Intravenous immunoglobulin (IV IG) and kidney injury

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1402/10/12 - 2/1/2024

Case

- A 40 year/old, **8 weeks' pregnant** woman was admitted to the hospital with C.C. of diarrhea, vomiting, fever and vaginal bleeding.
- She was prescribed 10 grams of IV IG, (immunorel®, Rliance, India,) with maltose stabilizer, by her gynecologist three weeks before admission for prevention of abortion.
- During infusion before running out of IVIG, she developed severe flank pain so infusion was discontinued.
- Then she took only three diclofenac suppositories for her flank pain next days.
- Also progesterone amp. for Vag. Bleed., recovered.

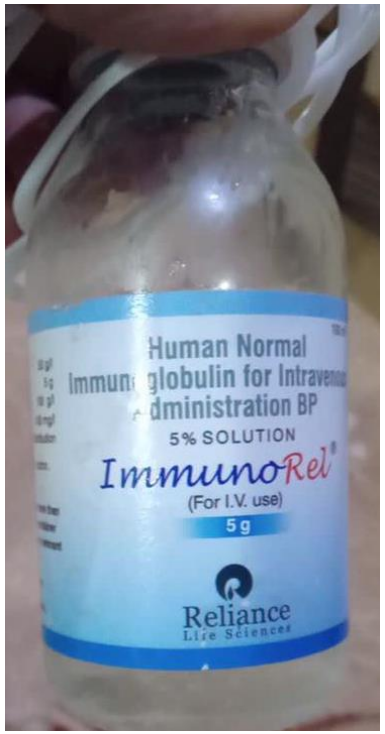
Case..

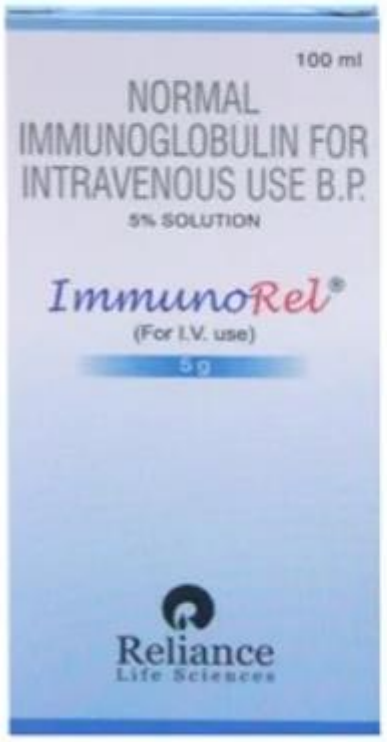
Past Hx:

- IVIG infusion in this and previous pregnancies with no complications.
- No history of renal, hematologic or autoimmune diseases except hypertension, depression and **three spontaneous abortions.**
- Before admission: Beta HCG more than 200 mIU/ml (high), normal renal function and urinalysis.

Case…

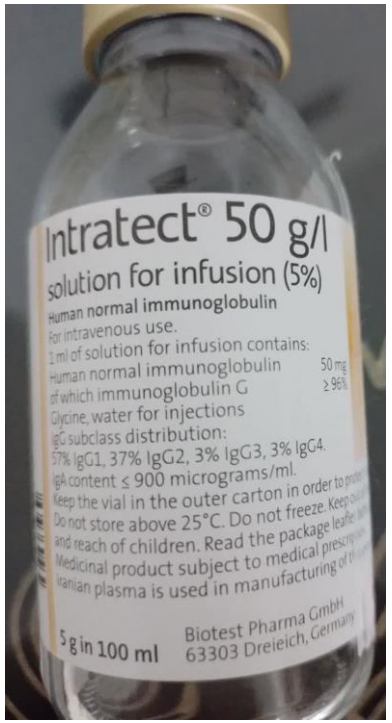
Last IVIG





Immunorel

Previous IVIG



Intratect

Intravenous immunoglobulin (IVIG)

- Purified from >10,000 liters of human plasma/ batch.
- Human plasma from >10,000 screened paid and volunteer donors.
- Takes approximately nine months that separate the immunoglobulin fraction from other proteins and plasma constituents.

WHO standards:

- At least 1000 individual donors
- As little IgA as possible
- Free from preservatives or stabilizers that might accumulate in vivo.

Intravenous immunoglobulin (IVIG)

- Generally >95 % polyvalent IgG.
- Stabilizers: stabilize or prevent aggregation of the IgG molecules: sucrose, glucose, maltose or amino acids such as glycine or proline.
- Solvent/detergent: inactivating lipid-enveloped viruses (eg, HIV, HBV, HAV and parvovirus B19)

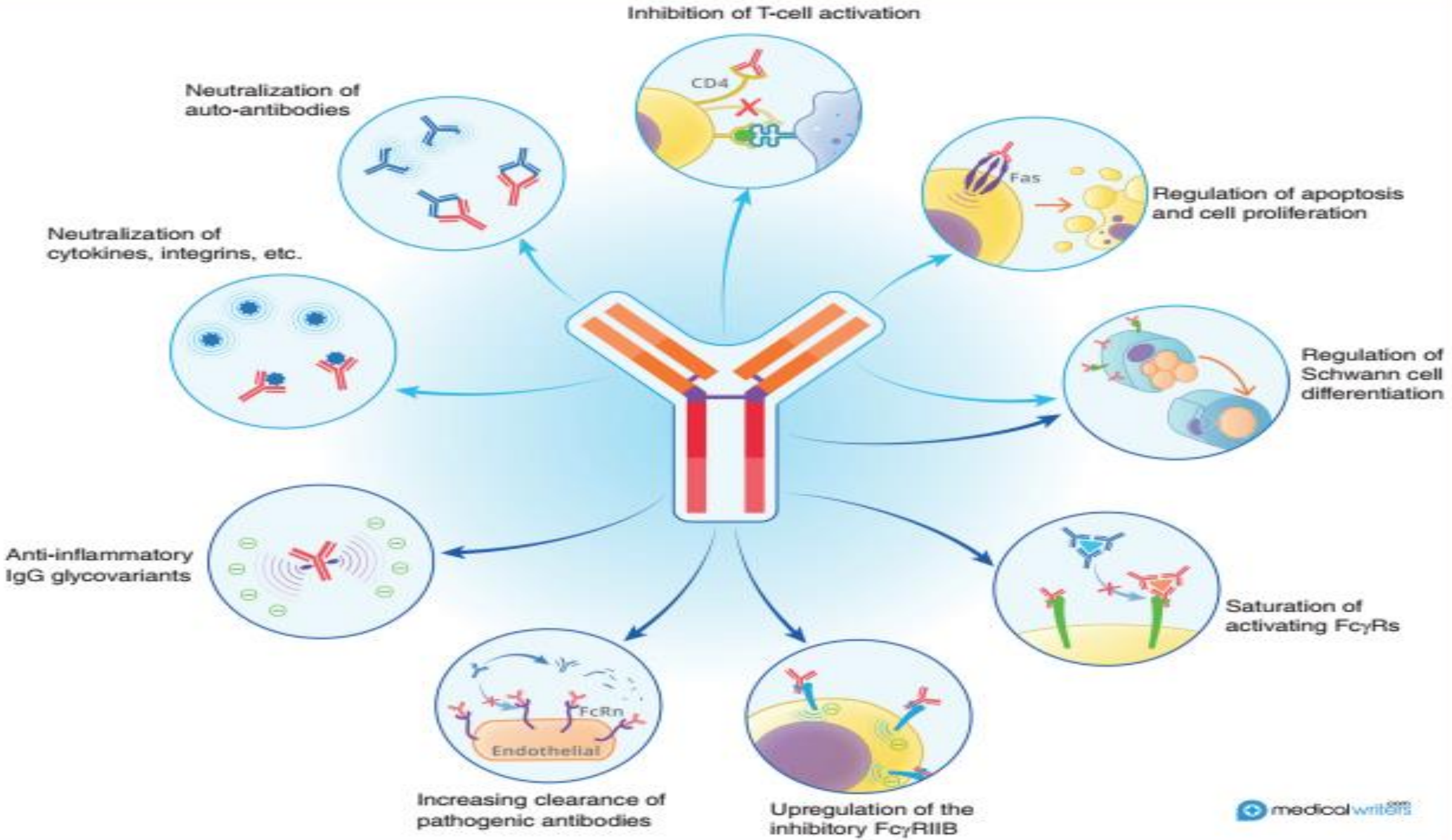
MECHANISMS OF ACTION

1. Protection against infection
    1. Hypogammaglobulinemia, antibody deficiency disorders
2. Alloimmunization
    1. RhD-negative woman with a RhD-positive fetus.
3. Suppression of inflammatory/autoimmune processes

MECHANISMS OF ACTION

3. Suppression of inflammatory/autoimmune processes

1. **Blocking of fc receptors** on phagocytic (chronic inflammatory demyelinating polyneuropathy (CIDP)
2. Prevent **reticuloendothelial uptake** of autoantibody-coated platelets (ITP)
3. **Blockade of leukocyte adhesion molecule** binding to the vascular endothelium (kawasaki disease),
4. Alterations in **regulatory T cells** (Tregs), (mouse model of multiple sclerosis).
5. Effects on the **complement** (membranous nephropathy and dermatomyositis),
6. Provision of **neutralizing antibodies** to microbial toxins (staphylococcal toxic shock syndrome)


Inhibition of T-cell activation
CD4
Neutralization of auto-antibodies
Neutralization of cytokines, integrins, etc.
Fas
Regulation of apoptosis and cell proliferation
Regulation of Schwann cell differentiation
Anti-inflammatory IgG glycovariants
Saturation of activating FcγRs
FcRn
Endothelial
Increasing clearance of pathogenic antibodies
Upregulation of the inhibitory FcγRIIB
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Uses for IVIG

1. Immunodeficiency states, both primary and secondary
2. Neuroimmunologic disorders
3. Autoimmune/inflammatory conditions
4. Infections and infection-related disorders
5. Alloimmune processes

Uses for IVIG

1. **Immunodeficiency states, both primary and secondary**
   - Inborn errors of immunity,
   - **CLL,**
   - **Multiple myeloma,**
   - Reduced immune function (**hematopoietic stem cell transplantation**
   - **Severe protein loss**

Uses for IVIG

2. Neuroimmunologic disorders

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy
- **Guillain-Barre syndrome**
- **Myasthenia gravis**

Uses for IVIG

3. Autoimmune/inflammatory conditions

- Immune thrombocytopenia (**ITP**)
- Autoimmune hemolytic anemia (**AIHA**)
- Autoimmune neutropenia
- Acquired von willebrand syndrome caused by autoantibodies against von willebrand factor
- Kawasaki disease
- Multisystem inflammatory disease in children (MIS-C) associated with COVID-19

Uses for IVIG..

4. Infections and infection-related disorders
   - Chronic **parvovirus infection** complicated by anemia,
   - Toxic shock syndrome
   - Measles post exposure prophylaxis (if the patient is immunocompromised or nonimmune)

Uses for IVIG ..

5. Alloimmune processes
   - Hemolytic disease of the fetus and newborn (HDFN),
   - Post-transfusion purpura,
   - **Antibody-mediated organ transplant rejection**,
   - Hyperhemolytic crisis in individuals with sickle cell disease who have received transfusions.

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REVIEW ARTICLE

AJRI American Journal of Reproductive Immunology WILEY

A systemic review of intravenous immunoglobulin G treatment in women with recurrent implantation failures and recurrent pregnancy losses

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Several publications support the use of IVIG in patients with RIF and RPL, especially those with abnormal immunity, and positive autoantibodies.

Pre-conception treatment seems more effective than post-conception treatment.

Am J Reprod Immunol. **2021**;85:e13395

PRETREATMENT TESTING

Passively transferred antibodies in the IVIG, especially EBV, CMV, and HBV.

- CBC, transaminases, glucose, serum creatinine, and urinalysis (identify pre-existing infection or risk for complications).

If clinically indicated:

- Viral infections (eg, hepatitis),
- Pathogen or autoimmune process,
- Bloodborne pathogens.
- Risk of transmission of viruses or other pathogens from IVIG is extremely low.

Administration of IVIG

- Store in refrigerators,
- Room temperature before administration,
- No microwave,
- No vigorous mixing causing excessive foaming
- Products with any evidence of particulates or broken seals should not be used.

Premedications

Many patients do **not require premedication**

If the first infusion, a severe reaction particularly headaches.

- **Acetaminophen** (650 to 1000 mg orally) **or** a NSAID (Ibuprofen 400 to 800 mg orally) **30 minutes prior** to the infusion.
- **Diphenhydramine:** 25 to 50 mg orally/IV/IM **(before or at the beginning**).
- **Glucocorticoids:** methylprednisolone 40 to 60 mg **30 minutes before** infusion, hydrocortisone sodium succinate 100 mg IV

- **Changing IVIG: severe adverse reactions**, particularly headaches

Prehydration

Hydrated prior to the high dose IVIG due to hyperviscosity.

Risk factors for thrombosis and/or renal complications:

- Pre-existing renal insufficiency,
- DM,
- Age > 65 years,
- Paraproteinemia,
- Heart disease,
- Use of nephrotoxic agents.

IVIG containing sucrose, osmotic renal damage, no longer available.

Hydration: Normal saline 10 to 20 mL/kg

Infusion rates

- Adverse effects associated with the rate of administration.
- Rate: 0.01 mL/kg/min. ~ 0.5 or 1 mg/kg/min. (5 or 10%), increase to 0.08 mL/kg/min.
- Increased at 20- to 30-minute intervals, monitoring vital signs or symptoms.

Selection among IVIG products

Rout: The SC. fewer adverse effects and less variable serum IgG levels than IV.

Stabilizers:

- **Maltose:** some glucose meters detect maltose as glucose,
- **Sucrose:** increased risk of osmotic renal injury
- **Sorbitol**: hereditary fructose intolerance: recurrent vomiting, abdominal pain and hypoglycemia
- **Proline and glycine**

Selection among IVIG products...

- Not to change products.
- Alternative products only with the clinician's approval.
- If alternative product to a patient on chronic therapy, use slow infusion rates initially and to monitor the patient closely.

Case...

- On admission she had no fever. BP:140/90, T:36.5, mild vaginal bleeding (spotting).
- There were many RBCs and RBC casts in her urine sediment.
- Ultrasonography (US): uterus and ovaries were normal, adnexal EP, kidneys length: right 111 mm and left 109 mm, no evidence of obstruction,
- In color Doppler US, renal artery stenosis was not detected.
- During admission BHCG from 117 returned to 11mIU/ml (nl).

Case…

Lab values			
BUN (mg/dl)	182 → 80	**WBC** (/mm3)	10700
Cr (mg/dl)	19.5 → 10	**Hb**	10.9
Uric acid (mg/dl)	20 → 10	**Plt**	489000
AST	10	**Beta HCG**	117 (1-10 nl)
ALT	6	**Na** (mEq/L)	153
ALKP	200	**K** (mEq/L)	5.9

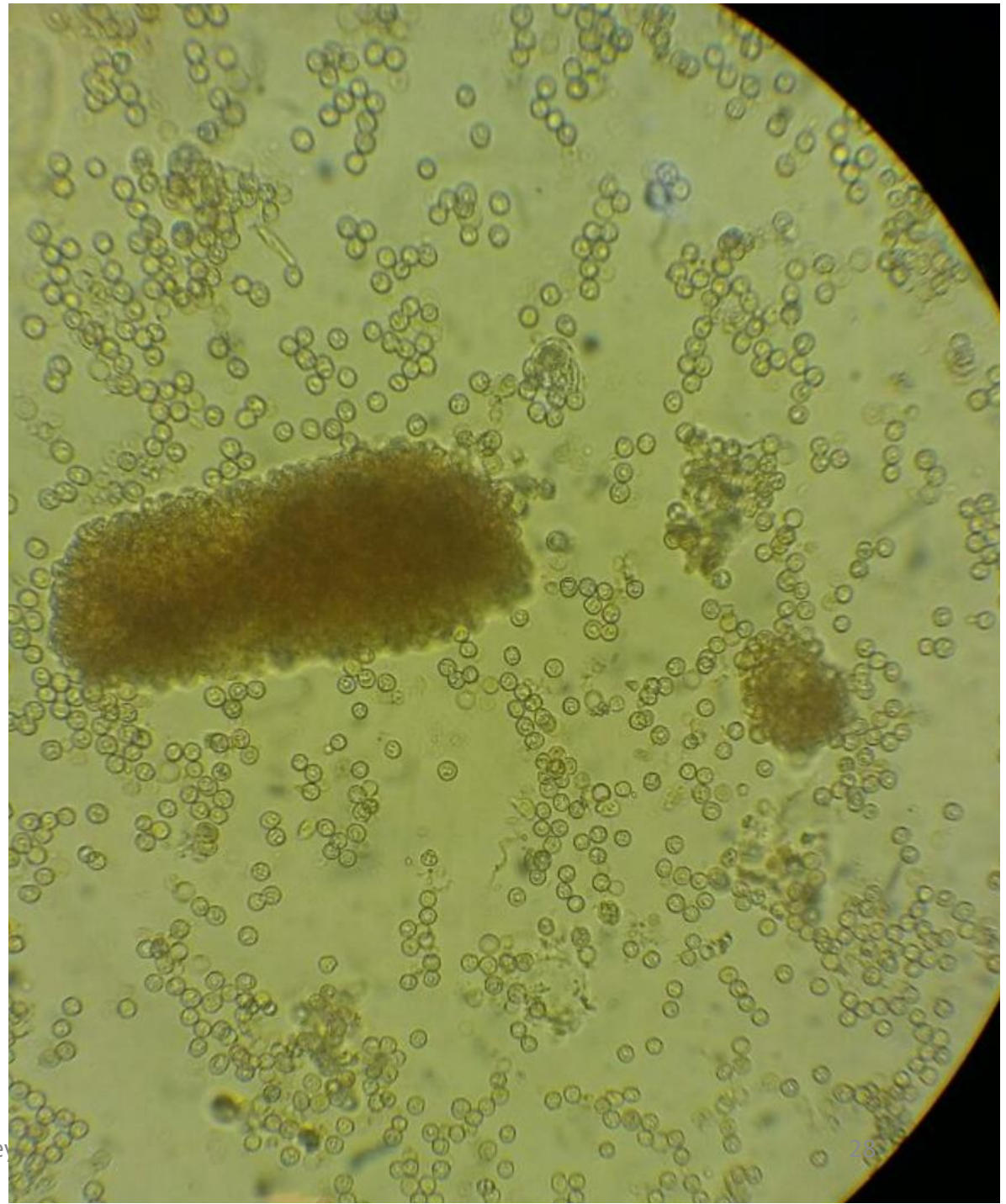
Case…

Bili total (mg/dl)	0.3	**INR**	1.24
Ca (mg/dl)	9.9	**aPTT**	28
Ph (mg/dl)	7.7	**Fibrinogen** (mg/dl) ⬆	518
Mg (mg/dl)	2.9	**HIV Ab**	Neg
LDH	764	**HBs Ag**	Neg
CRP	16	**HCV Ab**	Neg
B2-glycoprotein (IgM)	Neg	**B2-glycoprotein (IgG)**	Neg

IVIG and Kidney injury

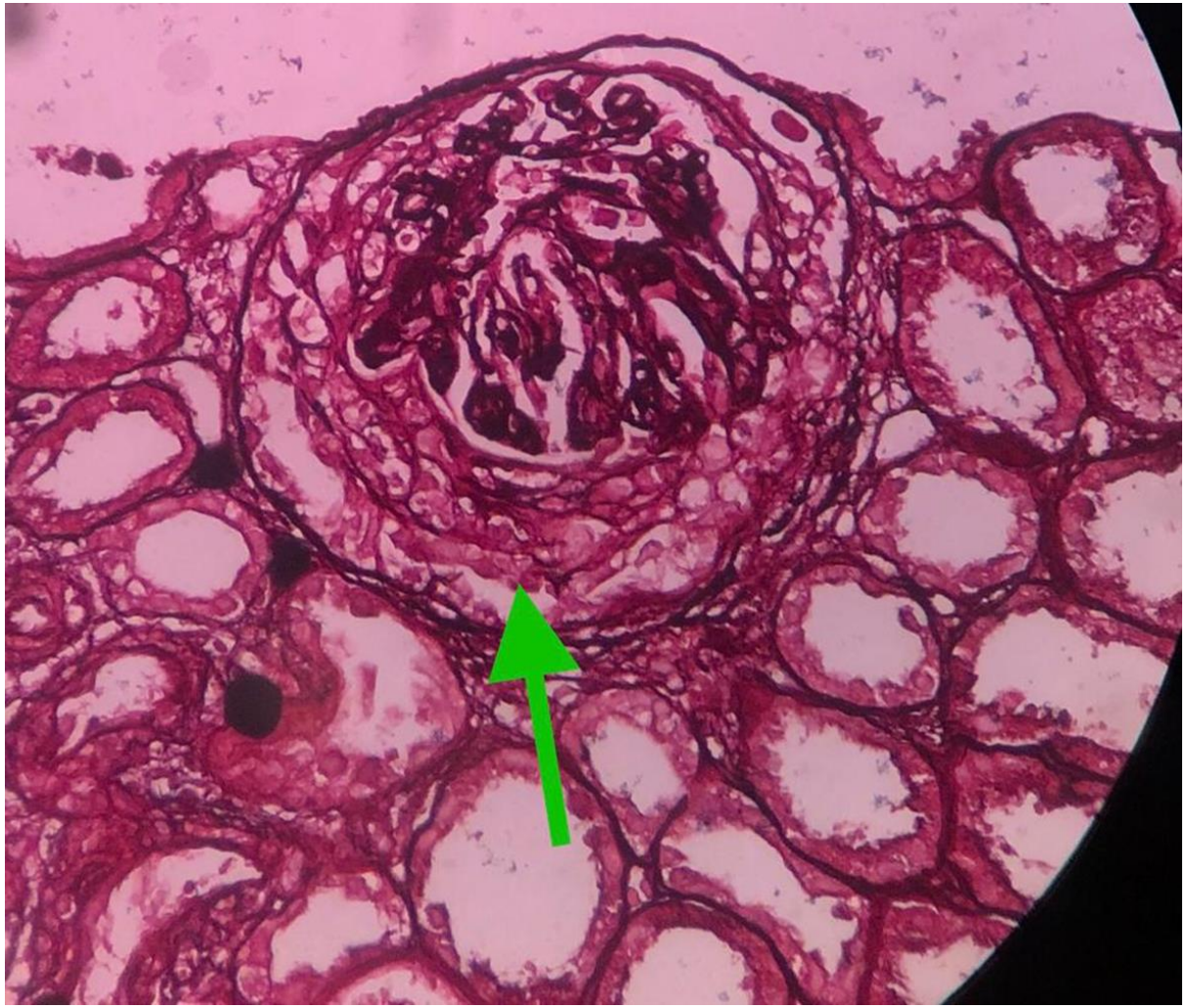
Case

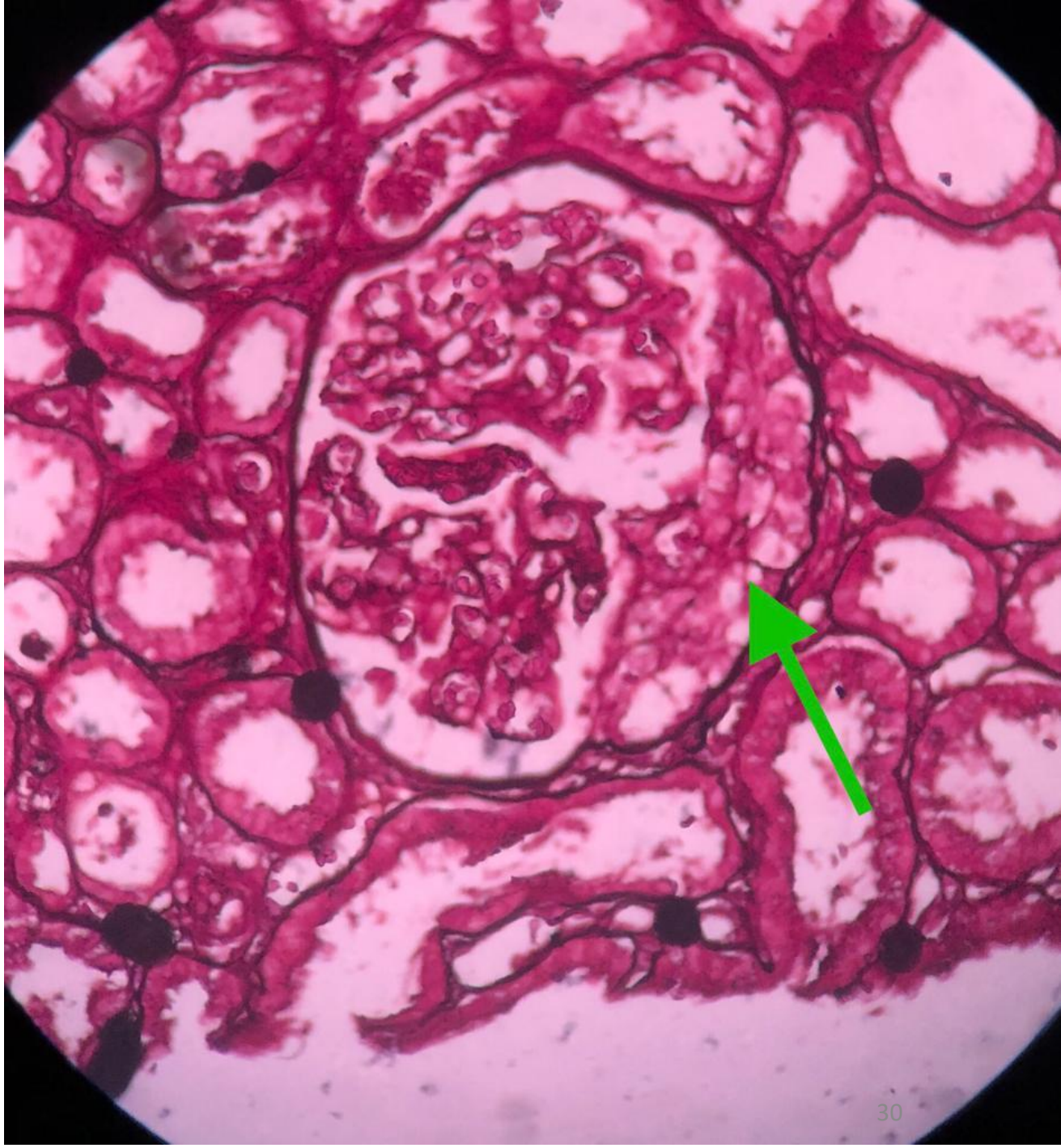
U/A	pr 2+, blood 3+, leuc estr–RBC many	ANCA: (MPO, PR3) (U/ml)	Neg
Ur. Pr. mg/d	576	Ur. Cr. mg/d	427
Ur. vol.	600	ANA(IF) (titer)	Neg
B/C	Neg	CH50 (mg/dl)	Nl
U/C	Kleb, 80.000 CFU/ml	C3 (mg/dl)	Nl
pH	7.28	C4 (mg/dl)	42(40)
HCO3	10	Cryoglobulin	Neg
pCO2	23	Anti-dsDNA (mIU/ml)	Neg
T3,T4, TSH	Nl	Anti-GBM (U/ml)	Neg



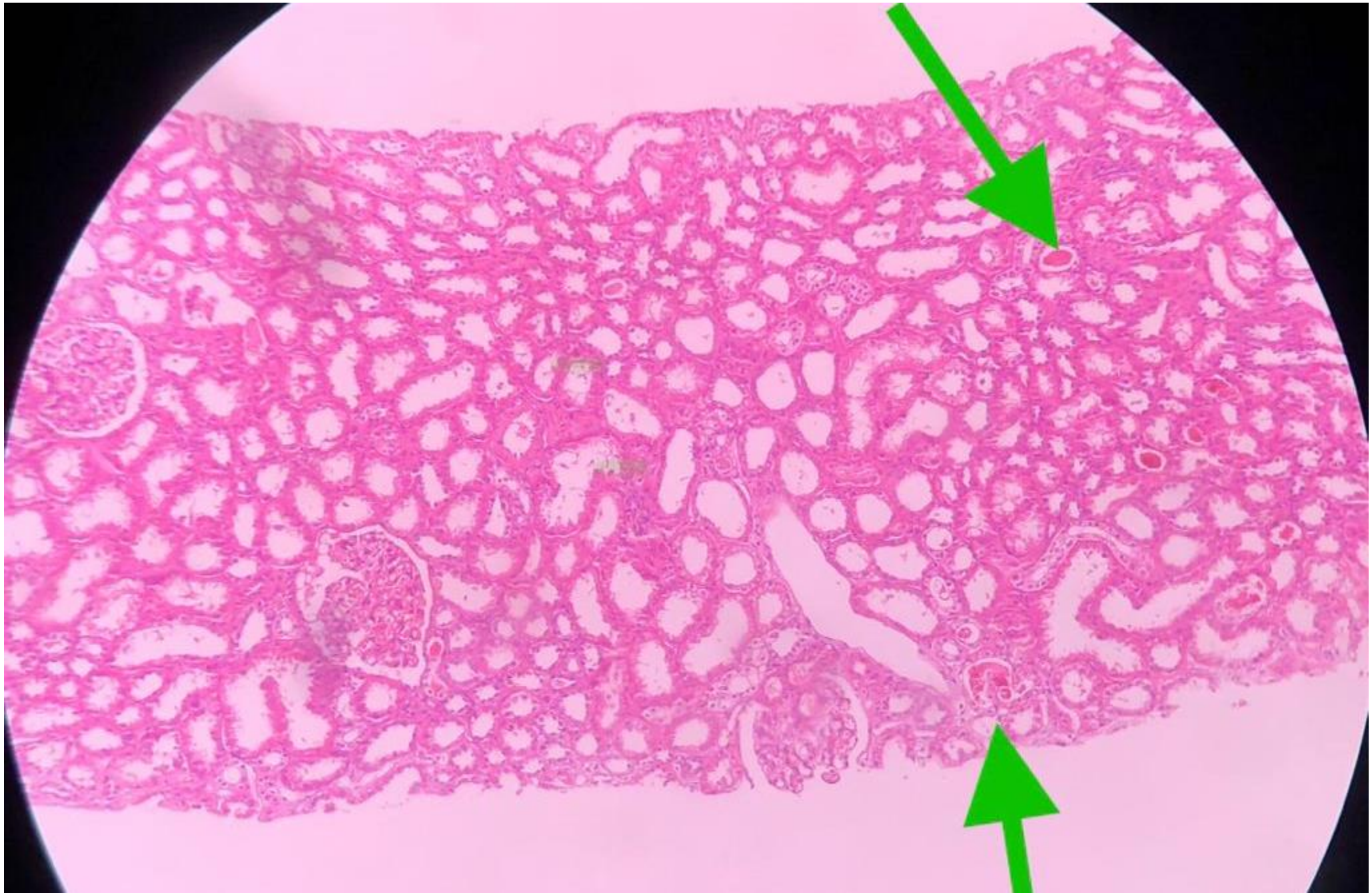
Case...

- She underwent hemodialysis, four sessions.
- High dose methylprednisolone (750 mg) daily for 3 days was started on third admission day.
- 6 days after admission kidney biopsy was done.

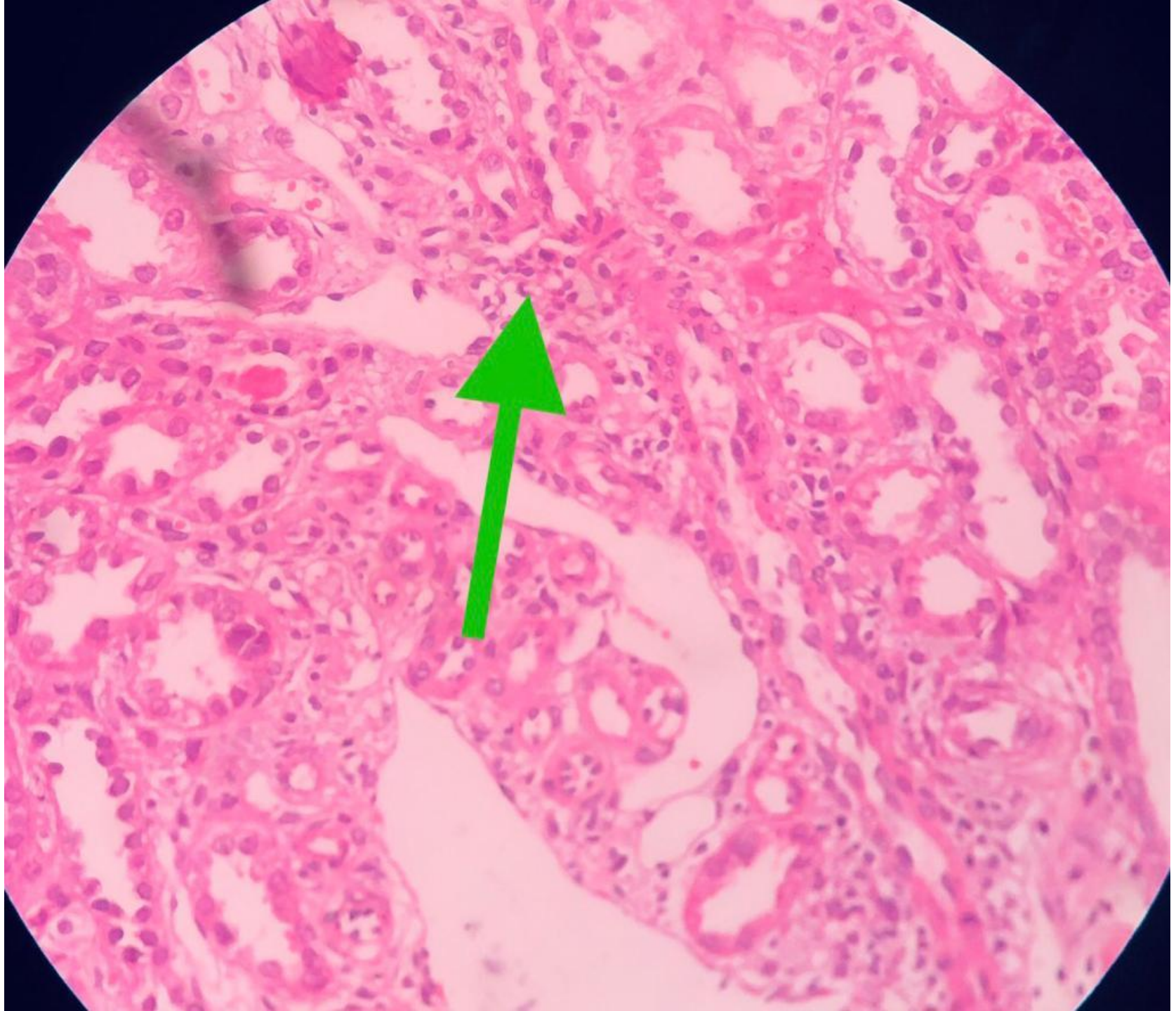




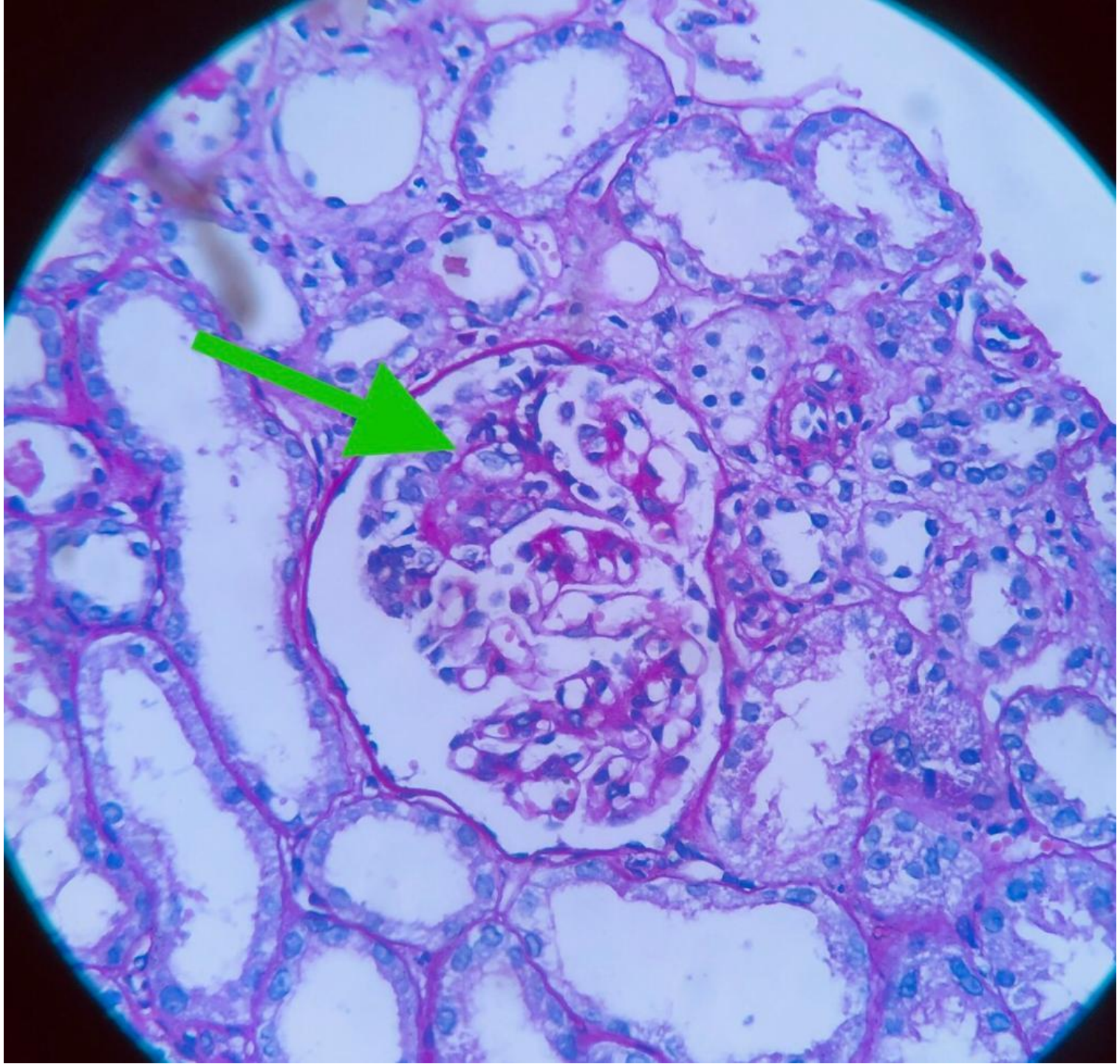
IVIG and Kidney injury



IVIG and Kidney injury

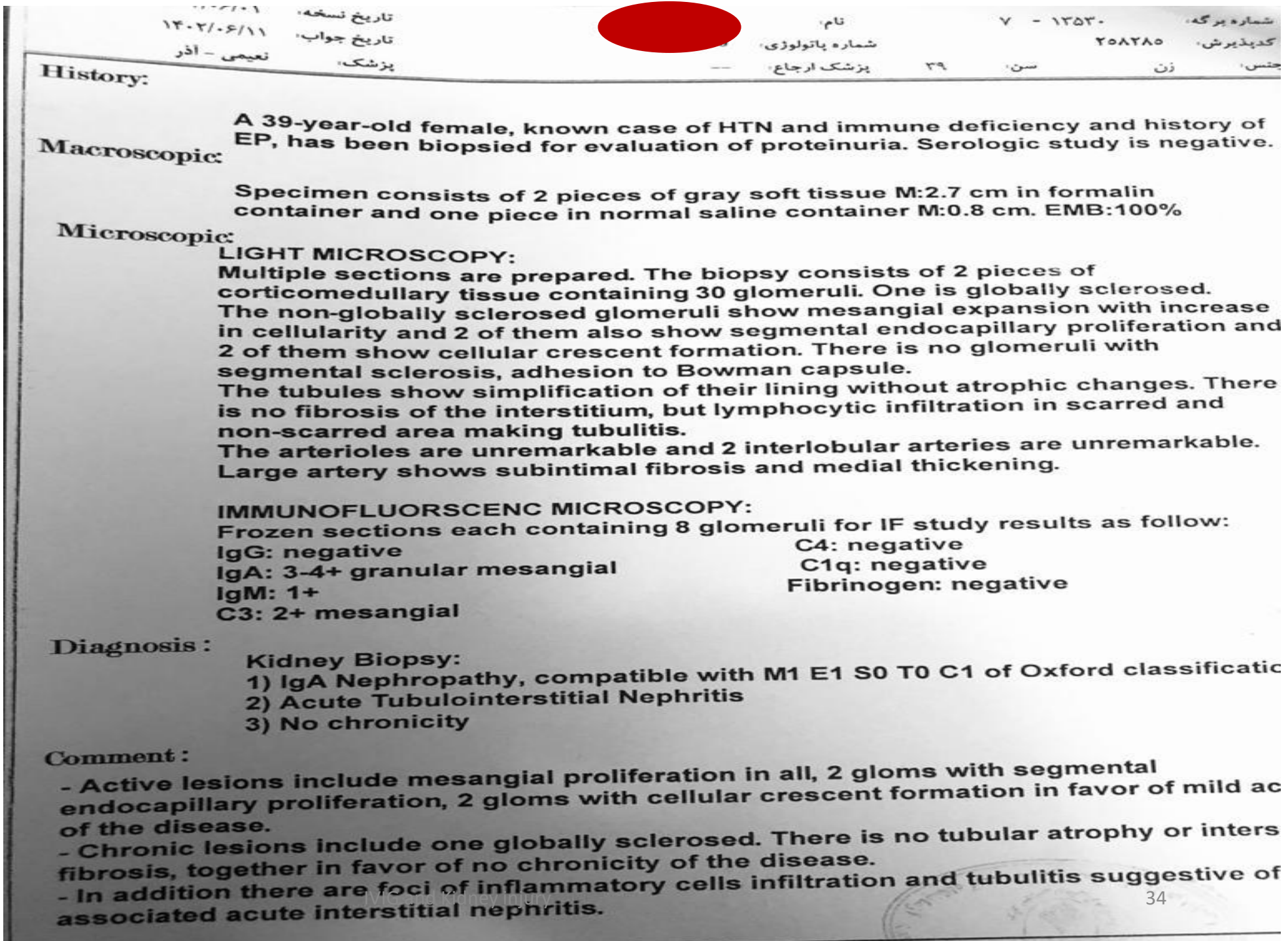


IVIG and Kidney injury



IVIG and Kidney injury

Case...



تاریخ نسخه:
تاریخ جواب: ۱۴۰۲/۰۶/۱۱
پزشک: نعیمی – اذر

نام:
شماره پاتولوژی:
پزشک ارجاع: —

شماره برگه: ۱۳۵۳۰ - ۷
کدپذیرش: ۲۵۸۲۸۵
جنس: زن سن: ۳۹

History:

Macroscopic:

A 39-year-old female, known case of HTN and immune deficiency and history of EP, has been biopsied for evaluation of proteinuria. Serologic study is negative.

Specimen consists of 2 pieces of gray soft tissue M:2.7 cm in formalin container and one piece in normal saline container M:0.8 cm. EMB:100%

Microscopic:

LIGHT MICROSCOPY:
Multiple sections are prepared. The biopsy consists of 2 pieces of corticomedullary tissue containing 30 glomeruli. One is globally sclerosed. The non-globally sclerosed glomeruli show mesangial expansion with increase in cellularity and 2 of them also show segmental endocapillary proliferation and 2 of them show cellular crescent formation. There is no glomeruli with segmental sclerosis, adhesion to Bowman capsule.
The tubules show simplification of their lining without atrophic changes. There is no fibrosis of the interstitium, but lymphocytic infiltration in scarred and non-scarred area making tubulitis.
The arterioles are unremarkable and 2 interlobular arteries are unremarkable.
Large artery shows subintimal fibrosis and medial thickening.

IMMUNOFLUORSCENC MICROSCOPY:
Frozen sections each containing 8 glomeruli for IF study results as follow:
IgG: negative
IgA: 3-4+ granular mesangial
IgM: 1+
C3: 2+ mesangial
C4: negative
C1q: negative
Fibrinogen: negative

Diagnosis :

Kidney Biopsy:
1) IgA Nephropathy, compatible with M1 E1 S0 T0 C1 of Oxford classificatic
2) Acute Tubulointerstitial Nephritis
3) No chronicity

Comment :

- Active lesions include mesangial proliferation in all, 2 gloms with segmental endocapillary proliferation, 2 gloms with cellular crescent formation in favor of mild ac of the disease.
- Chronic lesions include one globally sclerosed. There is no tubular atrophy or inters fibrosis, together in favor of no chronicity of the disease.
- In addition there are foci of inflammatory cells infiltration and tubulitis suggestive of associated acute interstitial nephritis.

Case…

- Serum creatinine from 19 reached to 14, 7.5, 3.2 and 2.1 mg/dl after 7 days and urine volume increased, hemodialysis was discontinued, and she was discharged with oral prednisolone.

- After discharge her serum creatinine reached to 1.1 and 0.9 mg/dl.

Adverse effects of IVIG

- In 5-15% of all IVIG infusions.
- Uncommon in patients receiving IVIG on a regular schedule.
- **>50% occur during or within a few hours of the infusion**, especially **first infusion or after changing products**.
- Headache the most common, fatigue, abdominal pain, and myalgia.
- Most are mild, transient, reversible events such as headache, chills, or flushing.
- **The risk:** the dose (1 to 2 grams/kg) in each infusion, the rate of infusion

Adverse effects

- Transfusion-related acute lung injury (TRALI)
- True or suspected anaphylaxis
- Pain or systemic (influenza-like) symptoms
- Headache and migraine (acute or delayed)
- Volume overload (TACO)
- Thromboembolic events
- Acute kidney injury , Hyponatremia
- Hemolysis
- Neutropenia

Complications affecting the kidney
1- Acute kidney injury

Less than 1 % of infusions

Risk factors:

1. Age greater than 65 years
2. Preexisting chronic kidney disease (CKD; ccl <60 mL/min)
3. Diabetes mellitus
4. Higher doses of IVIG
5. Hypovolemia
6. Concomitant use of nephrotoxic agents
7. Very high titers of rheumatoid factor

Complications affecting the kidney
1- Acute kidney injury…

Clinical manifestations:

- From asymptomatic rise in the creatinine to anuria.
- Spontaneous resolution, 4 to 10 days after IVIG is discontinued.
- Permanent kidney failure reported.
- Mostly with IVIG containing sucrose (discontinuation of these products).

The pathogenesis:

- **Osmotic mechanism:** sugar is taken up by tubules, the increased solute load, the cells vacuolated, swell, and obstruct the tubules,"osmotic nephrosis".
- **Renal heme pigment injury:** hemolysis, increased blood viscosity, and immune complex deposition.

Complications affecting the kidney
2- Hyponatremia

- Rare complication in individuals with underlying CKD or those who develop AKI from the IVIG therapy.

The mechanism:

1. **Dilutional:**

- The inability of the kidney to handle the free water load.
- Free water from the IVIG solution
- Translocation of water from the IC to the EC (high concentrations of maltose in IVIG).

2. **Pseudohyponatremia,** which is a laboratory artifact, patients with pseudohyponatremia should not have free water restriction, Distinction: normal serum osmolality.

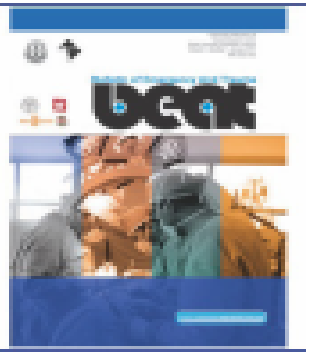
Maltose stabilizer

- Unlike sucrose, maltose is metabolized by kidney cells.
- The enzyme hydrolyzes maltose to glucose, in the brush border of proximal convoluted renal tubules.
- Conversion of maltose to glucose intracellularly in the kidney;
- **Falsely high blood glucose** meter readings in older systems based on glucose dehydrogenase pyrroloquinolinequinone or glucose-dye-oxidoreductase methods
- This issue has largely been **resolved** with the use of **modern glucose-specific blood monitoring** methods.

Case Report

Bull Emerg Trauma 2022;10(1):44-48.

Bulletin of Emergency And Trauma



Severe Acute Kidney Injury Secondary to Immunoglobulin Infusion in Life-Threatening Guillain Barre Syndrome

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İntravenöz İmmünglobulin Tedavisi ile İlişkili Akut Böbrek Hasarı: Olgu Sunumu

Acute Kidney Injury Related to Intravenous Immunoglobulin Therapy: A Case Report

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Muammer BİLİCİ[2]
Şebnem KARAÇAY ÖZKALAYCI[3]
Ali BORAZAN[4]

1 Zonguldak Atatürk Devlet Hastanesi, Nefroloji Bölümü,

ÖZ

İntravenöz immünglobulin hipogamaglobinemi tedavisinde kullanılmak üzere geliştirilmiş ve sonrasında birçok otoimmün, inflamatuvar sistemik hastalıkta kullanım alanı bulmuştur. Akut böbrek hasarı, intravenöz immünglobulin tedavisinin nadir bir komplikasyonu olup sıklıkla formülasyondaki stabilizatör maddeye bağlı gelişir ve günler içinde böbrek fonksiyonları geri kazanılır. Bu yazıda bir haftadır bacaklarında güçsüzlük ve his kaybı şikayeti ile akut inflamatuvar demyelinizan polinöropati (Guillaine Barre Sendromu) tanısı konulan; beş günlük intravenöz immünglobulin tedavisi sonrası akut böbrek hasarı gelişen ve bir ay sonra böbrek fonksiyonları tam olarak düzelen 81 yaşında kadın bir olgu sunulmuştur. İntravenöz immünglobulin kullanımı sonrası akut böbrek hasarı açısından hastalar mutlaka yakından izlenmelidir.

STRATEGIES FOR REDUCING ADVERSE EVENTS

- Appropriate indications,
- Adequately hydrated
- Slow infusion rates (new patients or change product),
- Substitutions of other products should be avoided
- Record of all lots of IVIG, a "look back" is ordered.
- Most vials of IVIG have a perforated sticker that can be removed and kept in the patient's personal log book, or the lot number can be requested from the hospital pharmacy or other provider.

Serology

Test	Result
C Reactive Protein (Quantitative)	3
Rheumatoid factor(RF)	9
Wright Agglutination test	Negative
Mercaptoethanol (2 ME)	Negative

Biochemistry

Test	Result
Blood urea nitrogen (BUN)	12.3
Creatinine	0.81
Glomerular Filtration Rate	84

Immunology & Serology

Test	Result
F-ANA	Negative

Urinalysis

Macroscopic

Urinalysis

Color	yellow
Appearance	Semi clear
Specific Gravity	1021
pH	5
Protein(urine)	Negative
Glucose	Negative
Bilirubin	Negative
Urobilinogen	Negative
Ketones	Negative
Nitrite	Negative
Blood	Trace

Unit	Method	Reference Interval
Titer	IF	Up to 1/100

Microscopic

W.B.C/hpf	1-2
R.B.C	3-4
Epithelial Cells/hpf	2-3
Bacteria	Not seen
Dysmorphic RBC	Negative
Cast (LPF)	Not seen
Yeast	Not seen
Crystals	Not seen

IVIG and Kidney injury


Thanks for your patience