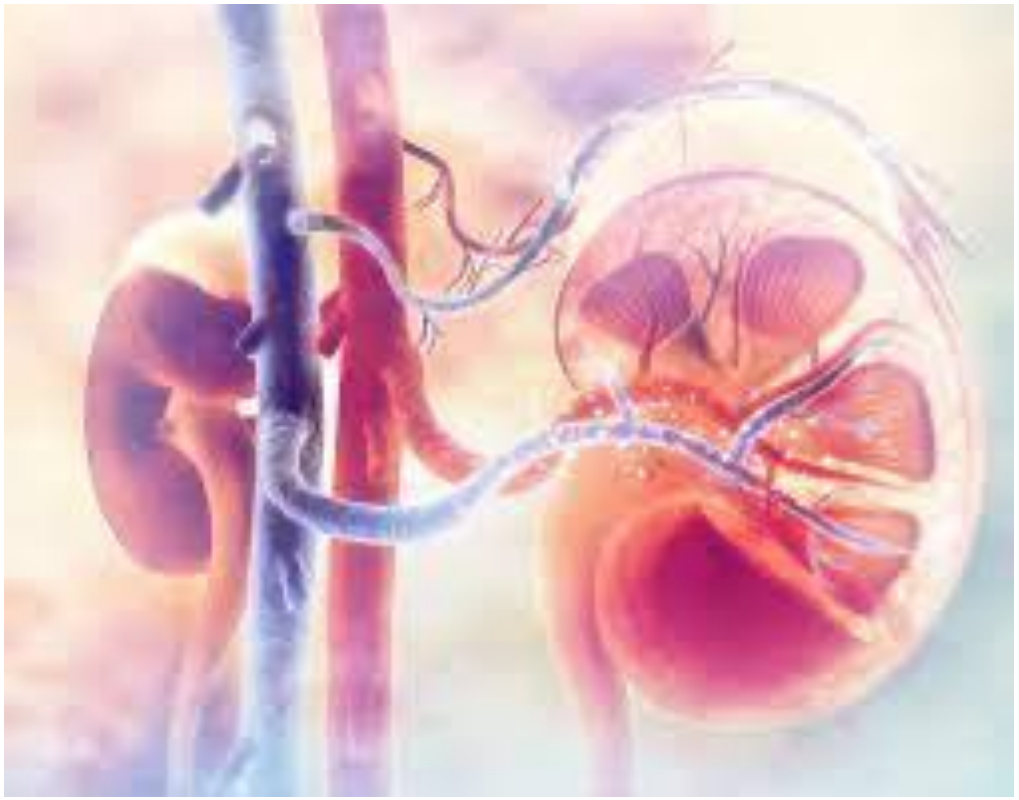
Renal Recovery in Multiple Myeloma



S.M.Razavi.MD

Associate professor of hematology & oncology

Department of internal medicine.IUMS

Introduction:

- About 50% of multiple myeloma patients will experience Aki or CKD
- About 3-10 % will need dialysis

- Kidney disease in monoclonal gammopathy due to:
  - Immunoglobulin
  - Light chain (LC)
  - Heavy chain

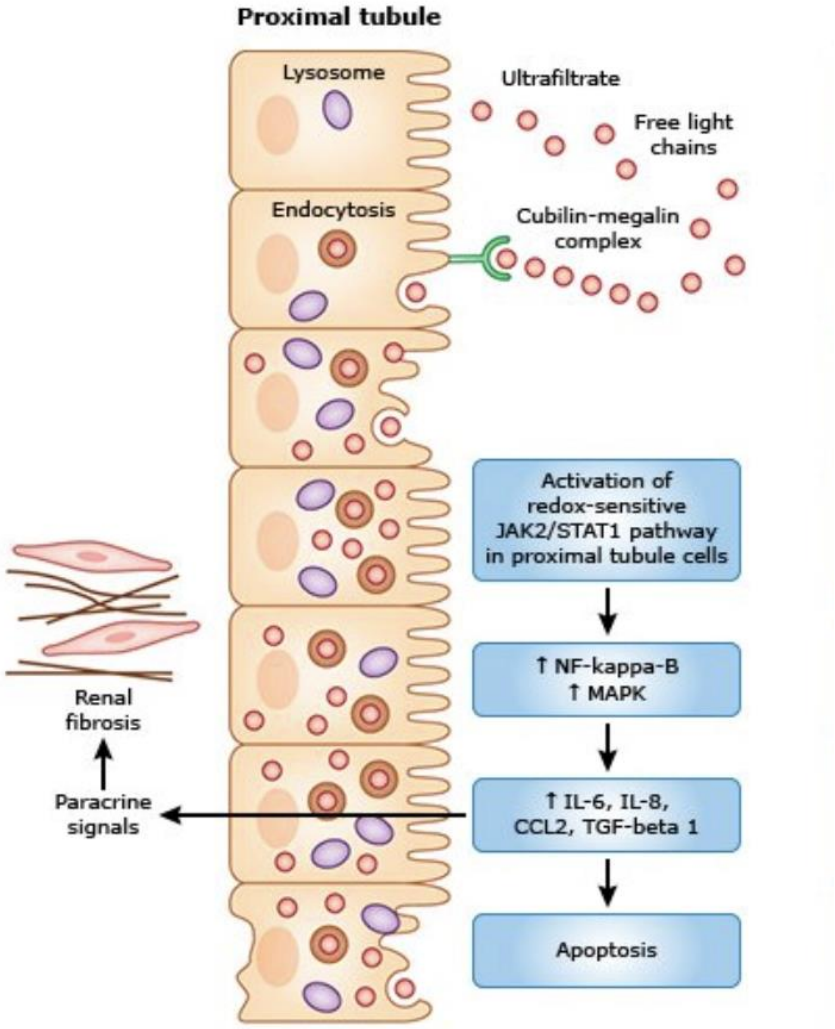
All LC (toxic or non toxic) can aggregate in tubule leading to light chain cast nephropathy (LCCN)

Introduction

- Kappa in ¾ LCDD
- Kappa in proximal tubulopathy
- Lambda in $^{2}/_{3}$ of AL amyloidosis (LC =➔ fibril)
- Normally LC in urine is under 30 mg /24hr
- In myeloma can be more than 20 gr /24 hr

Pathophysiology

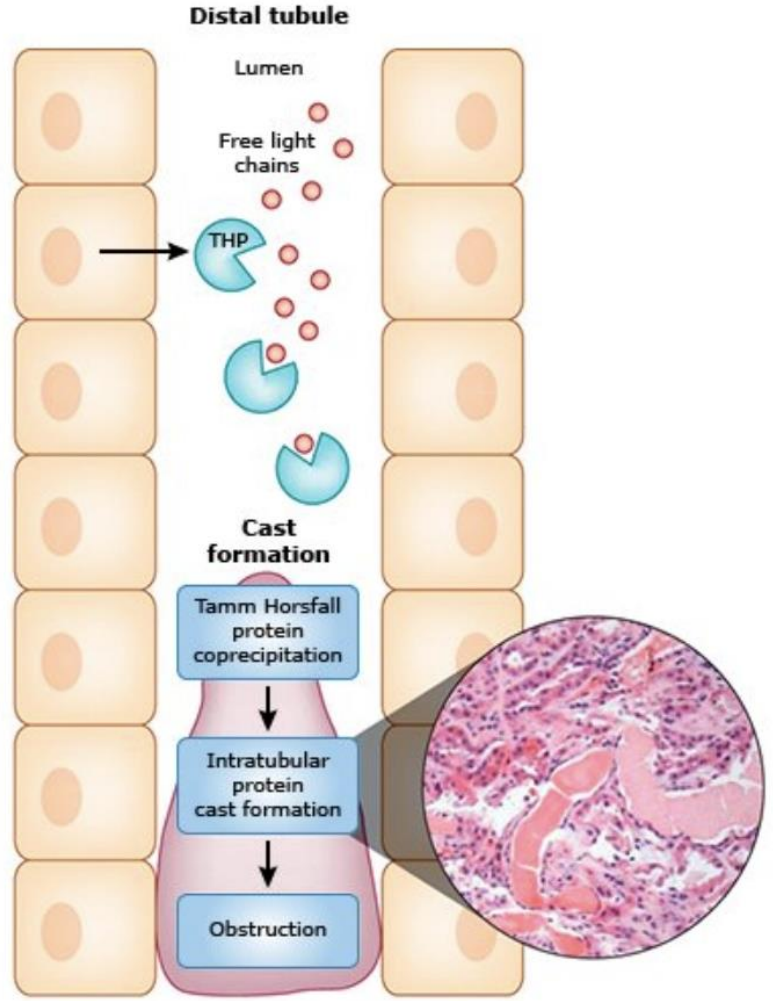
- LC + Uromodolin in proximal cells
  - ❖dense cast
- Giant cell reaction
  - ❖Interstitial inflammation and fibrosis
- Tubular rupture
  - ❖Extravasation of LC
  - ❖More inflammation



Pathophysiology

- **Inducing factors:**
  - Volume depletion
  - Metabolic acidosis
  - Loop diuretics
  - Hyper calcemia
    - (dehydration, vasoconstriction)
  - NSAID

- **Effective signaling of IL6,IL8,NFB,MCP,ASK1**



Aki or subacute kidney injury in plasma cell dyscrasia

- Light chain cast nephropathy (LCCN)
- Hypercalcemia
- Nephrotoxic agents (Radiocontrast-NSAIDs)
- Hyper viscosity syndrome
- Severe hyper uricemia
- Mono clonal Ig related gammopathies
  - Type 1 cryoglobulinemic glomerulonephritis
  - Proliferative GN with monoclonal immune globulin deposits(PGNMID)
  - C3 glomerulopathy with monoclonal gammopathy
  - Immunotactoid glomerulopathy

Other Causes of Aki:

- NSAIDS
- Bisphosphonate
- Anti Myeloma treatment agant
- Interstitial Nephritis
- Plasma cell Infiltration
- Thrombotic Microangiopathy
- Hyper viscosity
- Crystal Storing Histiocytosis

Cause of CKD

- LCCN
- Amyloid AL
- MIDD
- LC proximal tubulopathy
- Dm
- HTN

Cause of albuminuria

- AL amyloidosis (LC –HC-Ig)
- MIDD (LCDD –mixed –HCDD)
- Immunitactoid glomerulopathy
- Monoclonal cryoglobulinemia
- Proliferative Gn with monoclonal Ig deposition
- C3 glomerulopathy
- Light chain crystalline podocytopathy

Pre Treatment Evaluation:

- Possible Nephrotoxics
- Volume and acid base
- U/A – Sediment
- P – ca – albumin - uric acid
- Serum Protein Electerophoresis(SPEP) , Immunofixation(SIEP)
- Serum Free Light Chain Assay
- 24 hr Urine,Urin Electerophoresis(UPEP) with immunofixation(UIEP)
- Kidney Ultrasound
- Kidney Bx

Prognosis

Despite aggressive TX significant kidney dysfunction at presentation trend to have wares outcome

- Rate of improvement =➔ 50 -80%
  - On dialysis or Cr > 5 =➔ cr< 2
- Equal survival with normal kidney function
- Hyper ca and volume depletion most likely to recover but dense cast formation and significant tubular damage less likely to recover

Future direction

Cyclized peptide designed to interface with the binding of LC to Tomm-Horsfall protein
New paradigm treatment

Prevention

Minimizing the risk factors that promote LC filtration and subsequent tubular obstruction by cast may prevent LCCN

- High risk for LCCN
  - SFLC > 1500 mg/day

    - ❖ High intake of fluid
    - ❖ Alkalization in case of NSAIDs
    - ❖ Avoidance of loop diuretics
      - Coaggregation of LC with Tomm-horsfull and also volume depletion

Light chain cast nephropathy Tx

1- DC all potentially nephrotoxic

- NSAID , ACE ,ARB ,Diuretics

2-Correct hypercalcemia

3- IV or oral fluid: goal 3 lit urine output

- Volume repletion with isotonic fluids followed by half saline 150ml/hr (3 lit/24 hr)
- NaBic in acidic urine
- Loop diuretics in hypervolemia

4- Start Anti myeloma therapy

Anti myeloma Tx

- LCCN Tx:
  - Anti myeloma tx
  - Fluid management
  - Dialysis
  - Plasmapheresis / high cutoff dialysis
- Antimyeloma agants :
  - Bortezomib based with high dose Dexa +_ cyclophosphamide (specially in severe Aki)
  - Carfilzomib
  - Lenalidomide
  - Ixazomib
    - **BM Transplantation**

Fluid management

- IV fluid / daily urine out put 3 lit in LCCN
  - Hypercalcemia / Volume Depletion / Hyper Uremia
- Na Bicarbonate
- Loop diuretic
- Dialysis (fluid overload –hyperkalemia- uremia)

Extracorporeal methods for LC removed

- Plasmapheresis 1/day 5-6 time with albumin as replacement
  - 50 -60% LC reduction
- High cut-off dialysis
  - Permit efficient passage of proteins as large as 25-50 KD
  - Should not be performed without chemotherapy

Given possible reduction in dialysis dependency in AKI since the overall risk are low and potential benefits in terms of reversing kidney function are high , the results of MYRE trial support extra corporeal LC removal using plasmapheresis or high cut-off dialysis

Treatment .....

- **Hyper calcemia :**
  - ❖Bisphosphonate **cautiously**
    - Hypocalcemia
    - Nephrotic syndrome and AKI due to collapsing FSGS and glomerular lesions
    - Increased risk of aki associated with zoledronic acid
    - Denozumab is a good alternateive

- **Nephrotoxics:**
  - ❖Should be stopped
    - NSAID ,ACE ,ARB
  - ❖ should be avoided
    - Radio contrast and diuretics

Less common cause of Aki

- Plasma cell infiltration
- Hyper uricemia
- Hyper viscosity
- Thrombotic microangiopathy (rare)in the setting of proteasome I
  - DC Carfilzomib and switching to ….

This class of MAH are not typically responsive to plasmaphresis

Chronic kidney disease Tx

- Optimal tx is uncertain in slowly progressive LCCN:
  1. Limited data supporting plasmapheresis in CKD
  2. Chemotherapy
  3. Hemodialysis or PD

Survival

- Of patients with ESRD/MM who survive first 2 months , survival is 45% at one year , 25-30% at 2-3 years
- Median survival of patients with and without hemodialysis is equal after BMT

Kidney transplant after BMT ??

Maintenance of lenalidomide after auto BMT increased the risk of t cell mediated rejection

Bone Marrow Transplantation

- Kidney transplantation is an option for highly selected patients who have undergone successful and have achieved a hematologic stringent CR.

- Successful combines Allo BMT and KT has been reported in small number of patients .

Albuminuria or Nephrotic Syndrome

- Patients with albuminuria or nephrotic syndrome can be caused with:
  - Amyloidosis
  - MIDD
  - Monoclonal cryoglobulinemia
  - PGNMID
  - Immunotactoid glomerulopathy

- A kidney Bx is required

Treatment

- Amyloidosis

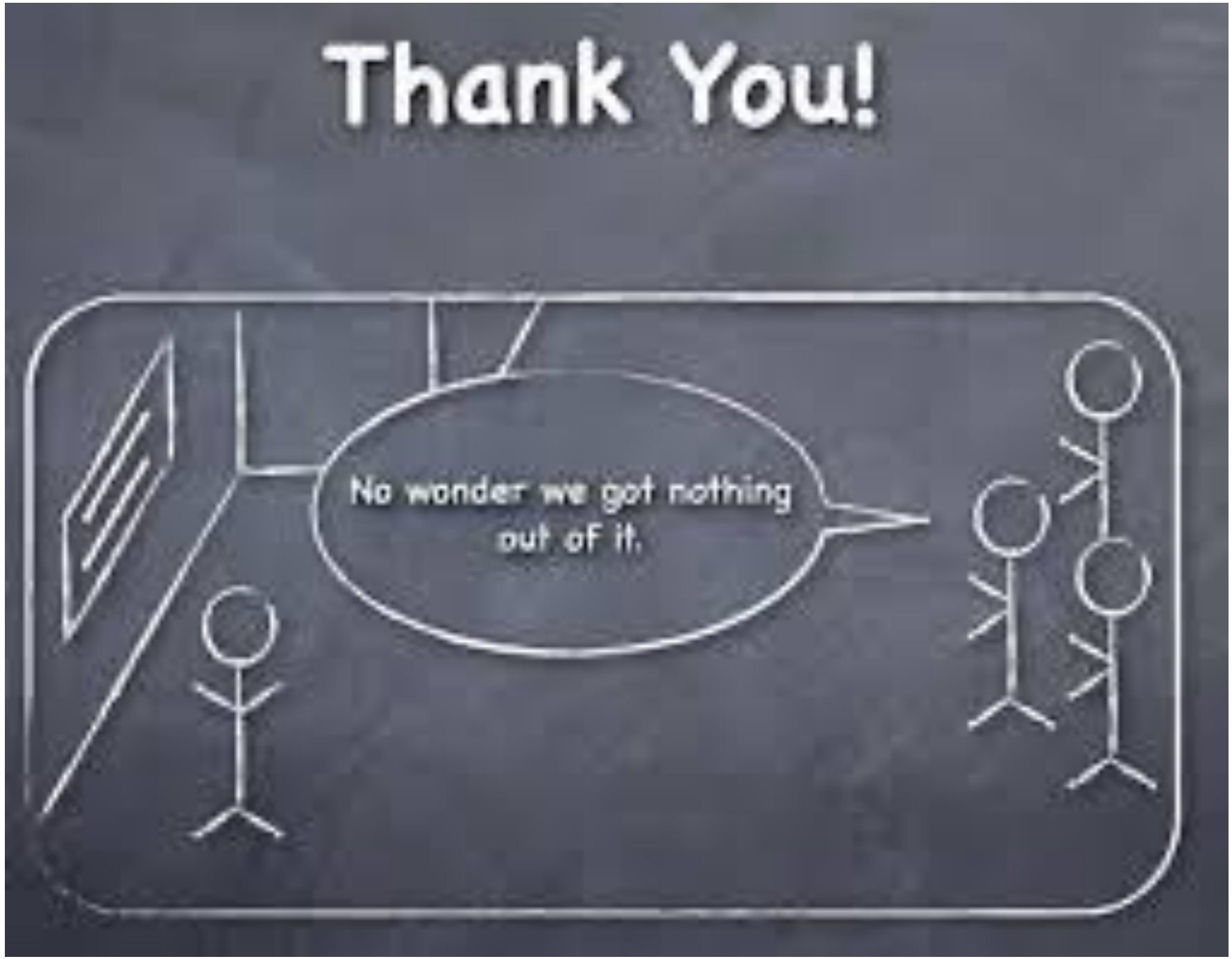
  Tx :

  - Targets the plasma cells clone
  - Avoidance of ACE ,ARB
  - Diuretics with caution in overloud (risk of ↓BP)

- Monoclonal Ig Deposition Disease
  - Tx :Targets the plasma cells clone or B cell clone

- Monoclonal cryoglobulinemia
  - Tx: Targets the plasma cells clone or B cell clone

- Proliferative GN with monoclonal Ig deposits (PGNMID) and c3 glomerulopathy associated with mono clonal gammopathy
  - Tx : Targets the plasma cells clone


Thank You!
No wonder we got nothing out of it.