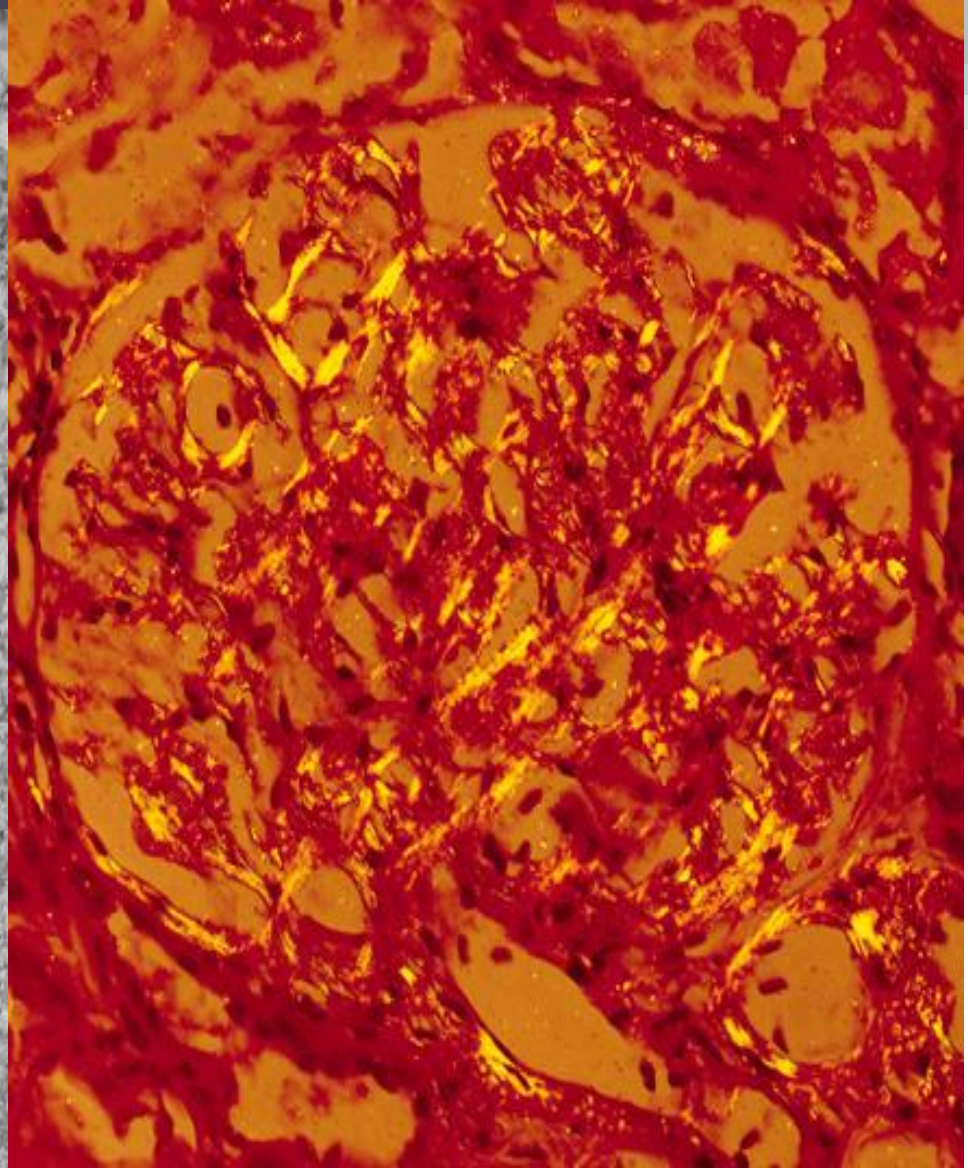
Amyloidosis

- Usually due to **lambda (λ)** light chains (AL)
- Pathogenesis is similar to LCDD, in that light chains are taken up and partially metabolized by macrophages and then secreted – then precipitate to form fibrils that are Congo red positive, β-pleated
- Like LCDD, due to tubular injury and also presents as nephrotic syndrome

Kyle. Adv Nephrol Necker Hosp 28 : 383–399, 1998



Renal amyloidosis, ultrastructural appearance. Amyloid deposits are seen as randomly arranged, 10-nM fibrils of indefinite length



Glomerulus stained with Congo red

Hypercalcemia

- Hypercalcemia occurs in multiple myeloma due to bone resorption from lytic lesions
- Serum calcium > 11.0 mg/dL occurs in 15% of pts with multiple myeloma
- Hypercalcemia commonly contributes to renal failure by renal vasoconstriction, leading to intratubular calcium deposition

Renal Tubular Dysfunction – Acquired Fanconi syndrome

- On occasion, light chains cause tubular dysfunction without renal insufficiency
- Most commonly occurs with kappa light chains
- Light chains are resistant to protease degradation and have tendency to accumulate in tubule epithelial cells and form crystals

Renal Tubular Dysfunction – Acquired Fanconi syndrome

- Tubular … effects or indire… lular lysosoma…
- This pres… roximal renal tub… otassium, phospha…

Renal affection in MM

Two main pathogenetic mechanisms:

- ***Intracellular cast formation***
- ***Direct tubular toxicity by light chains***

Role of IL-6

- IL-6 is an important growth factor for plasma cells in multiple myeloma, and may play a role in myeloma kidney
- IL-6 stimulates acute phase reactants from liver, promoting cast formation and possibly impairing light chain resorption
- IL-6 also contributes to hypercalcemia by stimulating osteoclasts

Tr

- Hydration with IV fluids
- Tre
  - L
  - C
- Tre
  - P
  - V
  - A
- Possible role for plasmapheresis
- Dialysis, as necessary

Indian J Nephrol. 2010 April; 20(2): 94–96.
doi: 10.4103/0971-4065.65304
PMCID: PMC2931142

Complete remission of lambda light chain myeloma presenting with acute renal failure following treatment with bortezomib and steroids

M. Pavan, K. A. Ashwini, R. Ravi, and L. H. Suratkal

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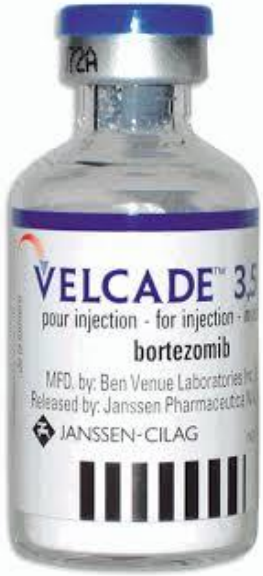
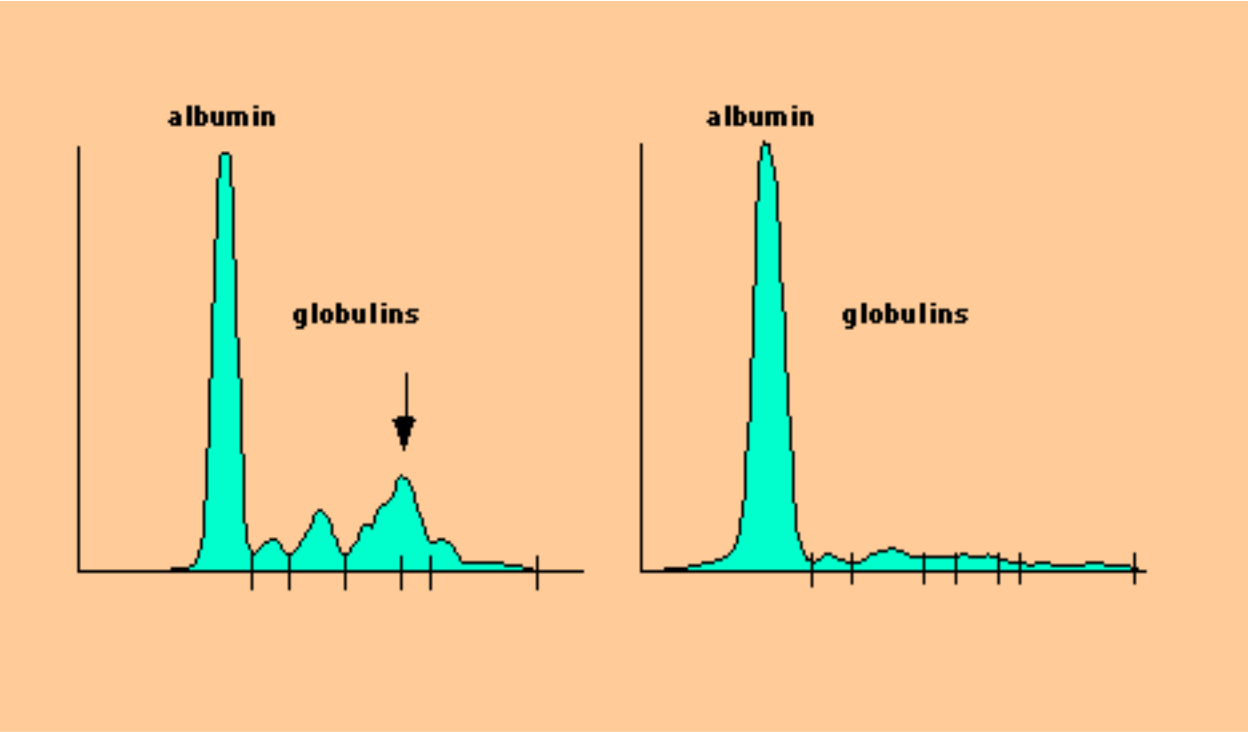


Plasmapheresis in MM

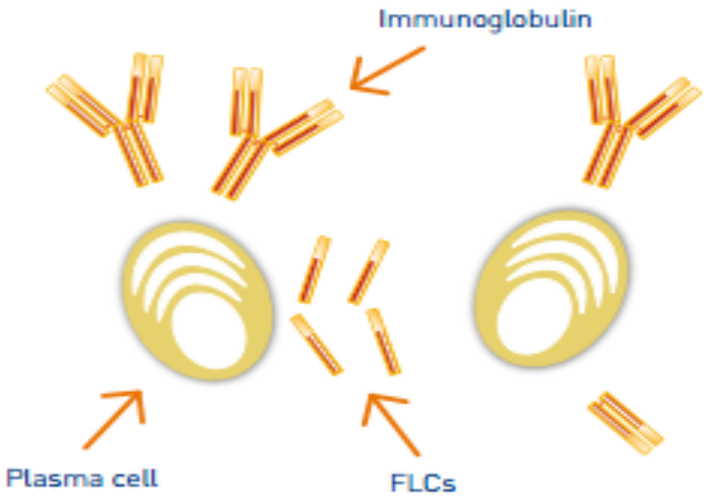
- Theoretical benefit in removing the toxic circulating light chains to spare renal function
- Limited data to support efficacy
- Treatment of choice if hyperviscosity symptoms are present
- Potential risk for bleeding if Dx is needed due to pheresis-induced removal of coagulation factors

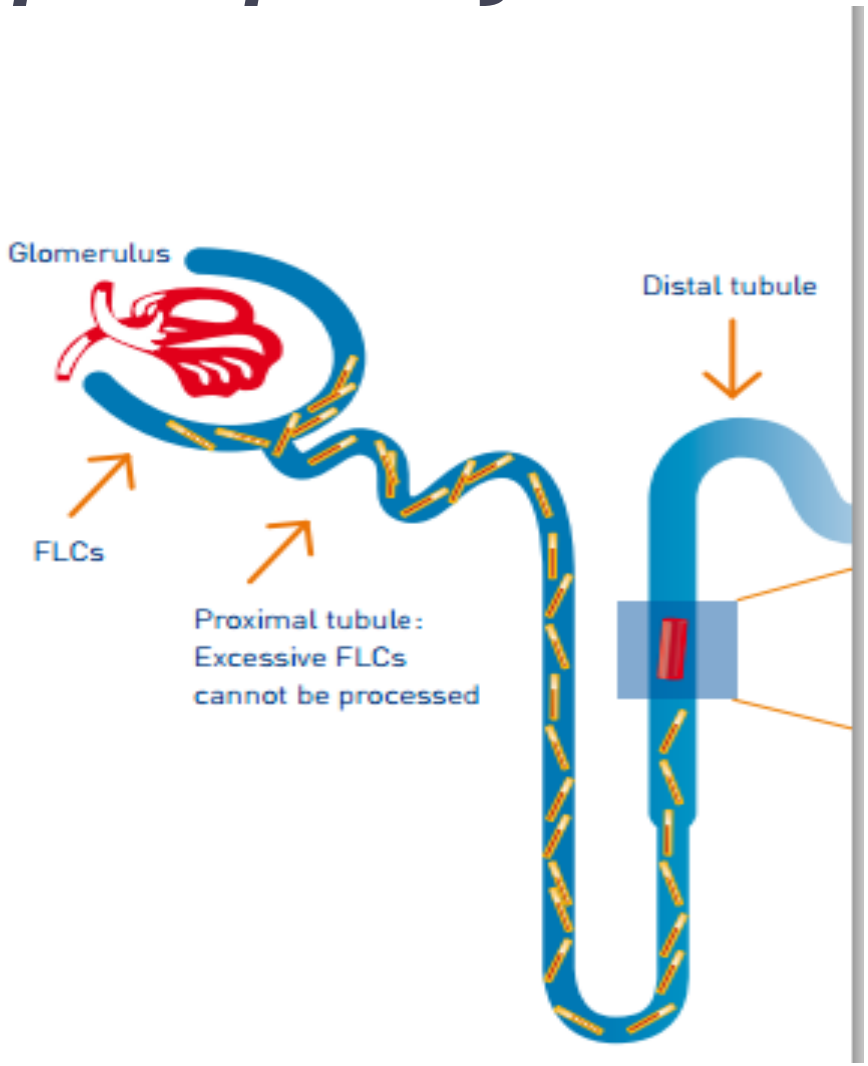
Plasmapheresis in MM



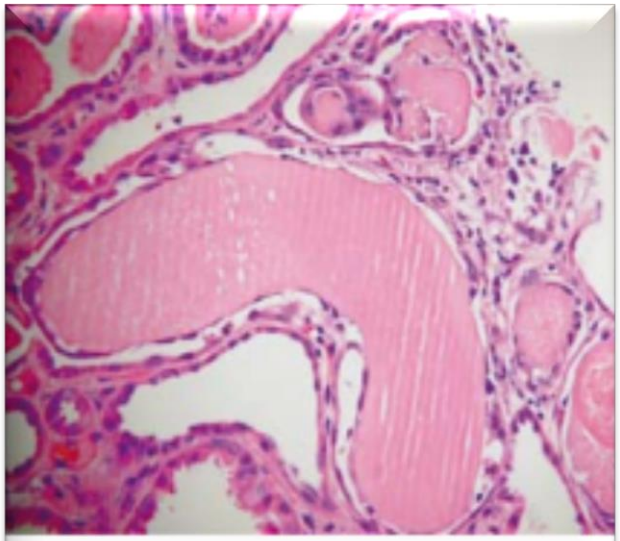
Efficacy of plasmapheresis in multiple myeloma Serum protein electrophoresis before (left panel) and after (right panel) four consecutive daily plasma exchanges in a patient with multiple myeloma and acute renal failure. The monoclonal peak representing the circulating light chains (arrow) has essentially disappeared. Courtesy of Andre Kaplan, MD

FLCs and cast nephropathy





- Plasma exchange is a logical approach, but shows no clinical benefit.
- A 3.5 L plasma exchange removes 65% of intravascular FLCs but has very little impact on overall FLC levels—because they are also present in similar concentrations in the extravascular compartment and tissue edema fluid
-
- On the whole, dialyzers are similarly ineffective.

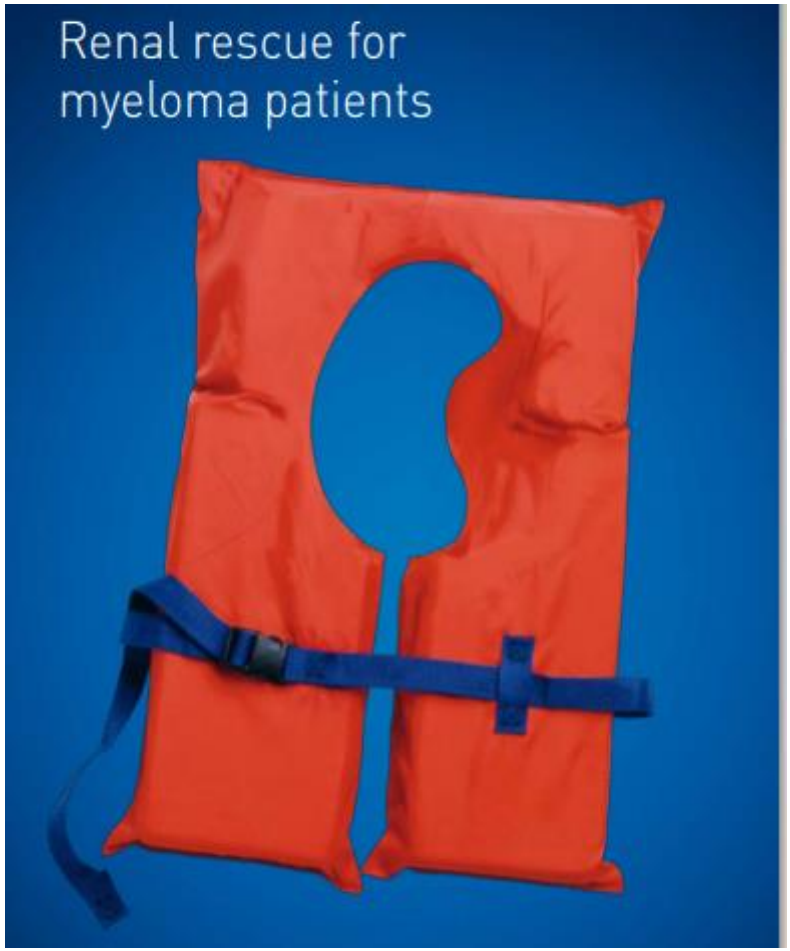


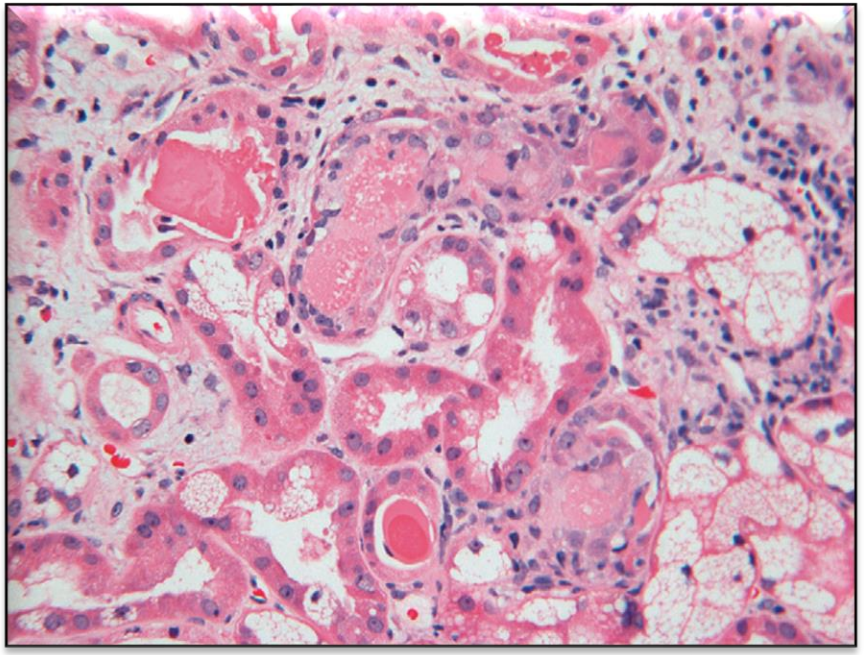
FLCs + Tamm-Horsfall proteins produce casts (cast nephropathy)

New option for FLC removal

- Until now, there has been little success in attempts to use blood purification

Perhaps….





Theralite™ High Cut-off technology

- It is with a new technology for the efficient and direct removal of FLCs
- E[illegible]n
  r[illegible]
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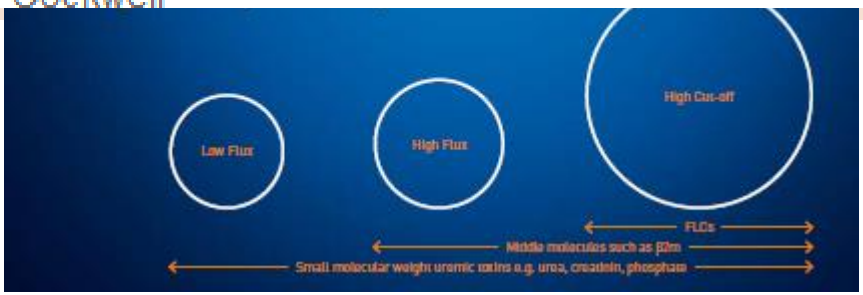
Colin A Hutchison

Journal Article

European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE): a randomised control trial.

Colin A Hutchison, Mark Cook, Nils Heyne, Katja Weisel, Lucinda Billingham, Arthur Bradwell, Paul Cockwell



Hutchison et al. Clin J Am Soc Nephrol 2009;4:745–754

Prevention of renal failure in MM

- IVF hydration
- Discontinuation of nephrotoxic drugs (i.e. NSAIDs, etc.)
- Chemotherapy/steroids – treatment of multiple myeloma to decrease the filtered light chain load

Thank s for your kind attention