Rare Cause of Chronic Kidney Disease in Young

Particulars outside hospital

- 36 yrs old Male, presented with h/o :
- Generalised weakness

  Nausea on-off

  ↓ Appetite

  ↓ urine output since 2 months.
- No Fever

  Hematuria

  DM/HTN/CVA

  NSAID abuse

  Parallel therapy

- Hemodialysis initiated in view of progressive renal dysfunction
- Underwent kidney biopsy

- ANA - negative
- Anti ds DNA - negative
- C3, C4 – normal

Biopsy report

- Includes 56 glomeruli of which 45 are globally sclerosed
- Remaining all other glomeruli are enlarged in size and shows diffuse mesangial nodularity
- Nodules are PAS positive, Silver & Congo red negative and are Blue on Trichrome stain

- Diffuse thickening of glomerular basement membrane (GBM) is noted
- Lobular accentuation & tram tracking is seen in all glomeruli
- Capillary lumina is partially obliterated & Bowman’s space is reduced
- Periglomerular fibrosis is also noted

- Possibilities are :

- Immunotactoid glomerulopathy
- Fibrillary glomerulonephritis
- Paraprotein deposition disease (LCDD or HCDD)

Treatment outside

- Steroids started at 40 mg OD
- Tapered by 5 mg weekly
- Hemodialysis (HD) sessions thrice a week
- HD access : left femoral uncuffed non-tunnelled HD catheter
- left brachiocephalic AVF was created

At our center

- Came for Kidney Transplant work up with wife as a prospective donor
- Admitted and further work up was done
- His kidney biopsy was reviwed

Examination – General

- Consious, Oriented
- Afebrile
- PR- 76/min
- B.P.- 140/80 mm Hg
- RR-18/min
- No Pallor
- Edema – absent

Examination-Systemic

- CVS-S_1 S_2 Heard, No Murmur
- CNS-No Focal Deficit
- Respiratory System-B/L Normal Vesicular Breath Sounds
- P/A-Soft, Non tender

Investigations-Urine

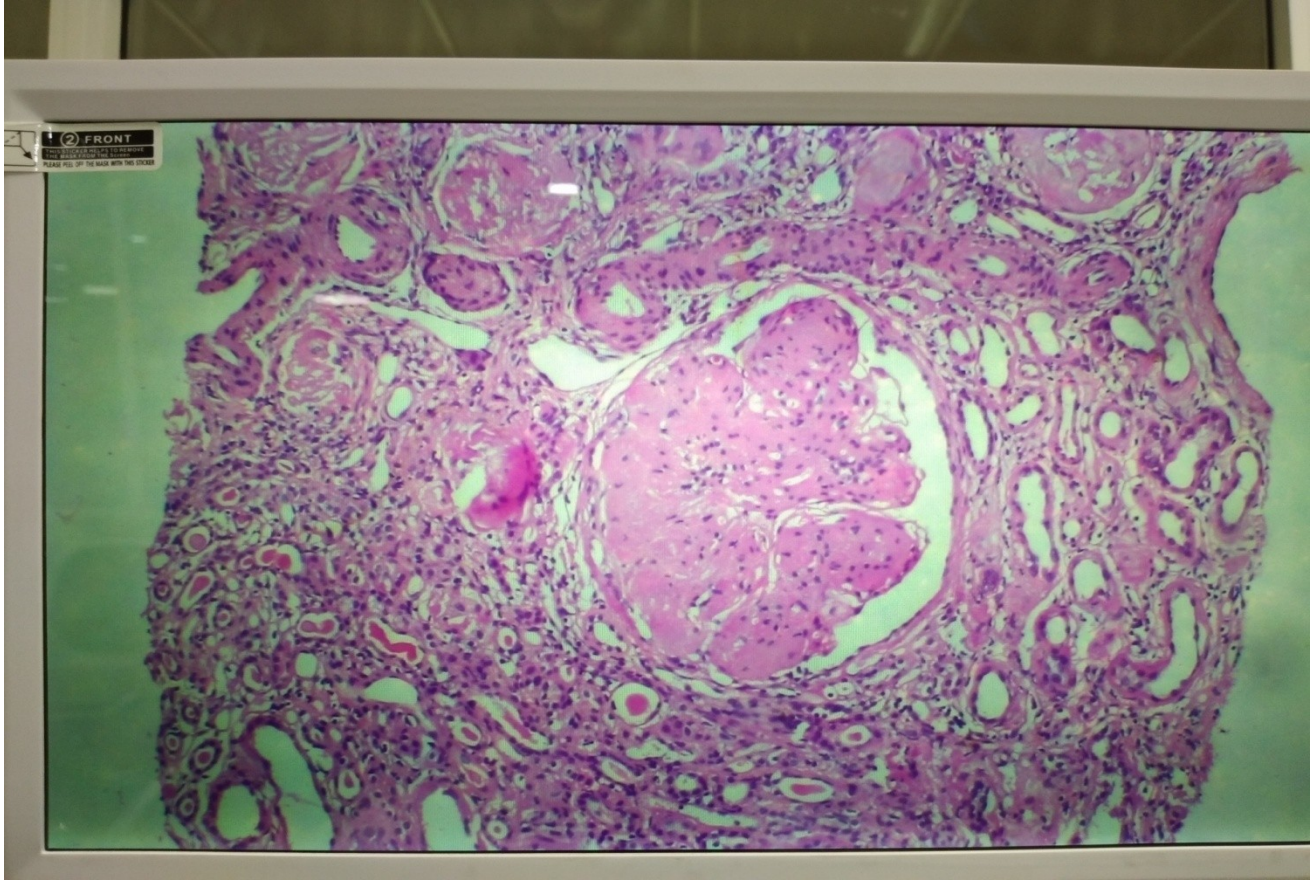
- Urine R/M-
- Protein-++
- RBC-1-2/ hpf
- Pus cells-2-3/hpf
- UPCR- 1.0

Investigations-Routine

- Hb- 10.3gm%
- TLC- 10,400 cells/cumm
- Platelet- 2.6 lacs/cumm
- Blood Urea- **153 mg/dl**
- Serum Creatinine- **12.3mg/dl**
- Serum Na- 139 mmol/l
- Serum K- 5.0 mmol/l

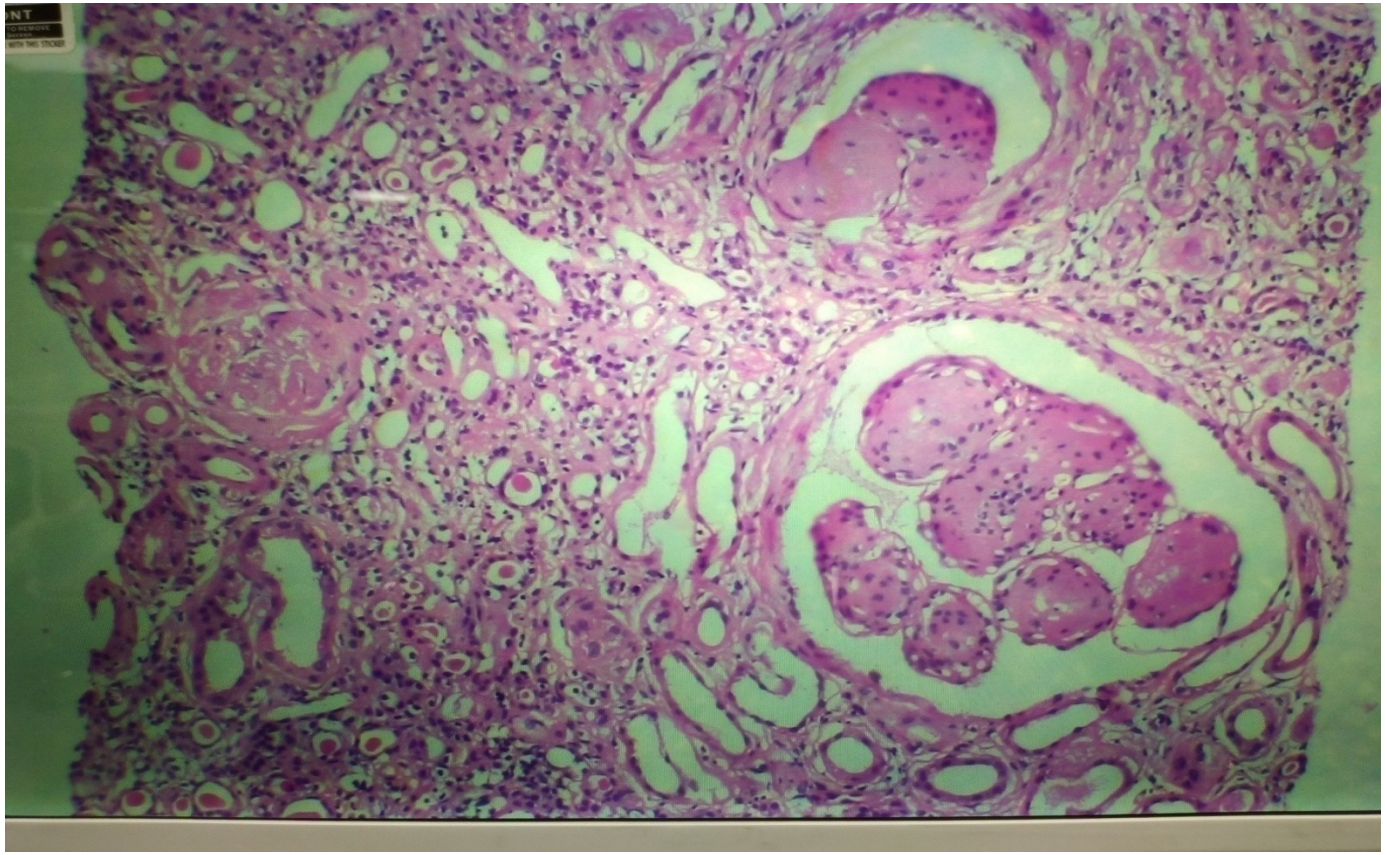
Investigations

- Serum Uric acid – 10.8 mg/dl.
- Serum Phosphorous – 5.4 mg/dl.
- Serum Calcium- 7.9 mg/dl
- Sr total protein- 5.9, Sr albumin- 3.7
- Corrected calcium : 8.62 mmol/L.
- HIV, HBsAg, Anti HCV- Negative
- USG : RK 8.8 x4.3 cm, LK 9.3 x 4.3cm with B/l normal Echogenicity, CMD maintained



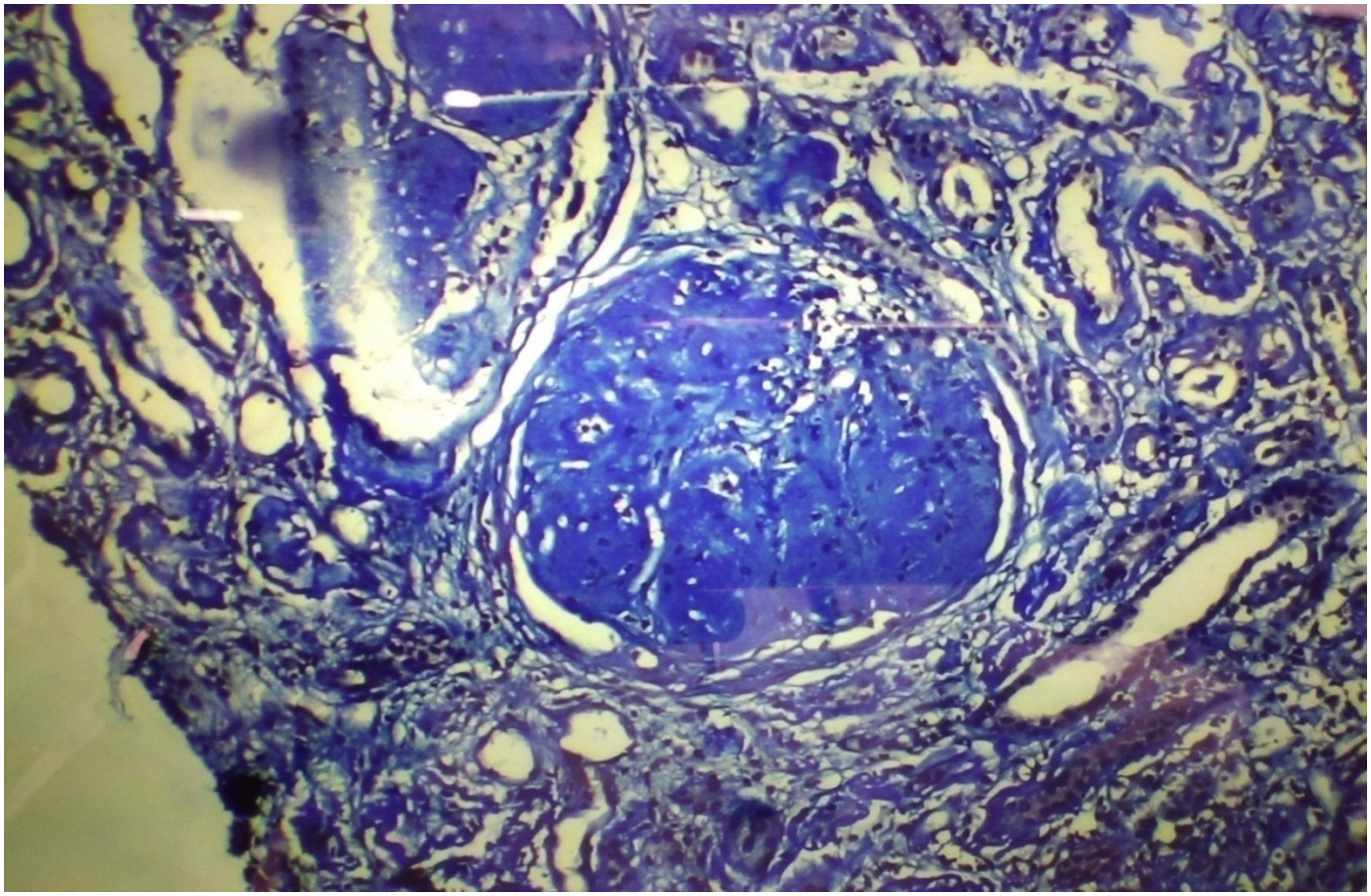
H & E stain

Sclerosed Glomeruli with mesangial expansion



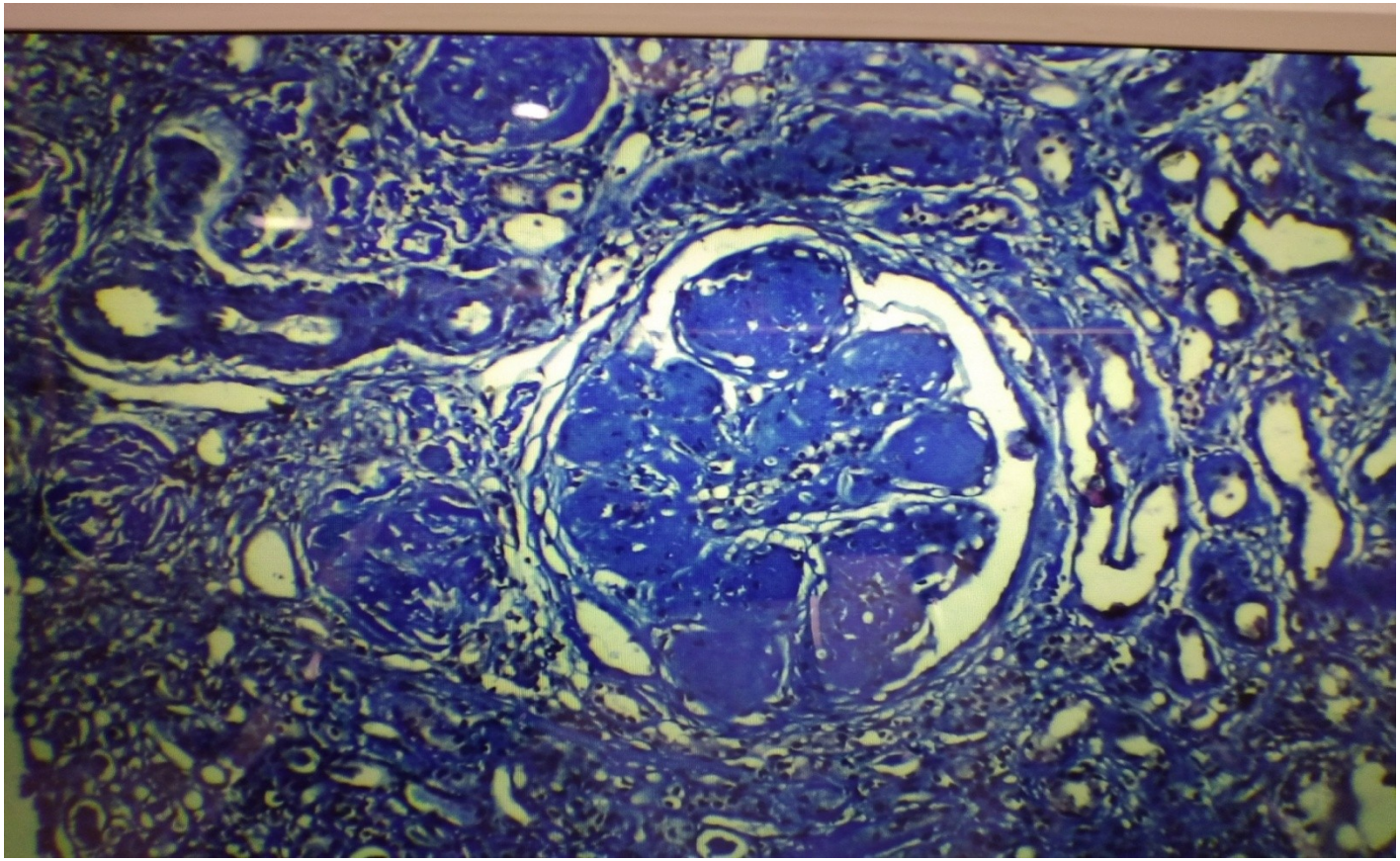
H & E Stain

Diffuse mesangial nodularity

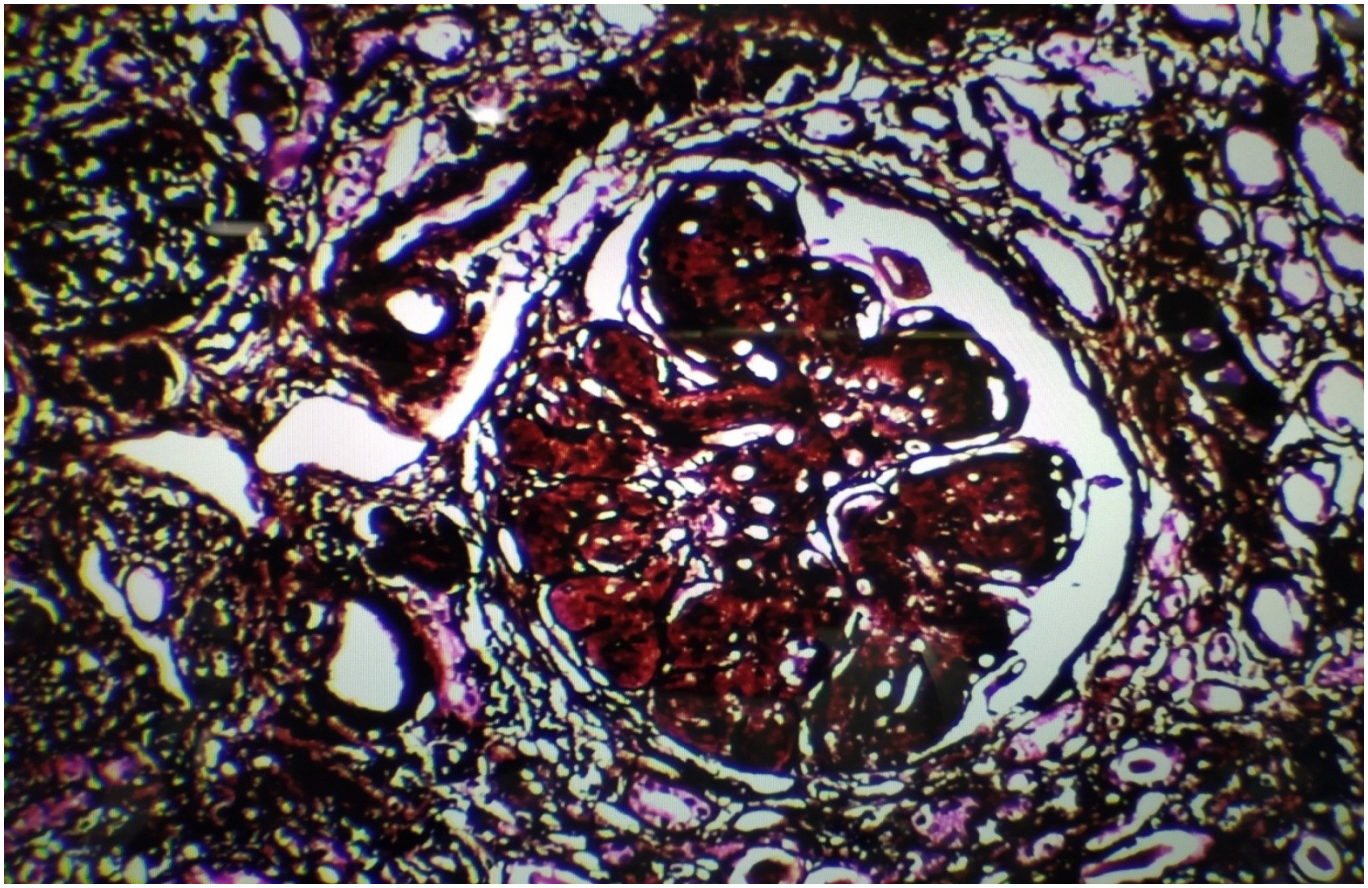


PAS stain

Diffuse thickening of GBM

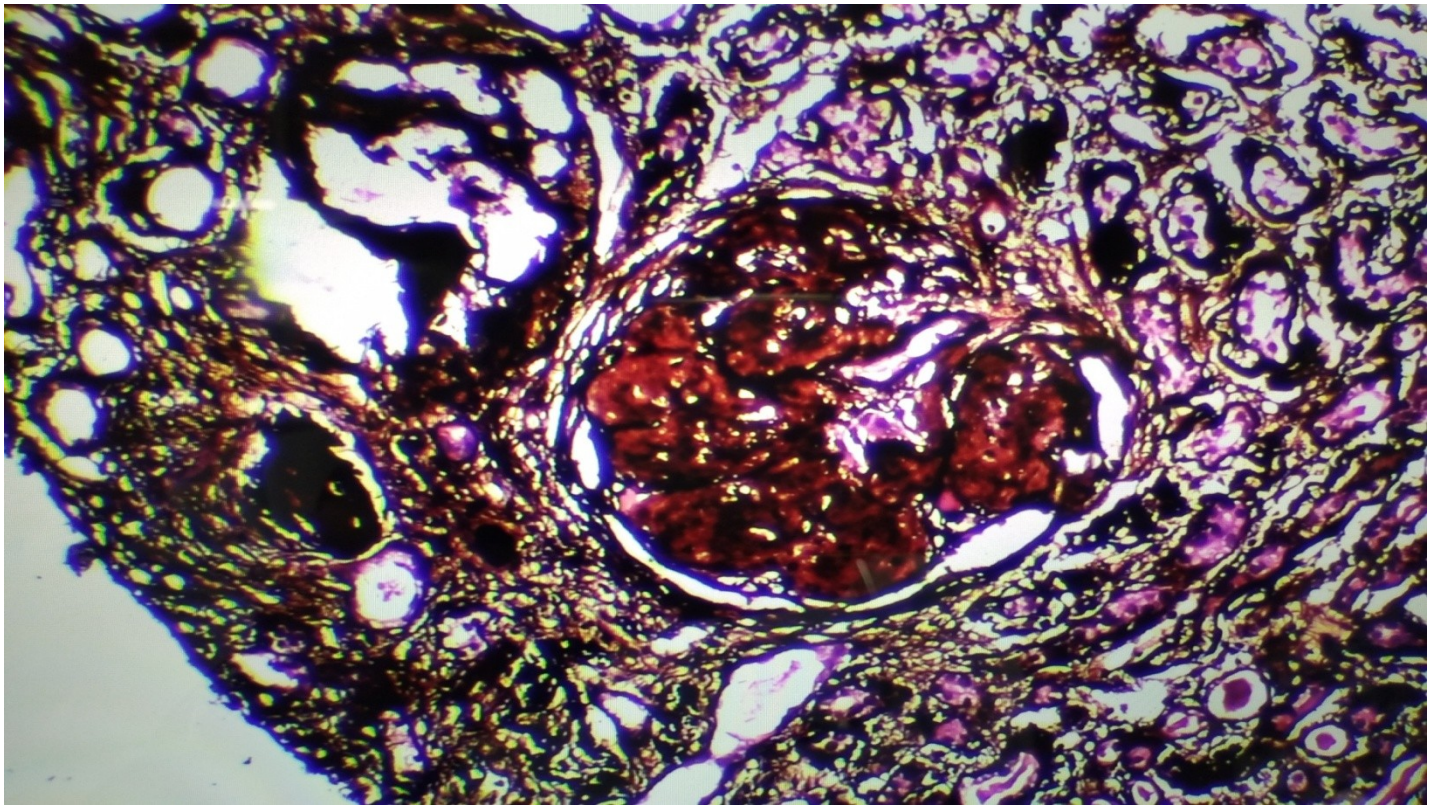


PAS stain



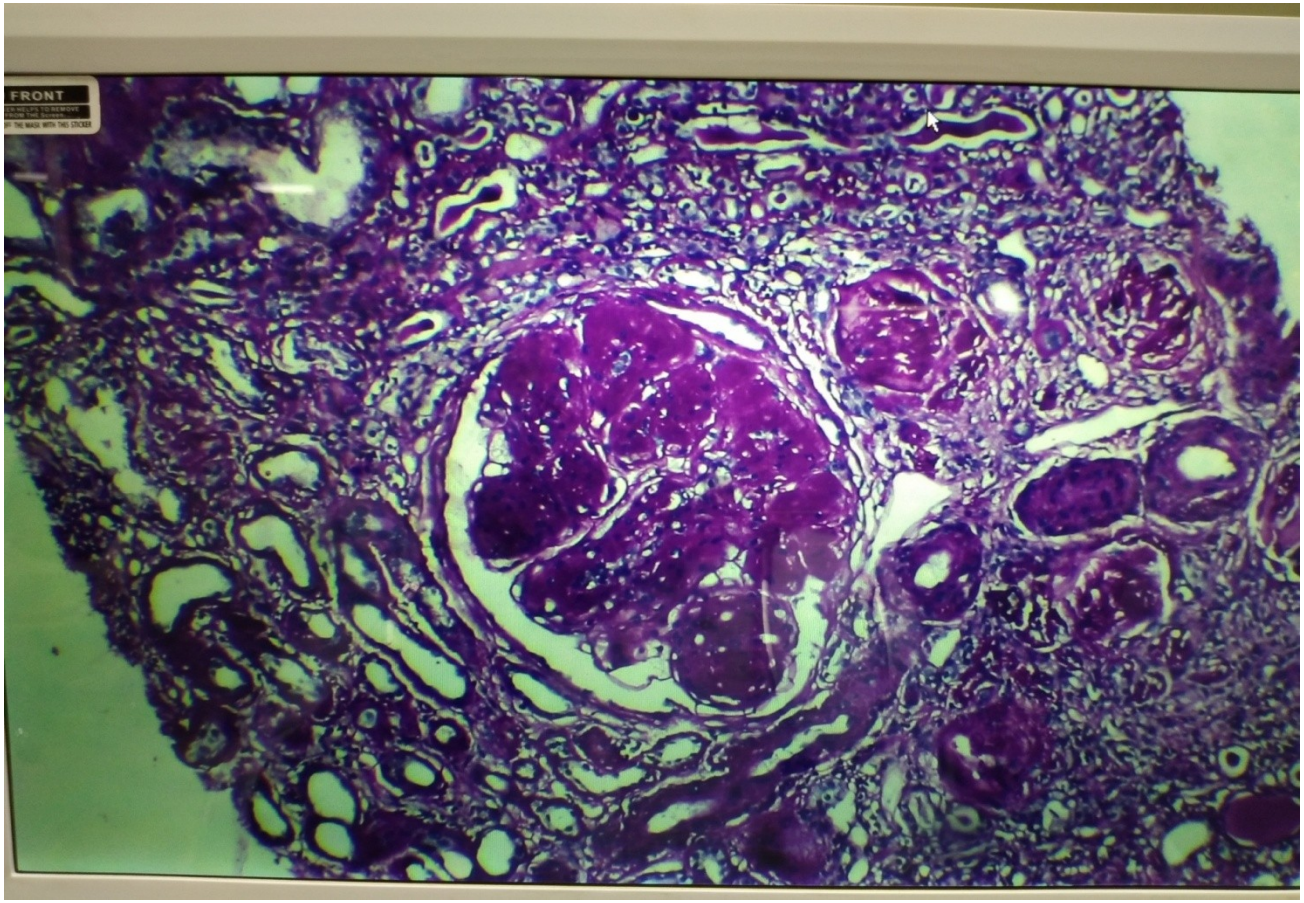
Silver stain

Capillary lumina obliterated and Bowman’s space is reduced



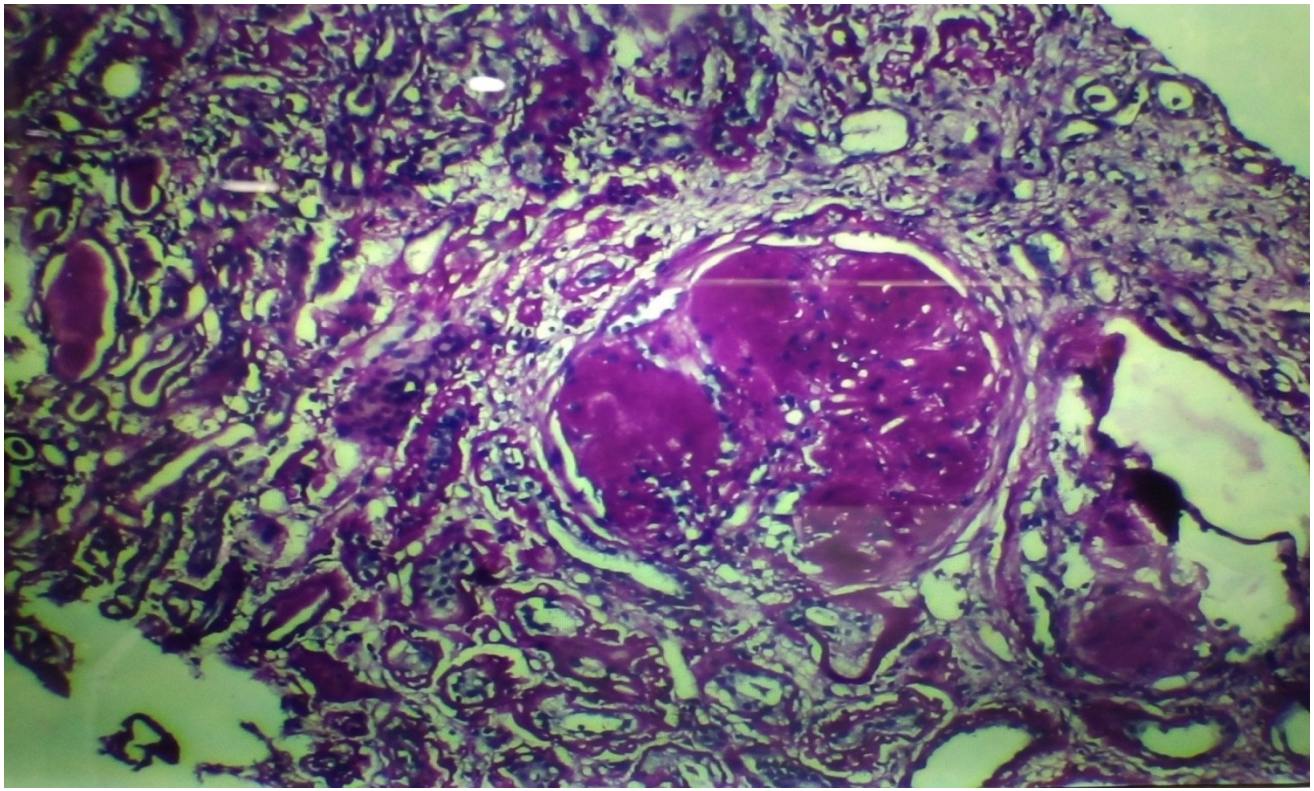
Silver stain

- Foci of tubular atrophy & interstitial fibrosis are noted (70%).
- Few proximal tubules are dilated & show mild hyaline droplet change
- Interstitium shows diffuse mononuclear cell inflammatory infiltrate
- Blood vessels show hyaline arteriosclerosis s/o benign hypertension



Masson’s trichrome stain

Periglomerular fibrosis



Masson’s trichrome stain

Capillary lumina obliterated and Bowman’s space is reduced

WHAT NEXT ?

- Urine for B-J Protein : Absent
- Free light chain ratio altered significantly

➢ Free kappa : 1050 mg/l (3.3 – 19.4)

➢ Free lambda : 37 mg/l (5.71 – 26.3)

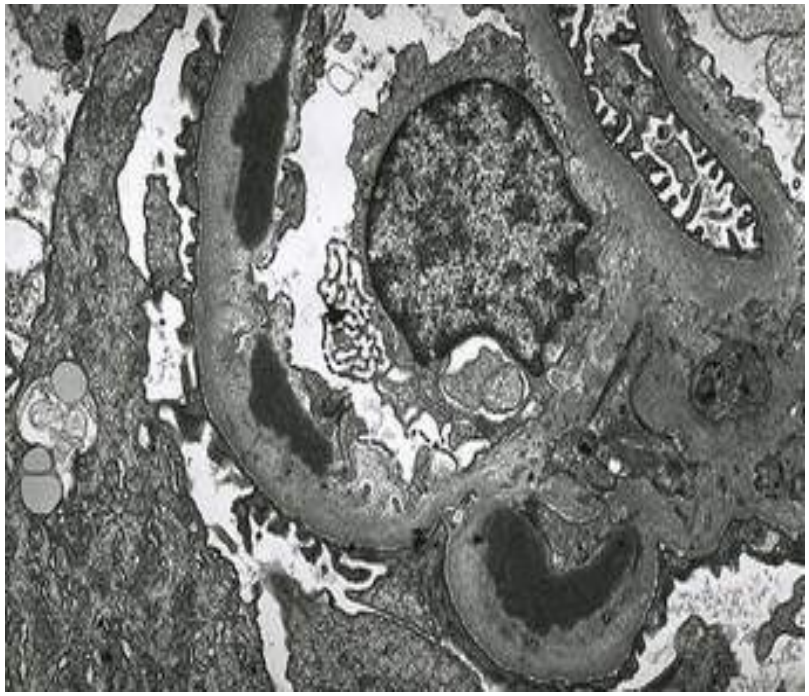
➢ Free kappa/lambda ratio : 28.38 (0.26 – 1.65)

- Xray skull (AP & lateral view) : No abnormality detected
- Sr protein electrophoresis : M band not detected
- Bone marrow aspiration & biopsy : No abnormality detected

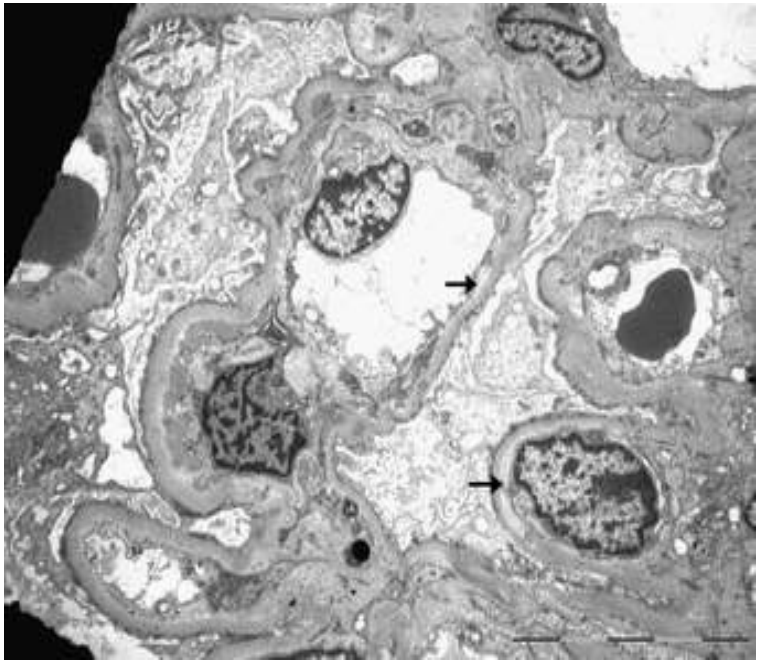
Immuno fluorescence

- IgA – Negative
- IgG – 1 + mesangial & capillary wall coarse granular
- IgM – Negative
- C3 – Negative
- C1q – Negative
- Kappa light chains – 2+/3+ mesangial & capillary wall coarse granular
- Lambda light chains – 2+/3+ mesangial & capillary wall coarse granular

Electron microscopy



- Widespread loss of foot processes of visceral epithelial cells
- Several tubules show electron luscent vacuolar inclusions in cytoplasm and thickened, homogenous appearing GBM



Massive expansion of mesangial areas which reveal intermediate electron dense deposit

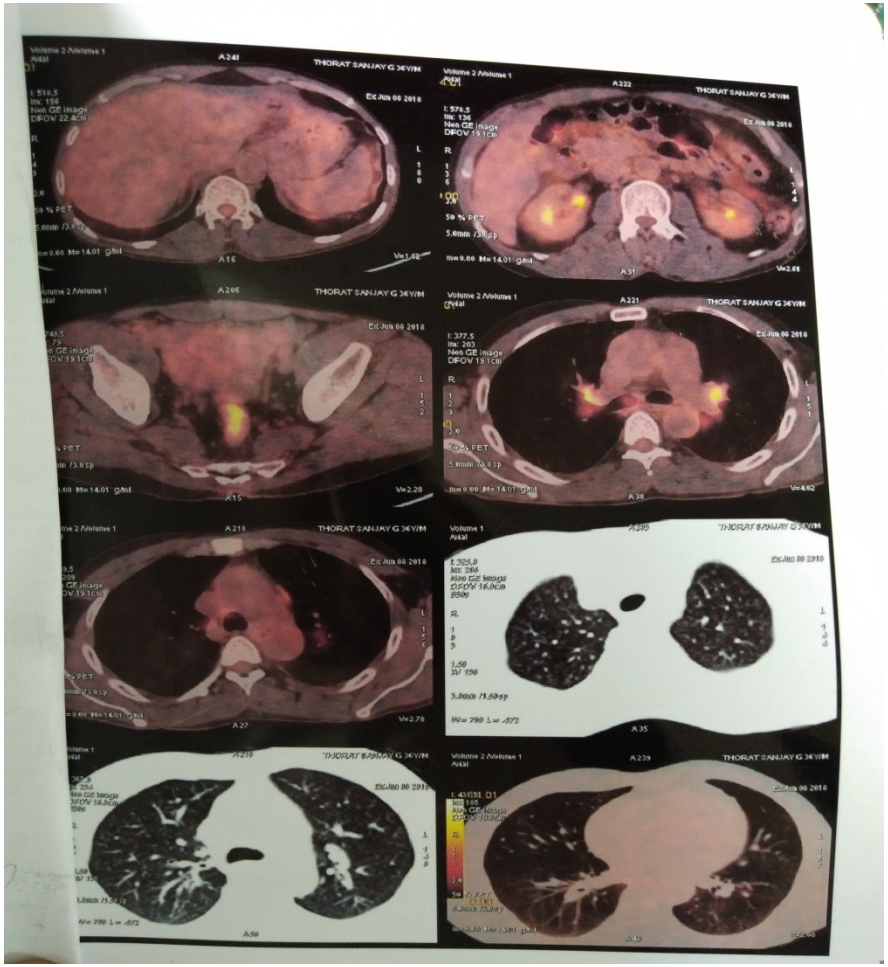
Impression

- Widespread effacement/ loss of visceral epithelial foot processes
- Massive mesangial accumulation of intermediate electron dense deposits with fine granular/ short fibrillary appearance.

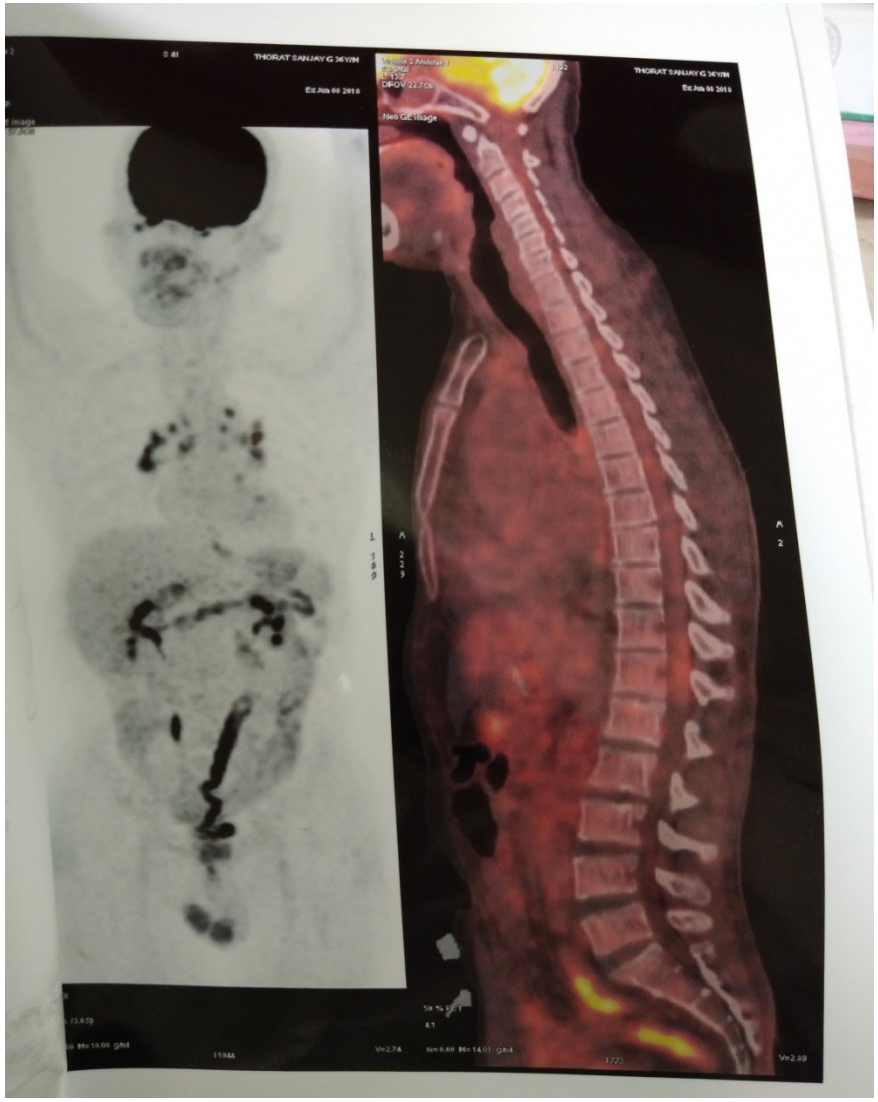
Final Diagnosis

- Chronic kidney disease/ stage Vd/ Fibrillary glomerulonephritis

PET SCAN



- Hypermetabolic mediastinal and bilateral hilar nodes
- No obvious Fluorodeoxyglucose avid skeletal lesion seen


THORAT SANJAY G 36Y/M
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At present

- Asymptomatic
- Thrice a week HD at our center
- Underwent 2 out of 6 cycles of Bortezomib and Dexamethasone (Once a week regimen) as per Hematologist’s opinion
- Plan to repeat Free light chain ratio after completion of 6 cycles

Discussion

Definitions

- Monoclonal gammopathy of undetermined significance (MGUS) is consistent with immunoglobulin precipitation or deposition diseases occurring with B cell proliferation[1].
- The International Kidney and Monoclonal Gammopathy Research Group proposed monoclonal gammopathy of renal significance (MGRS) to stress the relationship between monoclonal gammopathy and the renal disease[2].

1. Merlini and Stone, 2006
2. Leung et al., 2012

Definitions

Diagnostic Criteria of International Myeloma working group:

	MGUS	Smoldering myeloma	Symptomatic multiple myeloma
Proportion of plasma cells in bone marrow	<10%	≥10%	≥10%
M Protein in serum	<30g/L	≥30g/L	Detectable in serum and/or urine
End Organ Damage (CRAB)	No	No	Present

CRAB

- Hypercalcaemia: serum calcium > 1mg/dL higher than the upper limit of normal or > 11mg/dL
- Renal insufficiency: CrCl < 40 mL/min or serum creatinine >2 mg/dL
- Anemia: hemoglobin value of >20 g/L below the lower limit of normal or a hemoglobin value < 100 g/L
- Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT

Classification of diseases with tissue deposition

Organized			Non organized	
Crystals	Fibrillary	Micro tubular	MIDD	Others
Myeloma Cast Nephropathy	Amyloidosis (AL, AH)	Cryoglobulinemic Kidney	LCDD LHCDD HCDD	Proliferative GN with monoclonal IgG
Fanconi Syndrome	Non amyloid	Immunotactoid		MPGN (IgG, IgA or IgM)

Diagnosis

Glomerular disease	Clinical manifestations	Optical microscopy	Immunofluorescence	Electron microscopy
Proliferative glomerulonephritis with monoclonal Ig deposits	Proteinuria, variable microhaematuria, hypertension. Kidney disease. Frequent C3 hypocomplementaemia	MPGN. Less common: mesangial proliferative, crescentic, sclerosing or diffuse proliferative	IgG (G3 > G1 > G2) with restriction of κ or λ light chains in mesangium and capillary wall. Less common: IgM or IgA. C3 or C1q deposits.	Double image of glomerular capillaries' profile. Mesangial and subendothelial electron-dense deposits. Less common: subepithelial or intramembranous
Type 1 cryoglobulinaemia-associated glomerulonephritis	Arthralgia, arthritis, purpura, neuropathy. Proteinuria, microhaematuria, kidney disease. Frequent hypertension. Frequent C3 and C4 hypocomplementaemia	MPGN or endocapillary proliferative glomerulonephritis. PAS+ intraluminal deposits	Granular deposits in mesangium and capillaries. Monoclonal IgG, IgM or IgA deposits (more common with κ chains). C3, C4 or C1q deposits.	Subendothelial and intracapillary deposits. Frequently organised in fibrils, microtubules or "in fingerprint".
Fibrillary glomerulonephritis	Nephrotic proteinuria, microhaematuria and kidney disease. Rarely a rapidly progressive course	Mesangial proliferation or MPGN. Sometimes presence of crescents. Congo red negative	IgG (G4 and G1) most commonly polyclonal	10–30 nm fibrils with random orientation in mesangium and capillaries
Immunotactoid glomerulopathy	Nephrotic proteinuria, microhaematuria and kidney disease. Often associated with chronic lymphocytic leukaemia or lymphocytic lymphoma	MPGN or membranous glomerulonephritis. Less common: proliferative endocapillary	IgG (most common IgG1) with restriction of κ or λ light chains. C3 deposits.	30–90 nm microtubules with subendothelial or subepithelial deposits
C3 glomerulopathy/atypical haemolytic uraemic syndrome associated with monoclonal gammopathy	By indirect deregulation of the complement system's alternative pathway. Proteinuria, nephrotic syndrome, microhaematuria, kidney disease, thrombotic microangiopathy	MPGN, proliferative endocapillary, mesangial or crescentic glomerulonephritis. Arterial thrombosis or glomerular capillaries	Intense deposits of C3 in mesangium and capillaries. Absence or lack of other reactants. Pronase treatment may be required to detect monoclonal Ig.	Mesangial, intramembranous and subendothelial deposits in C3GN, and mesangial and intramembranous in DDD

Fibrillary glomerulonephritis

- Clinical features :

➢ Nephrotic range proteinuria

➢ Microhematuria

➢ Renal dysfunction

➢ Rarely a rapidly progressive course

- **Light Microscopy :**
- Mesangial proliferation or MPGN
- Sometimes presence of crescents
- Congo red negative
- **Immunofluorosnce :**
- IgG (G4 and G1) most commonly present
- **Electron microscopy :**
- 10- 30 nm fibrils with random orientation in mesangium and capillaries

Treatment

- Proliferative glomerulonephritis : In cases of progressive CKD

✓ Bortezomib + Dexamethasone

Weekly regimen

Total 6 cycles to be given

- Check for Free light chain ratio afterwards

THANK YOU