Nephrotic Syndrome in a Chronically Infected Patient

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Case presentation

- A 37 y/o paraplegic male referred due to severe generalized edema and oliguria from 15 days ago and proteinuria from 1 month ago.
- PMH: **paraplegia** due to spinal cord injury after falling, **from 12 yrs. ago** with intermittent urinary catheterization. Several **buttock** pressure **ulcers from 4 yrs. ago**.
- Admission to Emam mousa kazem Hospital one week ago due to bed sore and had **proteinuria 4+, Cr=1.3-1.5, K= 5.9**.
- No other problem.

Case presentation..

- **SH**: smoking 1 py, no alcohol. DH: c-lax, alprazolam,
- **FH**: father ESRD on HD, is died.
- **PE:** BP=135/70, T=36, RR=18, PR= 82, O2 Sat=97 % in room air.
  4+ pitting edema in lower ex. and scrotum with plasma leakage.
- 3 pressure sore in buttock one was very deep, atrophic muscles in lower ex.

Case presentation…

Lab Tests

Cr	**1.49-1.96**	Mg	Nl	pH	7.39
BUN	29	WBC	9900	pCO2	33
Na	138	**Hb**	**7.6**	**HCO3**	**16**
K BS	**5.7** 106	Plt ALT	204000 29	**U/A**	**Pr3+, Bl 3+, RBC 24-26, 60% dysm, WBC 22-24, Renal cell, Granular cast**
AST	24	Al Ph	185		
Ca	**6.3**	**uric acid**	**9.6**	U/C	neg
Alb	**2 g/dl**	R.F.	Nl	Troponin	nl
P	**5.2**	CPK	Nl	Lipid profile	nl
Vit D	**23**	**PTH**	**99 ng**	**24 hr ur pr**	**10.800 gm**
Ferritin	274	ESR	67	24 hr ur cr	954 mg
				Ur Vol	1800 ml

Causes of nephrotic syndrome

Idiopathic	Medications	Allergens, venoms,	Infections
Minimal change, Membranous , FSGS Fibrillary GN Mesangioproliferative GN **Membranoproliferative GN** Proliferative GN	Inorganic, elemental mercury Organic gold Penicillamine, Bucillamine Street heroin Probenecid Captopril NSAIDs Lithium Interferon-α	Bee sting Pollens Poison ivy and poison oak Antitoxins (serum sickness) Snake venom Diphtheria, Pertussis, Tetanus toxoid Vaccines	PSGN, Infective endocarditis, Shunt nephritis, Leprosy, Syphilis, Mycoplasma **Chronic PN with VUR** Hepatitis B & C, CMV, EBV, Herpes zoster, HIV1

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Causes of nephrotic syndrome…

Multisystem disease	Neoplasms	Hereditary, familial, metabolic	Miscellaneous
SLE IgA vasculitis (Henoch-Schönlein purpura) **Immunoglobulin A nephropathy,** Systemic vasculitis: GPA (Wegener's granulomatosis), Mixed cryoglobulinemia Sjögren's syndrome, Amyloidosis (primary and secondary)	Lung Colon Stomach Breast Hodgkin's CLL Lymphoma Multiple myeloma (amyloidosis), GVHD	Diabetes mellitus Hypothyroidism (myxedema) Graves' disease Amyloidosis (familial Mediterranean fever Alport's syndrome Fabry's disease Nail-patella syndrome Lipoprotein glomerulopathy	Pregnancy associated (preeclampsia, recurrent, transient) Chronic renal allograft failure Accelerated or malignant nephrosclerosis Unilateral renal arterial hypertension

BRENNER & RECTOR'S THE KIDNEY - 2020

Case…

Immunologic tests:

- C3, C4, ANA, Anti ds DNA : nl or neg.
- ANCA (MPO, PR3): neg.
- **Anti GBM: 101, 100** (nl<10)
- Serum IgA; nl,
- **HBsAg: neg, HBcAb (IgM)= neg**
- **HIV Ab: neg**
- **HCVAb: neg,**
- **TSH, T3, T4 = nl**
- PPD= 4-5 mm

- **US:** RK=121 mm, LK=125 mm, mild

  bilateral hydroureteronephrosis, free fluid in abdomen and pelvic.
- **Chest CT:** mild pericardial effusion, bilat. mod. pleural effusion.
- **Doppler US** of LE: **no DVT.**
- **Echo:** EF 50%, mild pericardial effusion, bilat. Pl. Ef.
- **Wound culture: E-Coli & klebsiella**
- Sensitive: Tazocin, meropenem, amikacin

Suggested Initial Laboratory Tests for Nephrotic-Range Proteinuria

• Complete blood cell count	• Lipid panel
• Basic metabolic panel	• Phospholipase A2 receptor antibody
• Total protein and albumin	• HBsAg, anti-HBs, anti-HBc
• Hemoglobin A1c	• Hepatitis C virus antibody
• Erythrocyte sedimentation rate	• HIV ELISA
• Antinuclear antibody	• SPEP and UPEP and immunofixation
• C3 and C4	• κ:λ free light chain ratio
• Ferritin	• Spot urine albumin, urine protein, urine creatinine
• PT/INR and aPTT (for kidney biopsy)	• Urinalysis with sediment evaluation

AJKD Vol 75 | Iss 6 | June 2020

Patient: management

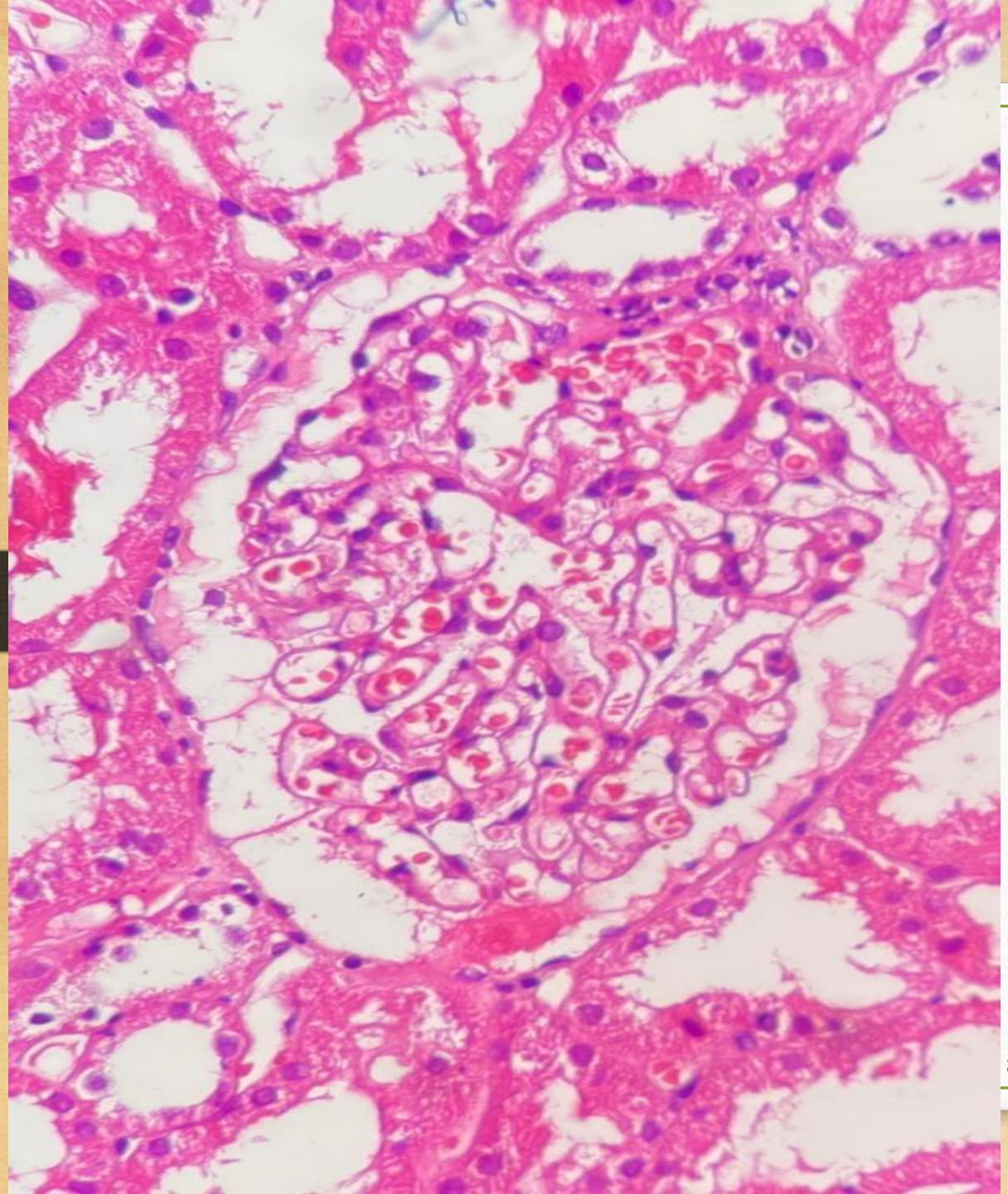
- Heparin prophylaxis
- Clindamycin
- Meropenem
- CaCO3
- Furosemide
- NaHCO3

- Kayexalate
- Pantoprazole
- Carvedilol
- Valsartan
- HCTZ

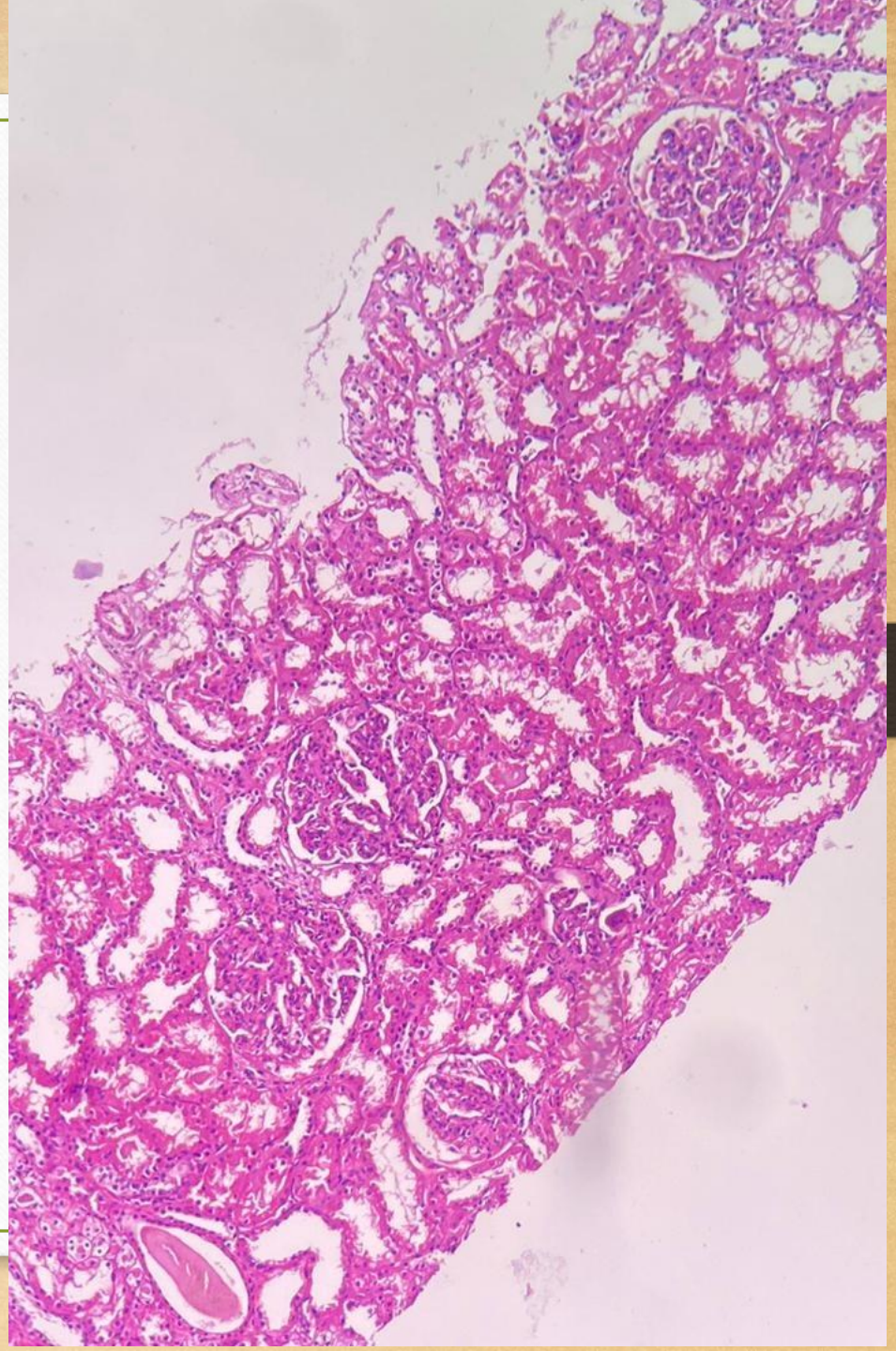
Kidney biopsy was done

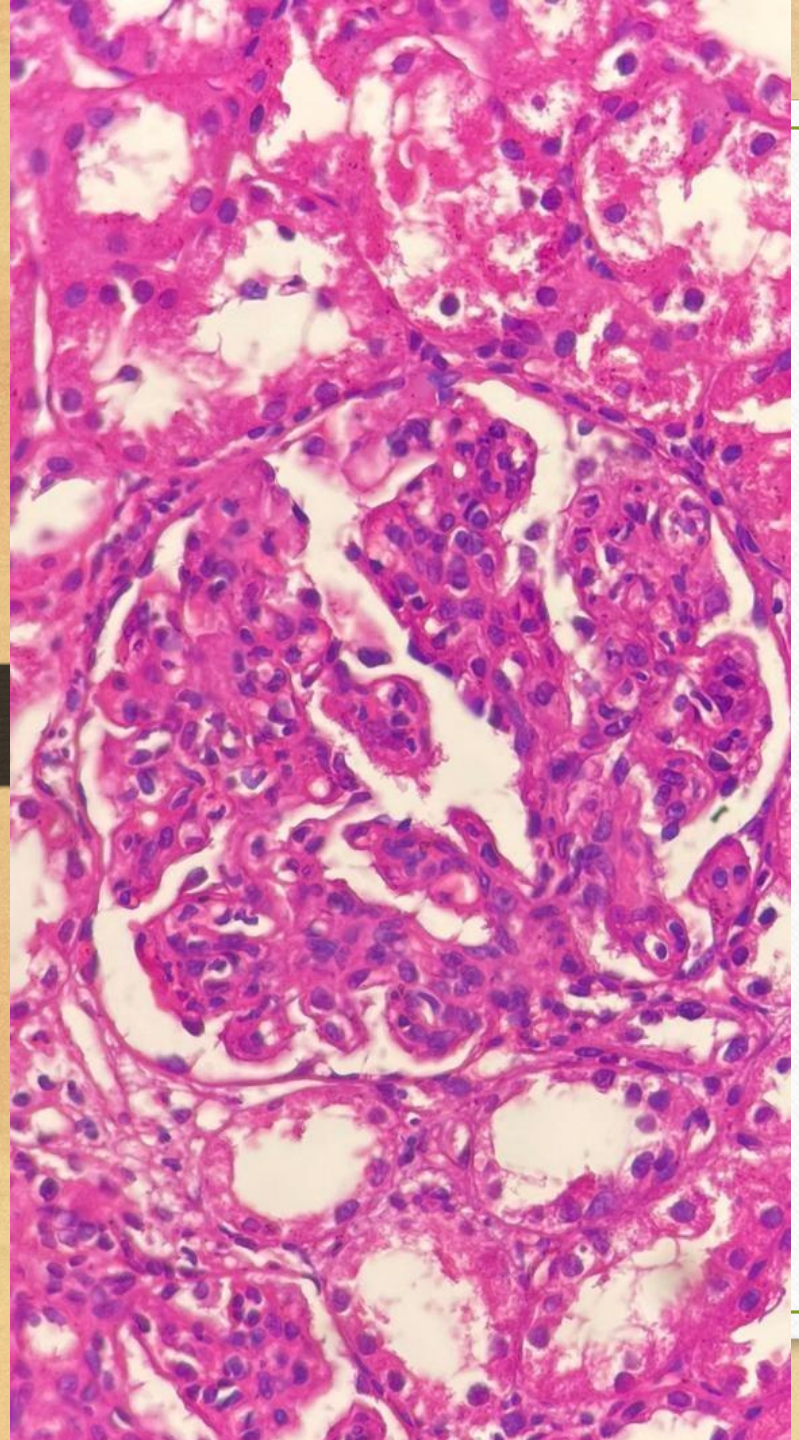
Report (1):

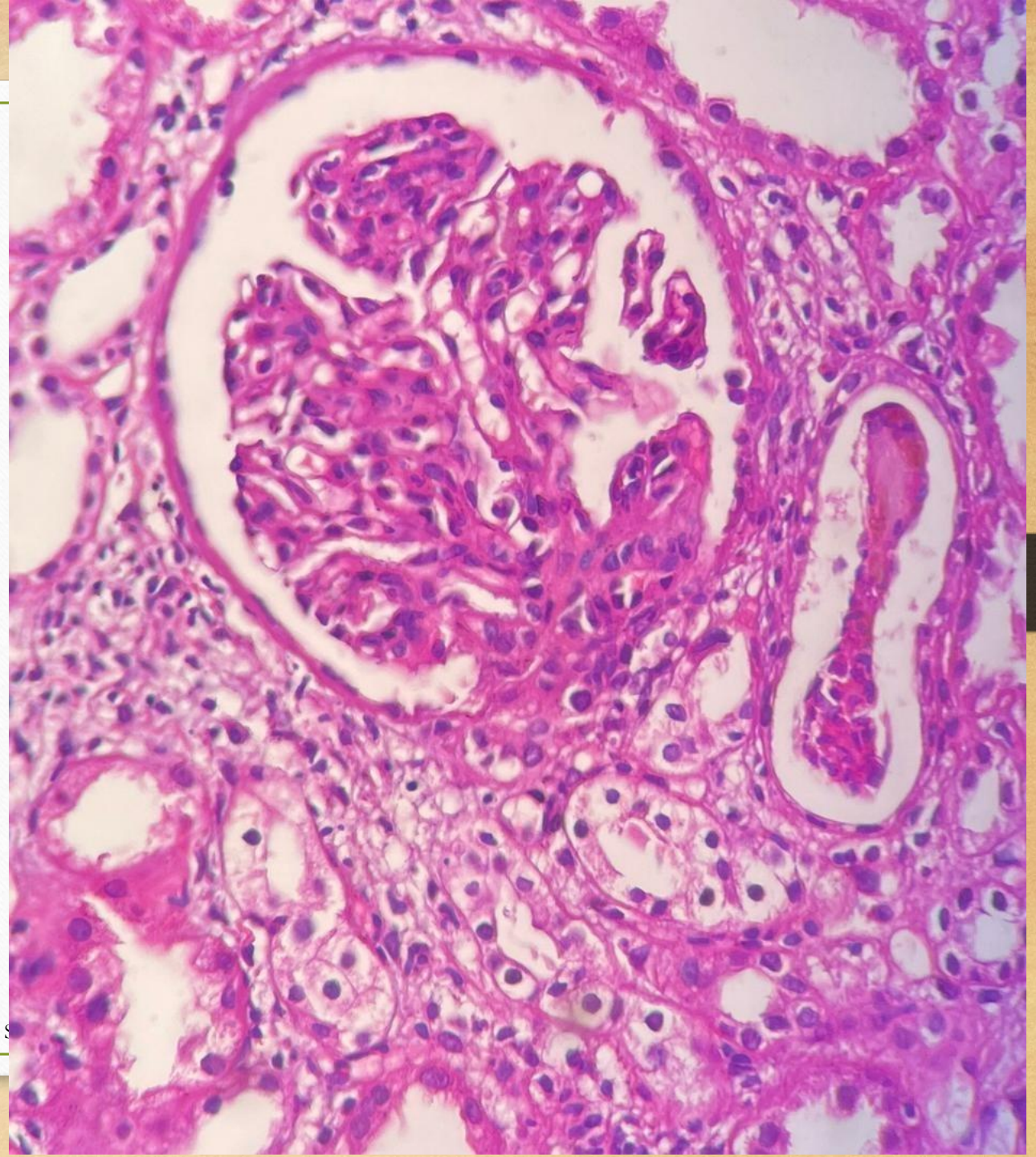
- Diffuse Membranoproliferative GN, immune mediated, IgA3+ dominant, mild focal tubulointerstitial nephritis
- IF: linear-granular deposits of **IgA+++** (mes & GBM)**, C3+ and C1q+** deposits, IgG: linear.
- Endocapillary proliferation in most glomeruli (severe activity of the disease, no chronicity of the disease)
- Work-up for infectious, autoimmune disease should be considered.

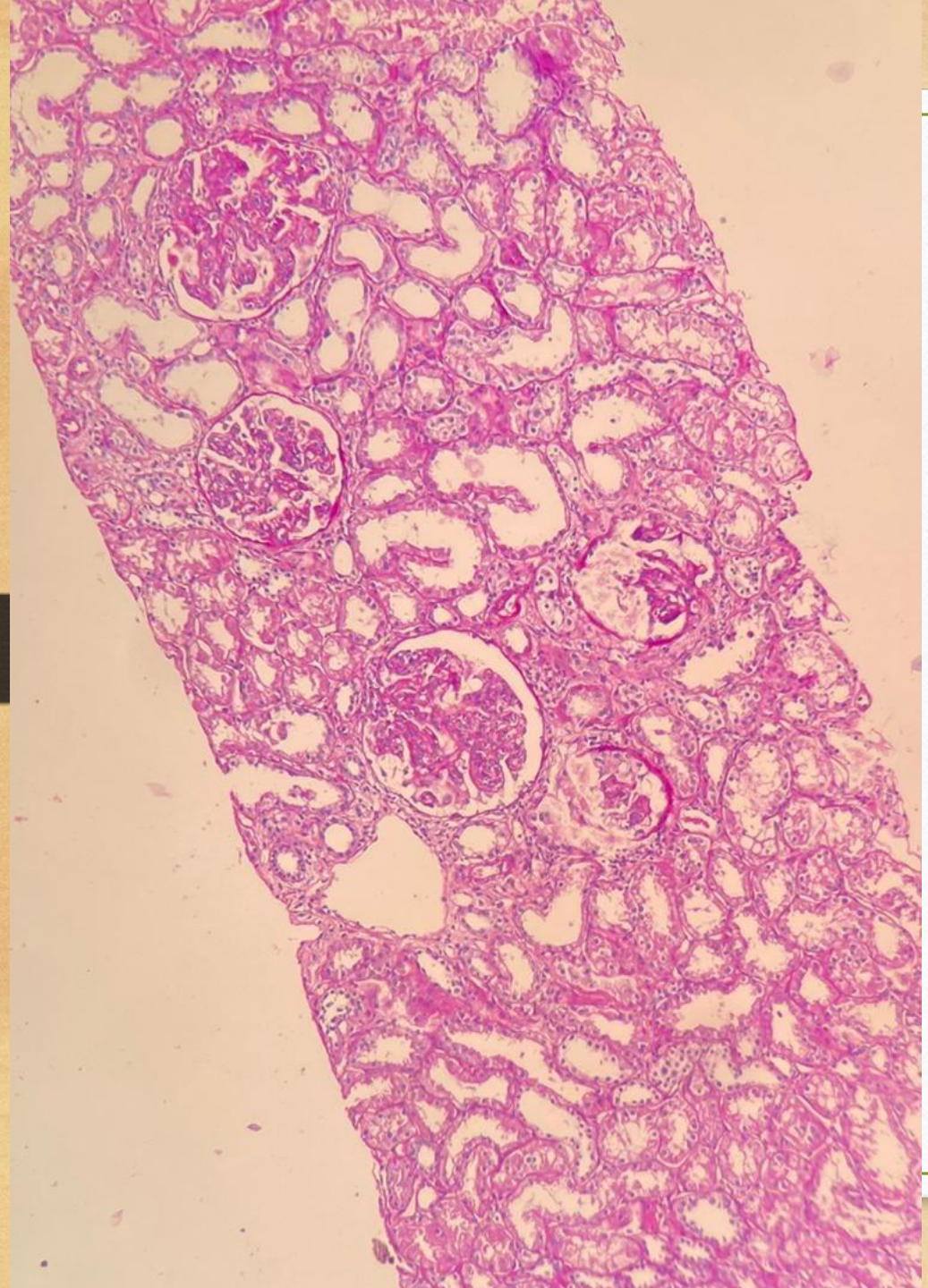


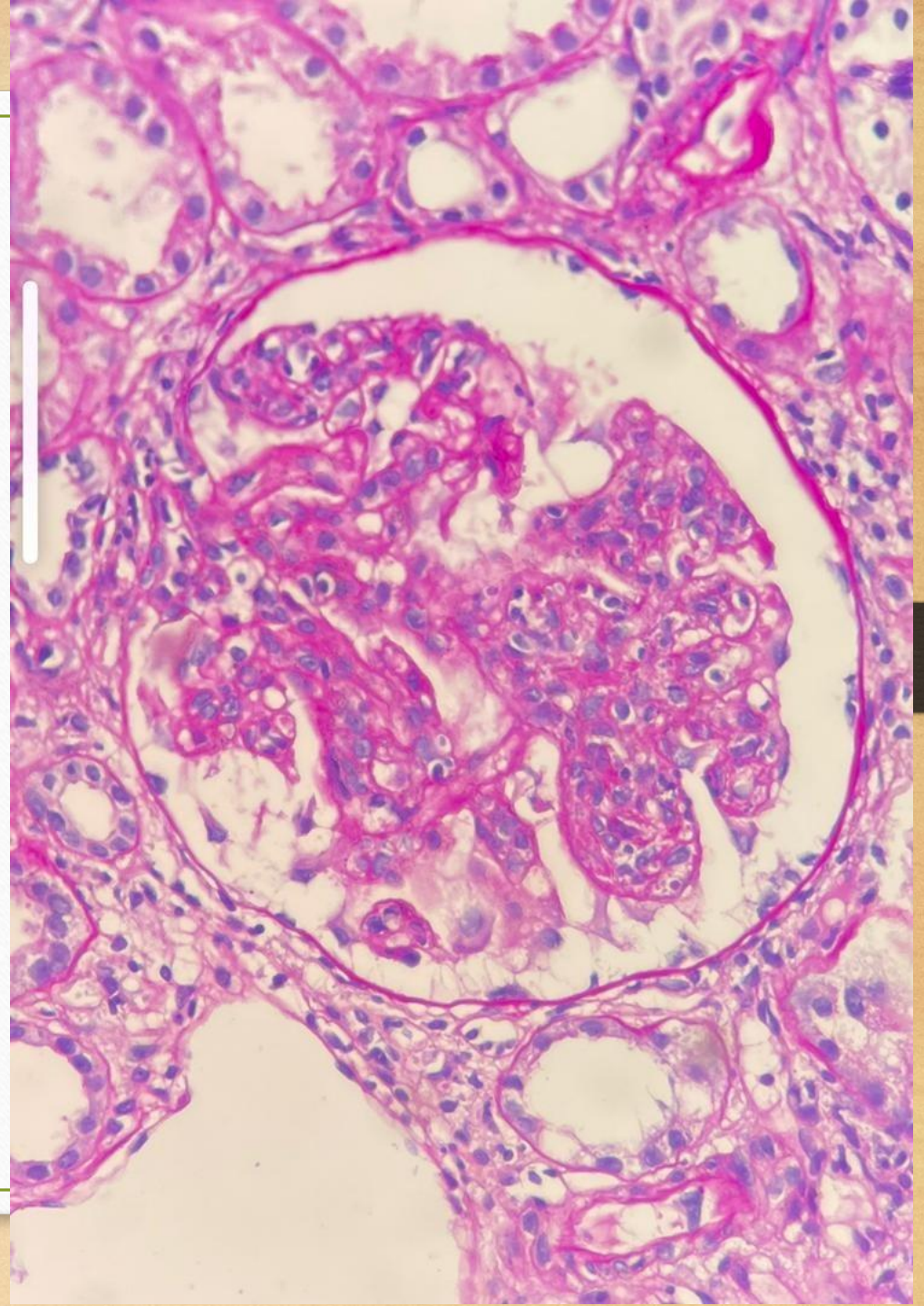
Seyrafian

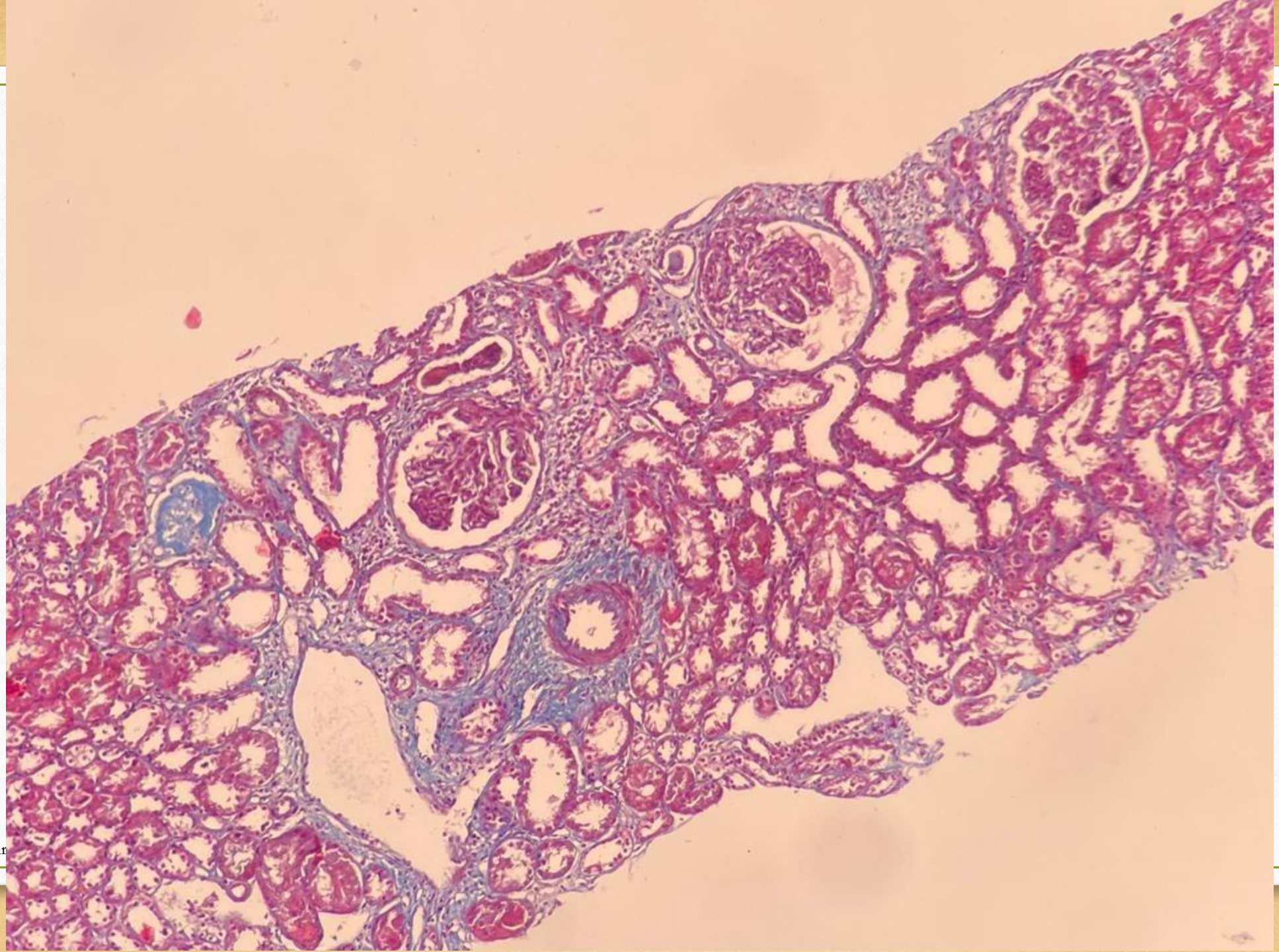




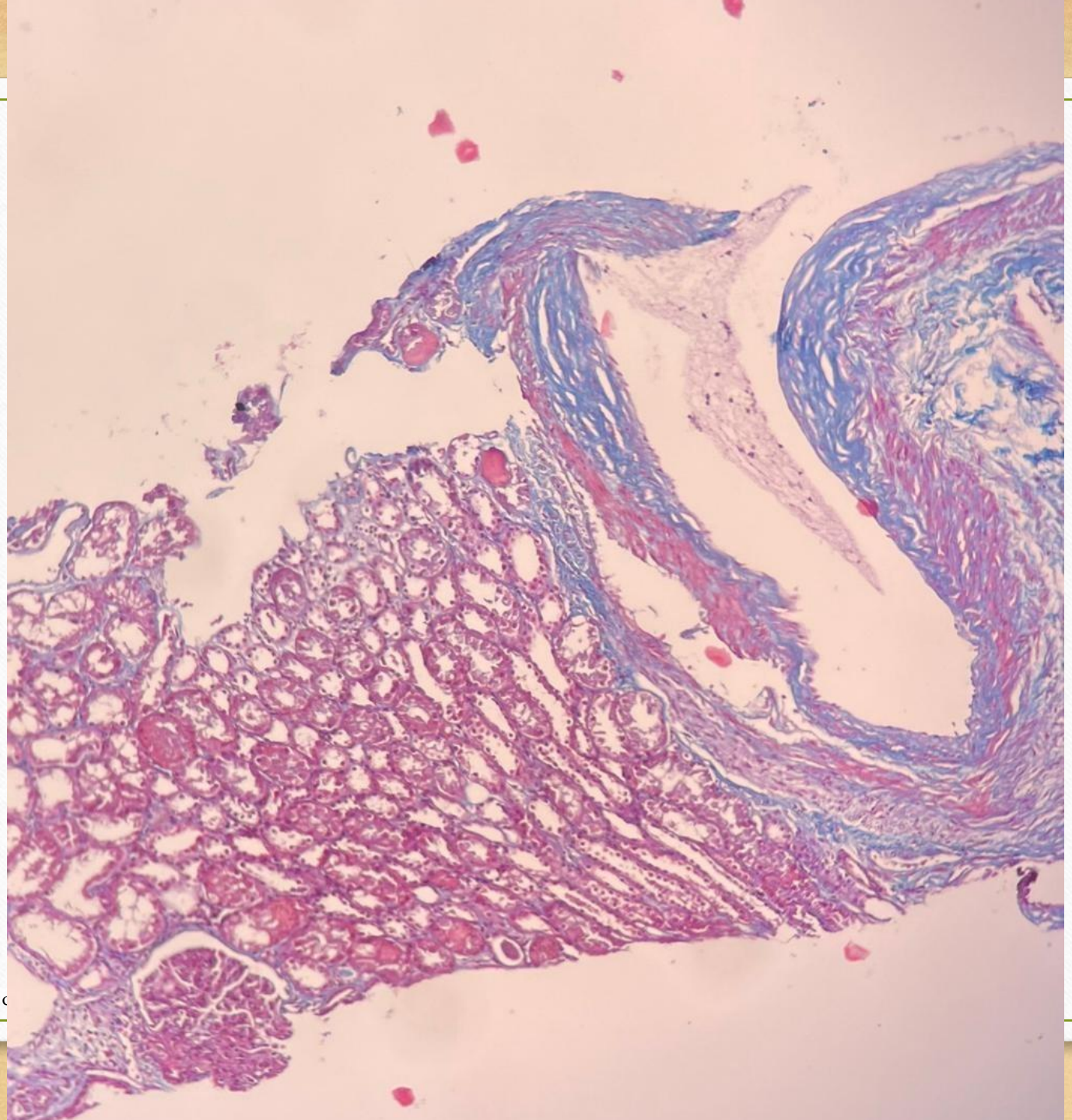








Nephr



Glomerular Involvement With Bacterial Infections (Visceral Infection)

- Abdominal, pulmonary, and retroperitoneal abscesses are known to be associated with glomerulonephritis.
- **Decreased serum complement** levels.
- All renal biopsies showed a diffuse proliferative **and crescentic** glomerulonephritis.
- If the infection was not cured or in whom therapy was delayed, chronic renal failure also developed.

The kidney (Brenner's) 2020

Anti GBM disease

Clinical features:

An abrupt, acute glomerulonephritis with severe oliguria or anuria. High risk of progression to ESRD if appropriate therapy is not instituted immediately.

Prompt treatment with plasmapheresis, corticosteroids, and cyclophosphamide results in patient survival of approximately 85% and renal survival of approximately 60%

The kidney (Brenner's) 2020

Anti GBM disease

Pathology:

LM: At the time of biopsy, 97% of patients have crescent formation, and 85% have crescents in 50% or more of glomeruli

- Mild: focal, segmental proliferative GN with segmental necrosis and small crescents.

The kidney (Brenner's) 2020

Anti GBM disease

Pathology:

IF: linear staining of the GBMs for Ig is indicative of anti-GBM glomerulonephritis.

- The immunoglobulin is predominantly IgG;
- Rare patients with IgA dominant,
- The diagnostic finding is an intense and diffuse linear staining for IgG.

The kidney (Brenner's) 2020

IgA nephropathy

The most common form of primary glomerular disease in Asia, (up to 30% to 40% of all biopsies,

Most common in the 2nd and 3rd decades of life and is much more common in males than females

Classification:

- **1- Primary**
- **2- Secondary**
- **3- Familial**

The kidney (Brenner's) 2020

IgA nephropathy

- Familial: 4% to 14% of patients with IgA nephropathy may have a family history of kidney disease, and systematic screening of asymptomatic first-degree relatives has detected hematuria in more than 25% of them.

The kidney (Brenner's) 2020

IgA nephropathy
Pathology

The **pathognomonic** finding is on **IF**:

- Dominant or codominant **mesangial deposits of IgA**, either alone, with IgG, with IgM, with a predominance for lambda light chains.
- C3 over 90 % of cases.
- **C1q** is **almost always absent**,

LM: mesangial hypercellularity, and matrix expansion is commonly focal.

Uptodate®- Clinical presentation and diagnosis of IgA nephropathy

Secondary IgA nephropathy

IgA vasculitis (Henoch-Schönlein purpura)	Crohn's disease	Cyclic neutropenia	Berger's disease
Human immunodeficiency virus infection	Liver disease	Immunothrombocytopenia	Leprosy
Toxoplasmosis	Alcoholic cirrhosis	Gluten-sensitive enteropathy	Pulmonary hemosiderosis
Seronegative spondyloarthropathy	Ankylosing spondylitis	Scleritis, Sicca syndrome	Dermatitis herpetiformis
Celiac disease	Reiter's syndrome	Mastitis	Neoplasia: Mycosi fungoides, Lung carcinoma, Mucin-secreting carcinoma

The kidney (Brenner's) 2020

Membranoproliferative GN

- The C3 level is persistently depressed in approximately 75% of MPGN patients.
- LM: **Infiltrating mononuclear leukocytes and neutrophils** contribute to the **glomerular hypercellularity**.
  IF: C3, immunoglobulin (IgG or IgM).
- **Rare specimens have a predominance of IgA and can be considered an MPGN expression of IgA nephropathy**.
- **Treatment:** Low-dose, alternate-day prednisone therapy may improve renal function.

The kidney (Brenner's) 2020

Secondary Causes of Membranoproliferative Glomerulonephritis (MPGN) Associated With Infection

Hepatitis B and C	Shunt nephritis
Visceral abscesses	Schistosoma nephropathy
Infective endocarditis	Mycoplasma infection
Quartan malaria	Osteomyelitis

The kidney (Brenner's) 2020

Patient: management

- **Prednisolone 75 mg oral daily + antibiotics**
- Refer to Khorshid Hospital, stayed less than one day and discharged.
- Patients referred to clinic one week later and complained of severe edema.
- Prednisolone dose decreased to 50 mg/ day and asked for another pathologist to report.

Post-infectious Glomerulonephritis

- **Clinical presentation:** benign asymptomatic to RPGN requiring dialysis.
- **IgA-dominant nephritis** entity recently defined associated with staphylococcal infections.
- Endocarditis-associated nephritis and shunt nephritis are special sub-subtypes of PIGN.

Journal Paediatrics and International Child Health, Volume 37, 2017 - Issue 4: Renal diseases and disorders of the urinary tract

Advances In Anatomic Pathology: September 2012 - Volume 19 - Issue 5 - p 338-347

nephron
Clinical Practice

Minireview

Nephron Clin Pract 2011;119:c18–c26
DOI: 10.1159/000324180

Published online: June 9, 2011

IgA-Dominant Postinfectious Glomerulonephritis: A New Twist on an Old Disease

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Nephron Clin Pract 2011;119:c18–c26

IgA-dominant PIGN..

- A morphologic variant of APIGN.
- The alternative designation 'IgA-dominant acute post-staphylococcal glomerulonephritis' has been applied.
- **IgA is the sole or dominant** immunoglobulin in IgA-dominant APIGN.
- This variant of APIGN must be distinguished from IgA nephropathy.

Nephron Clin Pract 2011;119:c18–c26

IgA-dominant PIGN..

- **The most common site of infection is skin**, (cellulitis, surgical wound infections, skin abscesses and IV line infection), lung, urinary tract, bone, heart, deep-seated abscesses and upper respiratory tract.
- **Clinical renal** presentations included renal failure (acute or rapidly progressive), hematuria, proteinuria and hypertension.

Nephron Clin Pract 2011;119:c18–c26

IgA-dominant PIGN..

- Serum **creatinine**: range **1.2 to 14.5** mg/dl (mean: 4.0 mg/dl.
- **Proteinuria**: range **0.15–15 g**/day,
- **Nephrotic range** in **51%** of patients.
- **Hypocomplementemia** in **69 %** of patients.

Nephron Clin Pract 2011;119:c18–c26

IgA-dominant PIGN

Features favoring IgA-dominant PIGN over IgA nephropathy	
Clinical features	***Pathologic features***
Intercurrent culture-documented staphylococcal infection	**Endocapillary proliferation with neutrophil infiltration on LM**
Hypocomplementemia	Stronger staining for C3 than IgA on IF
Presentation in older age	'Starry sky' pattern on IF
History of diabetes mellitus	Subepithelial 'humps' on EM
Acute renal failure at presentation	

Nephron Clin Pract 2011;119:c18–c26

IgA-dominant PIGN

Post-staphylococcal glomerulonephritis:

- IgA-dominant or codominant deposits
- Normal serum complement
- Only mesangial hypercellularity on LM
- No subepithelial deposits on EM.

Likely primary IgA nephropathy (in which an intercurrent infection has caused exacerbation or recrudescence of existing nephritis) rather than true APIGN.

Nephron Clin Pract 2011;119:c18–c26

J Nephrol (2014) 27:229–239
DOI 10.1007/s40620-013-0018-z

REVIEW

New trends of an old disease: the acute post infectious glomerulonephritis at the beginning of the new millenium

Piero Stratta · Claudio Musetti · Antonella Barreca · Gianna Mazzucco

Received: 2 April 2013 / Accepted: 9 August 2013 / Published online: 31 January 2014

Pathogenesos post staphylococcal acute GN with IgA-dominant deposits:

- Exotoxin superantigens stimulate an abnormal IgA production, forming IgA immune-complexes

Prevalence of infective agents cause acute PIGN

Species	Children and young adults	Elderly (>65 years)
Streptococcus	>95%	16-30 %
Staphylococcus	Uncommon	24-60 %
E-Coli	very rare	5- 10 %
Klebsiella, anterobacter	very rare	2 %

J Nephrol (2014) 27:229–239

	Species	Children and young adults	Elderly (>65 years)
Bacteria	*Streptococcus*	>95 %	16–30 %
	Group A Beta-hemolytic type 12		
	Type M 1–4, 18, 25, 31, 49, 52, 55–57, 59-61		
	Group C		
	Group G		
	Staphylococcus epidermidis, S. haemolyticus, S. aureus	Uncommon	24–60 %
	Escherichia coli	Very rare	5–10 %
	Pseudomonas		3 %
	Acinetobacter		
	Serratia, Proteus		2 %
	Klebsiella, Enterobacter		2 %
	Haemophilus influenzae	Very rare	1–2 %
	Enterococcus		0–2 %
	Salmonella, Campylobacter	Very rare	Rare (<1 %)
	Legionella, *Brucella*		Rare (<1 %)
	Borrelia, Treponema		Rare (<1 %)
	Mycobacteria (tuberculosis, avium, laprae)—might be associated with chronic GNs		Rare (<1 %)
	Neisseria (mainly associated with membranoproliferative GN and subacute endocarditis)		Rare (<1 %)

Patient management..
1 month later:

- Prednisolone 25 mg
- Furosemide 80
- Valsartan 160
- Vit D3 50.000 /wk
- Calcium-Zinc-Mg* 2
- Apixaban 10/d

- Tavanex 750 daily
- Clindamycin 600*3 daily
- Pantoprazole 40
- Carvedilol 6.25*2
- Nephrovit
- PD poetin 4000*2/ wk

Therapy of PIGN

- **Infection:**

  Antibiosis and supportive therapy

- **Immunosupressive:**

1. **Rapidly progressive renal failure and crescents** in 30–50 % of glomeruli, which is a strongly negative prognostic factor.
2. **Severe interstitial infiltrate**

   The preferred therapy is usually based on iv **steroid pulses** (500–1000 mg or 10–15 mg/kg each) for **three consecutive days**, followed by **oral steroids** according to clinical evolution and renal function recovery.

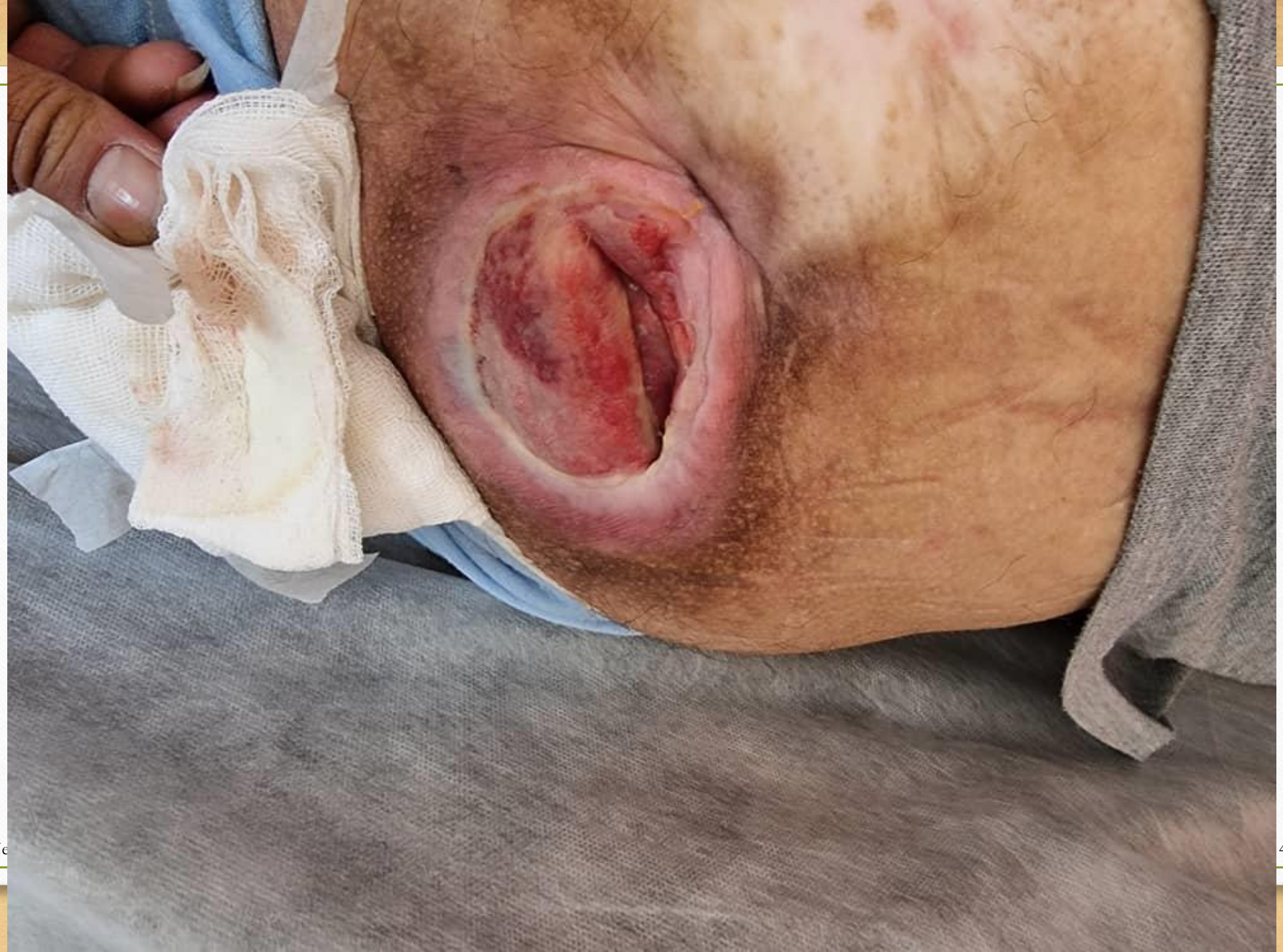
J Nephrol (2014) 27:229–239

Labs, 2 months later

- US: normal kidney size 121, 123 mm, no hydronephrosis and fluid in abdomen or pelvis, with Foley catheter balloon in the bladder.

- Cr=1.96 mg, eGFR~ 40
- **Serum Alb=3.1** vs. 2
- Hb=10
- **Urine protein** (24 hr)=**1900** mg vs. 10800 mg

Nephro



Definitions of Various Conditions in Nephrotic Syndrome in Adults

Steroid-sensitive nephrotic syndrome (SSNS)	nephrotic syndrome that had remission with prednisone, 1 mg/kg, daily or 2 mg/kg, every other day use within 4 mo
Steroid-resistant nephrotic syndrome (SRNS)	nephrotic syndrome that failed to achieve remission with prednisone, 1 mg/kg, daily or 2 mg/kg, every other day use for 4 mo
Steroid dependence (SD)	2 consecutive relapses during steroid therapy or within 2 wk of ceasing therapy
Frequent relapse (FR)	≥2 relapses within 6 mo of initial response or 4+ relapses within any 12-mo period
Infrequent relapse	1 relapse within 6 mo of initial response, or 1-3 relapses in any 12-mo period and treated with steroids
Remission	**reduction of proteinuria to < 3.5 g/d with stable serum creatinine level (change < 25%)**

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Prognosis of PIGN

- Excellent prognosis,
- But long-term follow-up may be needed.

Outcomes are poor:

- Elderly patients
- Underlying disease.

Nature Reviews Nephrology **volume 5**, pages259–269 (2009)

Probable Diagnoses

1. Anti GBM disease ≠ no crescent or AKI
2. Secondary IgA nephropathy ≠ no secondary infection
3. Secondary MPGN (post-infectious GN) ≠ no depressed C3
4. Amyloidosis ≠ negative congo-red
5. Primary IgA nephropathy


Thanks for your patience