

# Glomerulonephritis Associated with Bacterial Infection

The Emerging Role of Staphylococcus

Tibor Nádasdy, MD

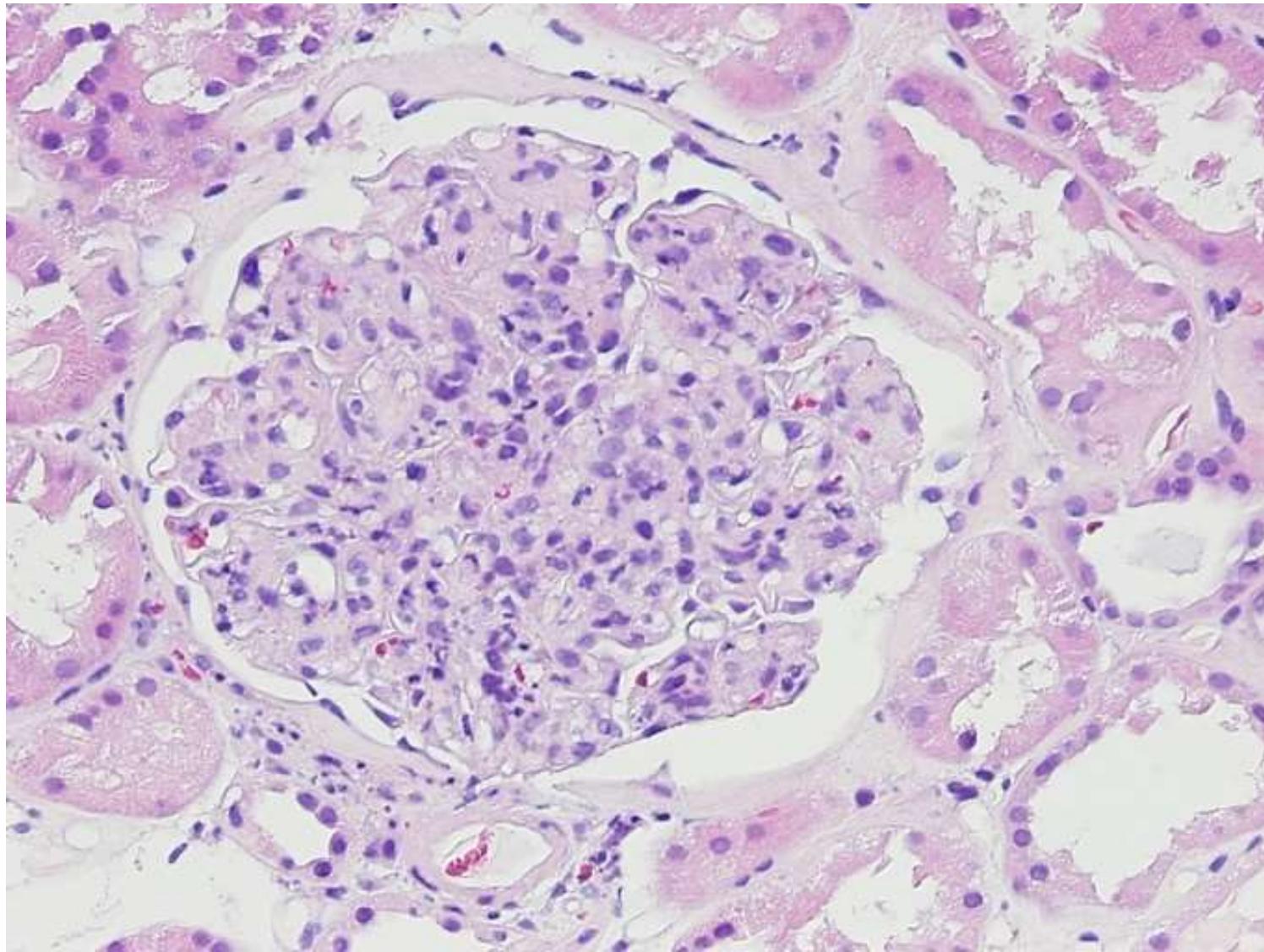




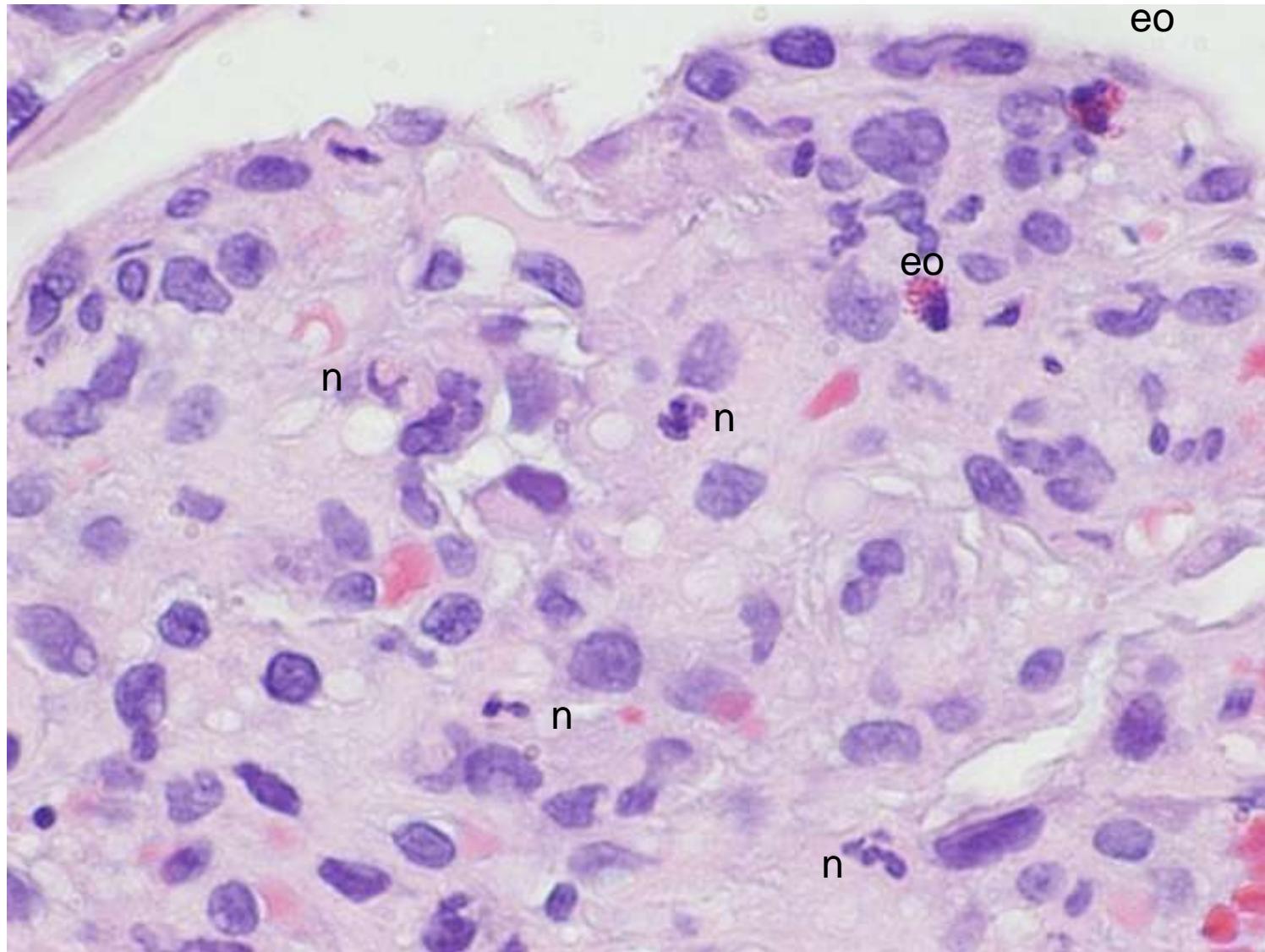
# Clinical history (Case #1)

- 60-year-old Caucasian male with insulin dependent DM, diabetic neuropathy, CAD, HTN, obesity.
- Presented with gangrene of left great toe.
- Blood and wound cultures positive for methicillin sensitive *Staphylococcus aureus*.
- Zosyn and vancomycin were started.
- After two days, amputation of the left great toe was performed.
- After surgery, he developed oliguria (425 ml per day) and over 6 days, serum cr. increased from 1.1 mg/dl to 3.8 mg/dl.
- Active urine sediment, Urine pr/cr 3.2, serum complement levels normal

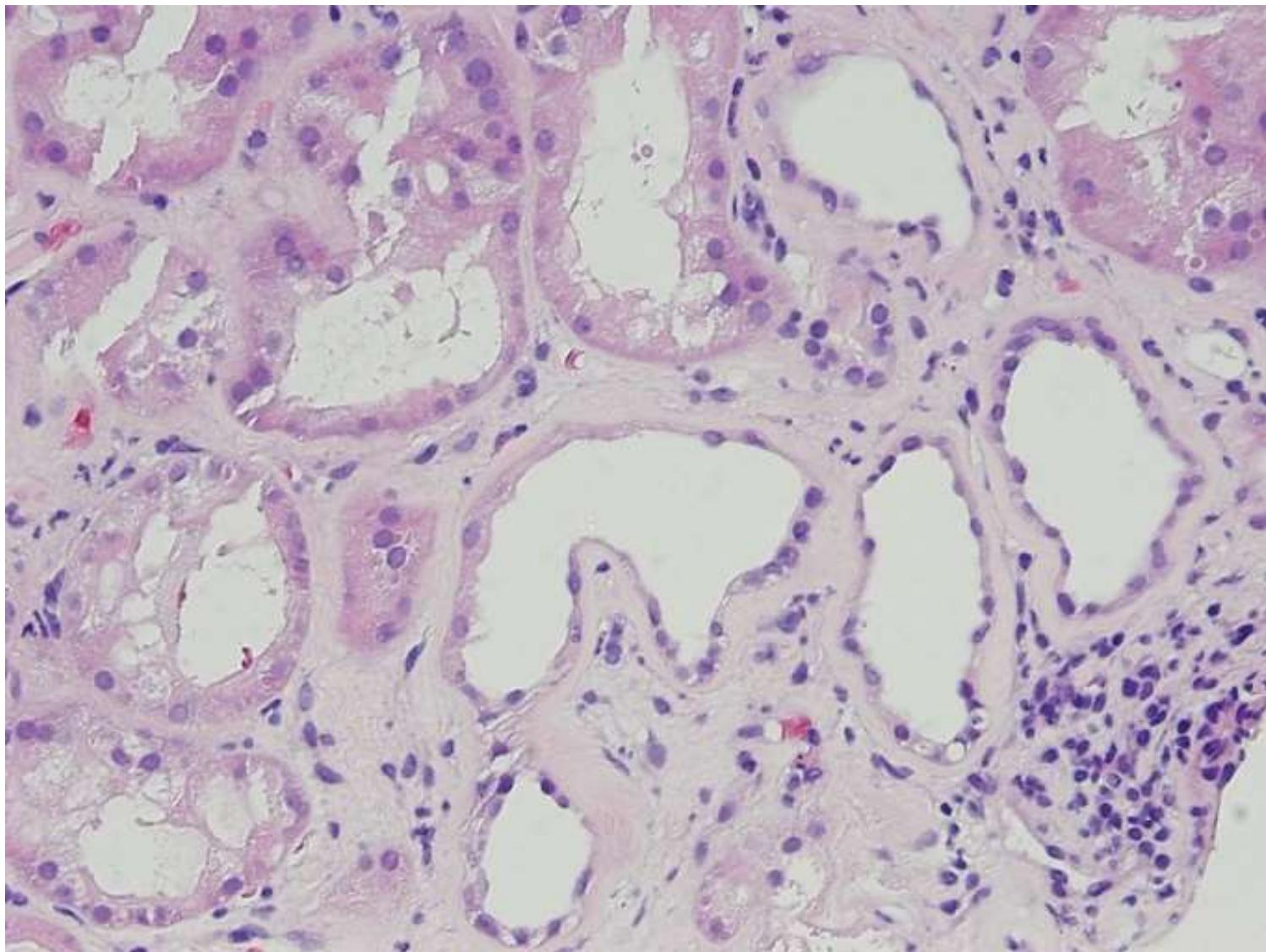
Glomerular intracapillary hypercellularity



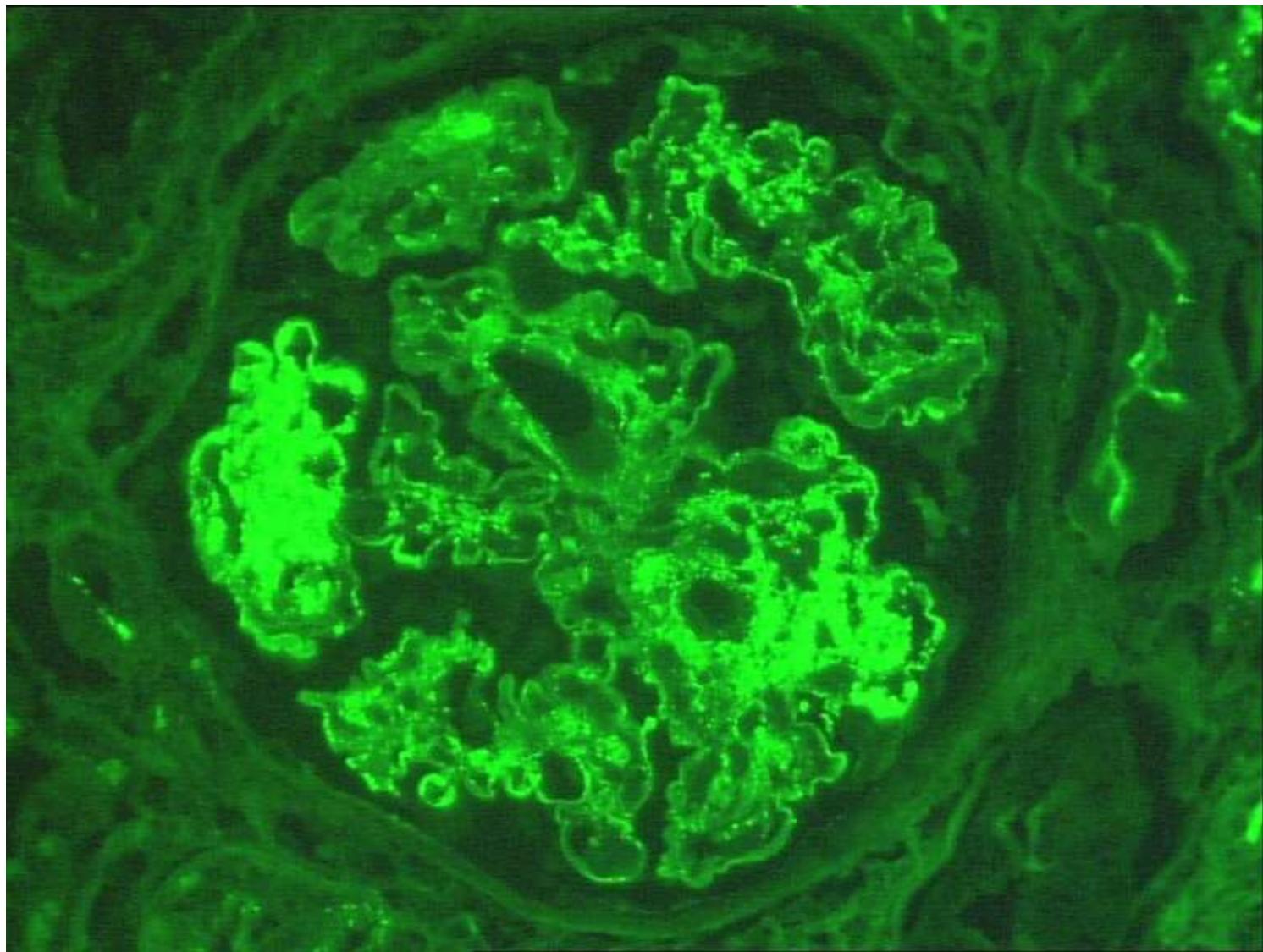
Glomerular capillaries contain inflammatory cells.  
Note neutrophil granulocytes [n] and eosinophil granulocytes [eo].



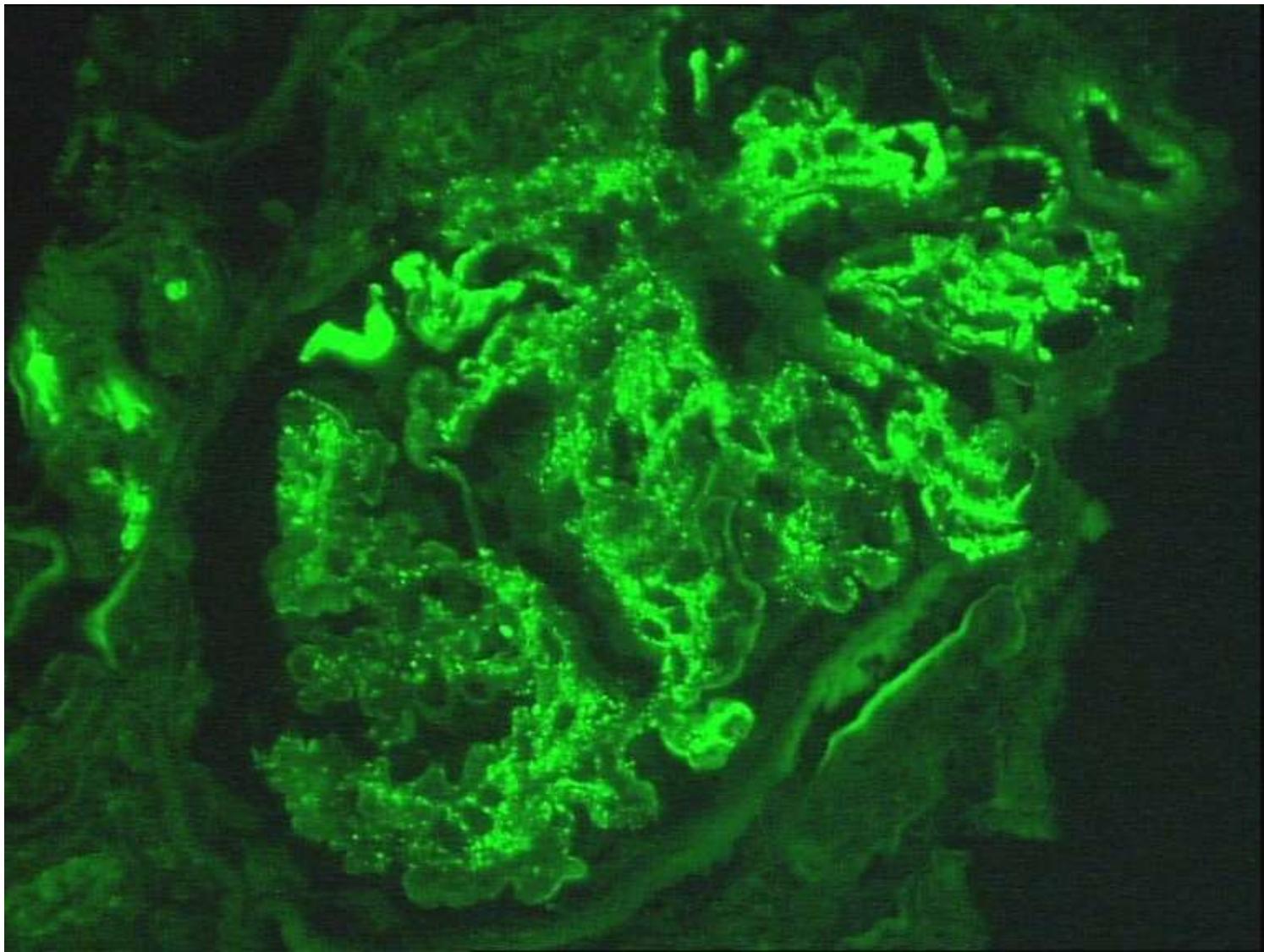
Acute tubular necrosis, affected tubules are lined by flat, irregular epithelium



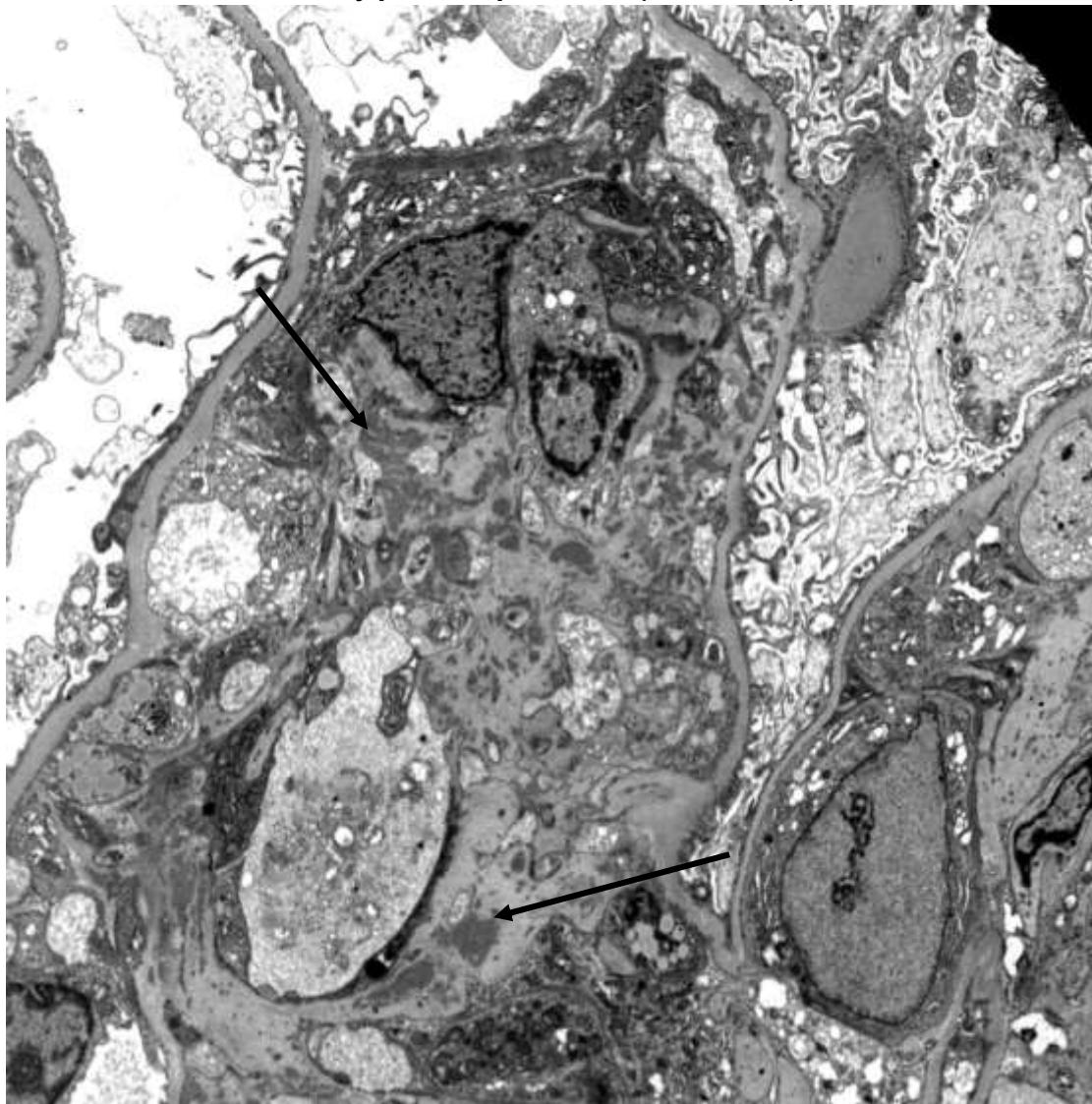
Strong primarily mesangial granular staining for IgA



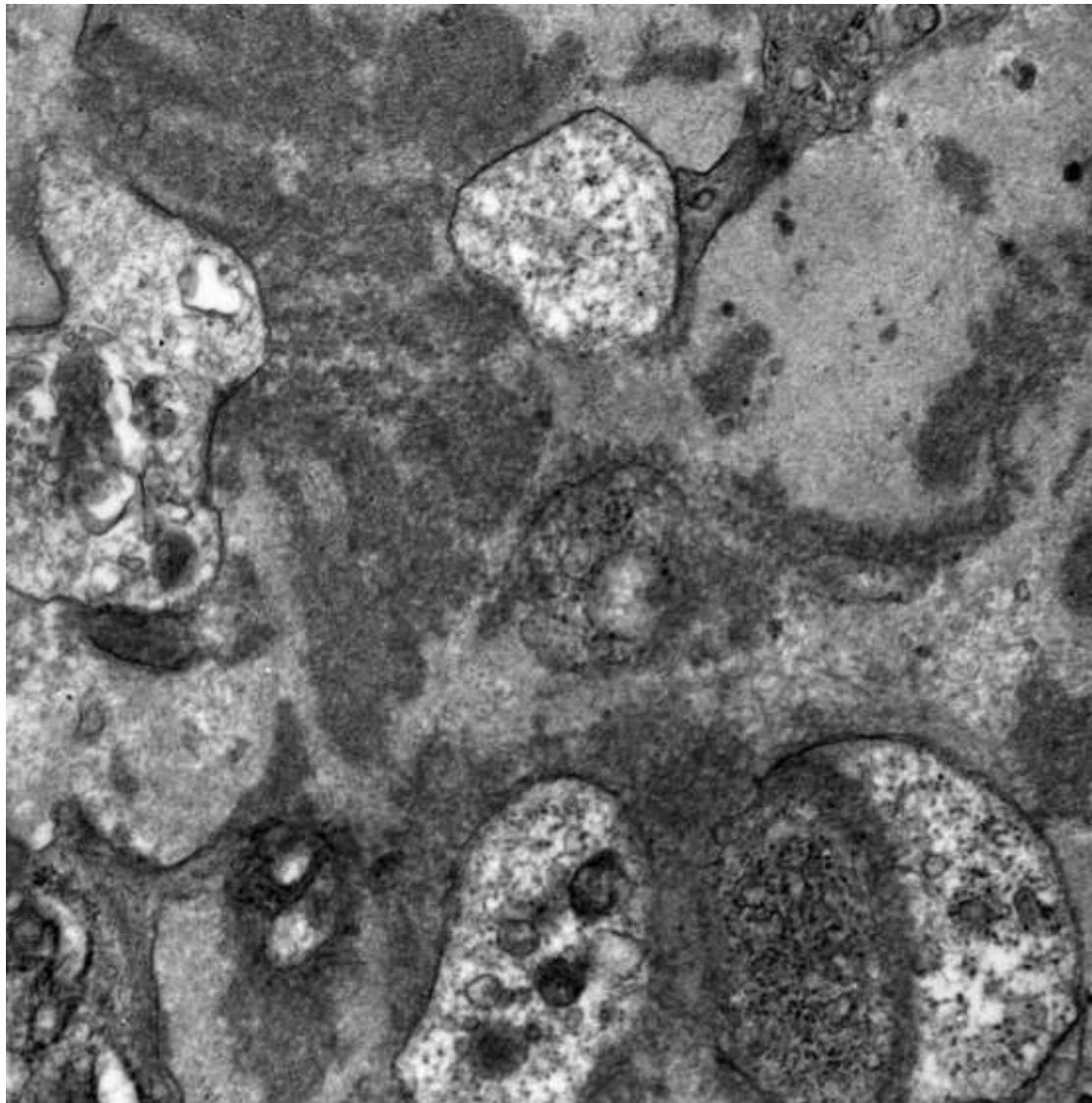
Immune complex deposits also stain for C3



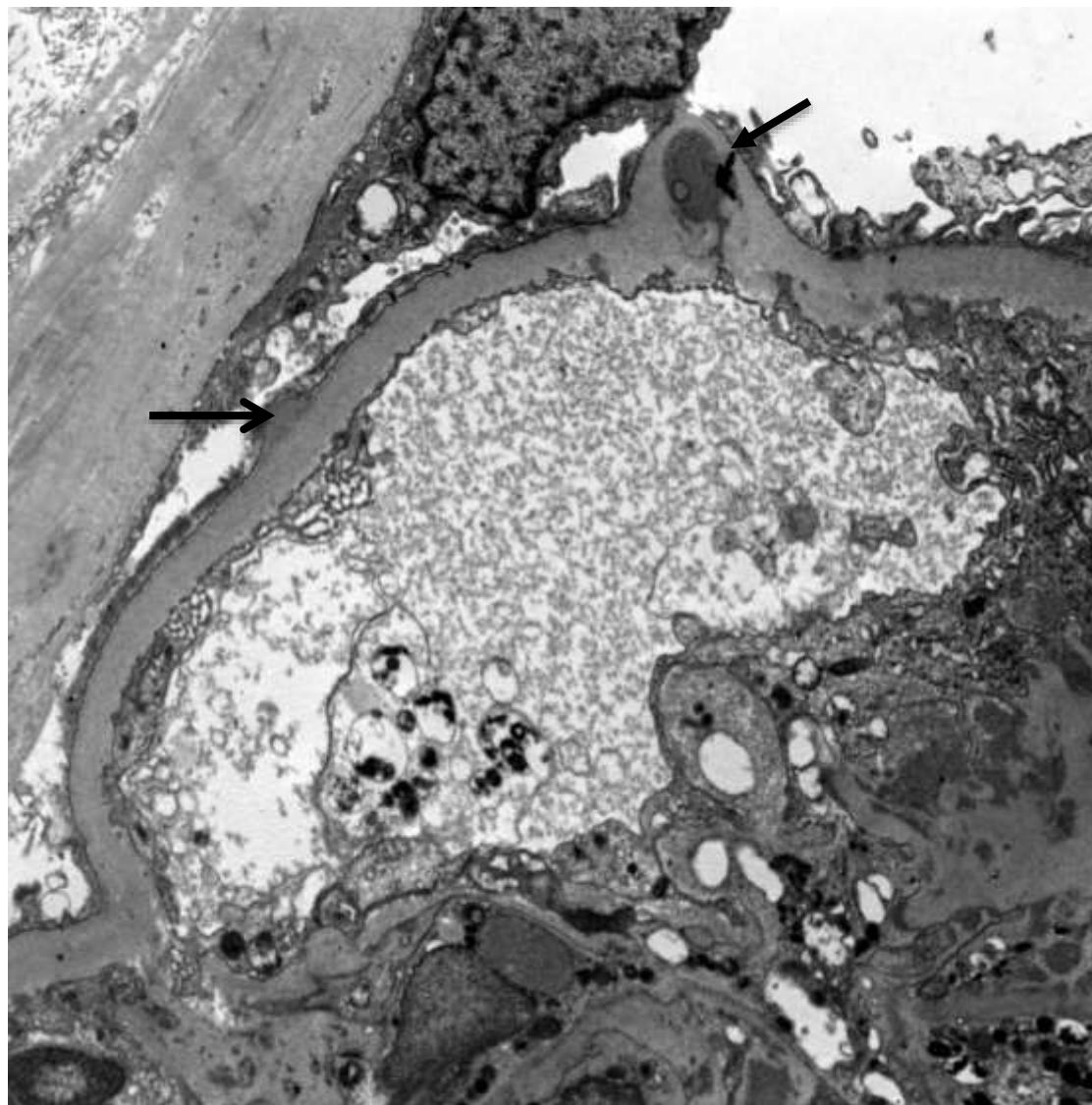
Expanded mesangium with electron dense immune-type deposits (arrows)



## Mesangial electron dense immune-type deposits



Few scattered immune-type deposits along the glomerular capillary loops, slightly thickened GBM



# Diagnosis

- Active intracapillary proliferative glomerulonephritis with IgA and C3-containing immune complex deposits, consistent with *Staphylococcus aureus* infection associated glomerulonephritis (SAIGN).
- Moderate diabetic nephropathy with mainly diffuse diabetic glomerulosclerosis.

# Follow-up

- Infection was successfully treated, renal function slowly improved
- Follow-up after 4 years and 5 months:
  - Serum creatinine stable at 2.0 mg/dl.
  - Blood pressure controlled.
  - Lasix daily, with low salt diet
  - Other problems – gastric ulcer with bleeding and anemia, diabetes, HTN, peripheral vascular disease.

# Bacterial infections and glomerulonephritis

## Post-infectious /post-streptococcal glomerulonephritis

“Post” – after infection resolves with or without anti-microbial treatment

Latent period of 1 to 4 weeks with normal state of health

Acute onset of glomerulonephritis

## Glomerulonephritis with active ongoing infection

### Staphylococcus infection associated glomerulonephritis (usually IgA dominant)

### Glomerulonephritis with other persistent infections

- Endocarditis
- Deep seated abscesses
- Shunt nephritis

**Table 3. Infectious agents (109 patients)**

Infectious agent <sup>a</sup>	No. of Patients (%)
<i>Staphylococcus</i>	50 (46)
<i>Streptococcus</i> <sup>b</sup>	17 (16)
<i>E. coli</i>	5 (5)
<i>Pseudomonas</i>	2 (2)
<i>Acinetobacter</i>	1 (1)
<i>Serratia marcescens</i>	1 (1)
<i>Proteus</i>	1 (1)
<i>Klebsiella</i>	1 (1)
<i>Enterobacter cloacae</i>	1 (1)
<i>Candida</i>	1 (1)
<b>Unknown</b>	<b>37 (34)</b>

<sup>a</sup>In seven patients, cultures grew two or three bacteria (staphylococcus and *E. coli* in three; staphylococcus and enterococcus in one; staphylococcus and *S. marcescens* in one; *E. coli* and enterococcus in one; and staphylococcus, proteus, and pseudomonas in one).

<sup>b</sup>Including five patients with infection by enterococci (group D streptococci).

# Staphylococcus infection associated glomerulonephritis (SIAGN)

- In developed countries, the incidence of post-streptococcal GN has declined because of successful treatment of acute streptococcal infections.
- Staphylococcal infection-related glomerulonephritis is on the rise because
  - 1. Emerging drug-resistant strains of *Staphylococcus* and both nosocomial and community-acquired staphylococcal infections.
  - 2. The growing elderly population with increasing prevalence of comorbidities, such as diabetes and morbid obesity
- Infection is ongoing at the time the glomerulonephritis is diagnosed.  
Therefore the term “post”-infectious is a misnomer and should not be used.
- IgA-dominant or co-dominant immune complexes are commonly seen, posing a diagnostic pitfall with idiopathic IgA nephropathy (and Henoch-Schönlein purpura).

# Characteristics of staphylococcus infection-associated GN (SIAGN)

- Culture-proven, ongoing *Staphylococcus aureus* infection (blood cultures are frequently negative) – commonly done first after the biopsy.
- Concomitant glomerulonephritis with acute kidney injury.
- Hematuria and proteinuria.
- Renal biopsy: diffuse mesangial and intracapillary hypercellularity (sometimes crescents and necrosis) frequently with ATN.
- IgA and C3 containing glomerular immune complexes by immunofluorescence.
- Mesangial, frequently also peripheral glomerular capillary electron dense immune-type deposits by electron microscopy (subepithelial humps may or may not be present – seen in approximately 1/3 of cases).

# Diagnostic difficulties in SIAGN

- Bacterial culture results are unavailable in a large percentage of patients despite characteristic clinical presentation and with kidney biopsies showing histologic typical features.
- Most patients are elderly with multiple co-morbidities, often treated empirically with multiple antibiotics. Cultures may become negative.
- Blood cultures may be negative in a large percentage of these cases. Cultures from the site of infection need to be taken.
- Also, clinical features of infection, in elderly patients can be subtle

## SIAGN is NOT “Post-Staphylococcal glomerulonephritis”

- Many case reports and case series address this condition as post-staphylococcal glomerulonephritis.
- “Post” means that the infection is gone (such as in post-streptococcal glomerulonephritis). This is not true in most cases of SIAGN
- Clearly differentiate the two conditions because postinfectious GN can be treated with steroids, whereas SAIGN and other forms of active ongoing infection-associated GN should not.

# Post-streptococcal versus SIAGN

## Post-infectious /post-streptococcal glomerulonephritis

“Post” – after infection resolves with or without anti-microbial treatment

Latent period of 1 to 4 weeks with normal state of health

Acute onset of glomerulonephritis, usually supportive treatment; sometimes steroid treatment may help.

### Biopsy:

**LM:** Proliferative GN

**IF:** C3 dominant granular deposits with or without IgG

**EM:** subepithelial humps, some mesangial deposits

## Staphylococcus infection associated glomerulonephritis (IgA dominant)

Infection is active and ongoing when the glomerulonephritis develops

Therapy: Antibiotics, sometimes requires amputation or debridement of infected area. Avoid steroids!

Glomerulonephritis will resolve after infection is treated, provided underlying chronic kidney injury is not severe.

### Biopsy:

**LM:** Variable degree of glomerular proliferative changes;

**IF:** C3 and IgA dominant deposits.

**EM** mesangial and glomerular capillary deposits, sometimes humps

# Common associations with SIAGN

- Predisposing Co-morbidities
  1. Diabetes Mellitus
  2. Post-surgery
  3. Post-trauma
  4. Prosthetic heart valves
  5. Intravenous drug use
  6. Hepatitis C
  7. Underlying malignancy

- Sites of Infection
  1. Diabetic foot ulcers
  2. Cellulitis
  3. Pneumonia
  4. Endocarditis
  5. Infected surgical sites
  6. Osteomyelitis.
  7. Visceral abscess
  8. Septic arthritis
  9. Infected pace-maker, heart valves, indwelling catheters, iv lines
  10. Infected abdominal mesh
  11. Dental infection
  12. Amputated limbs in diabetic patients

# Experience at Ohio State University Medical Center

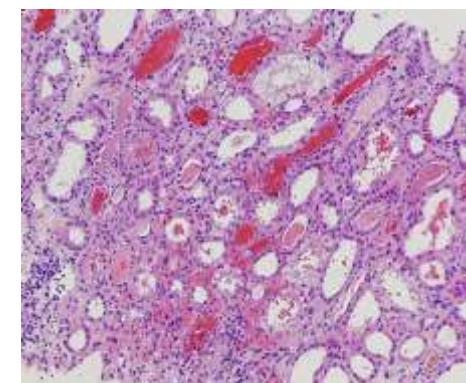
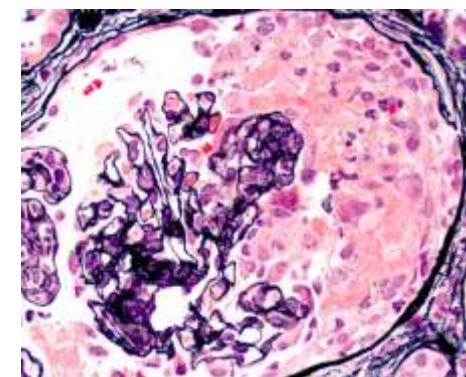
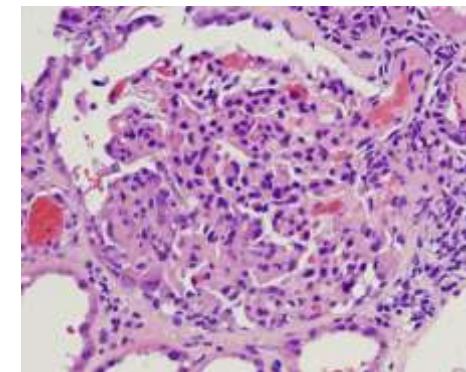
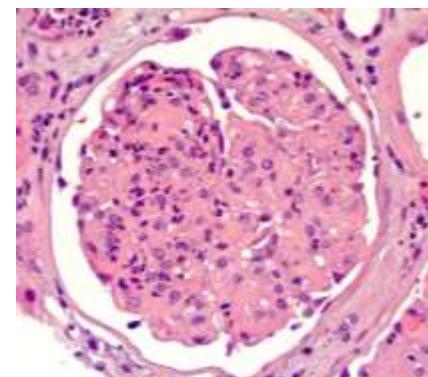
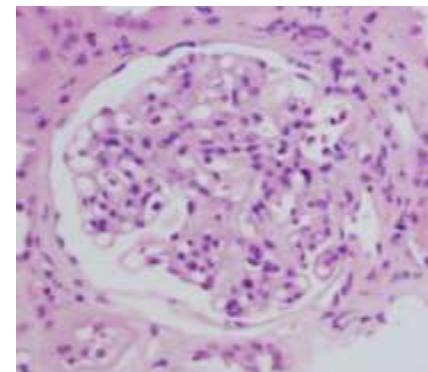
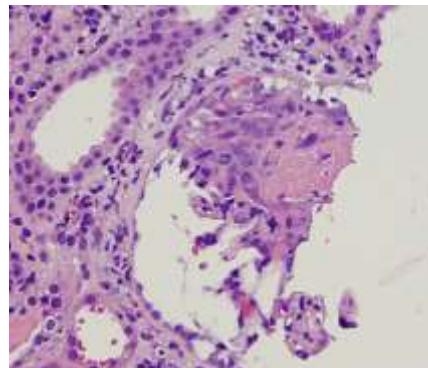
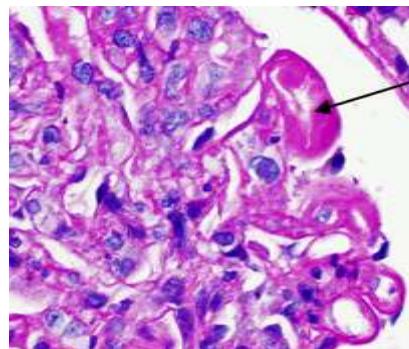
- During the period 2004 to 2014, out of 7,092 native kidney biopsies, 67 (0.94%) had culture proven SIAGN.
- At least 35 additional biopsies with typical histologic features and clinical presentation of SIAGN, but no documented culture results.

Clinicopathologic characteristics of the 68 cases of culture positive Staphylococcal infection associated glomerulonephritis from 2004 to 2014 at the Ohio State University Medical Center.

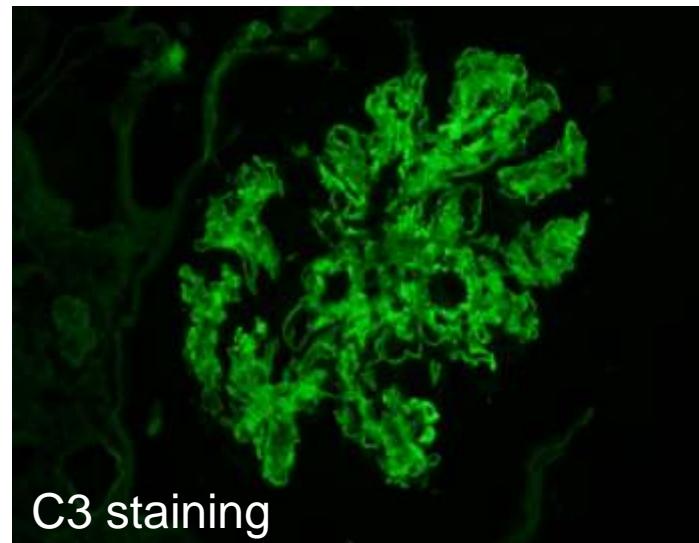
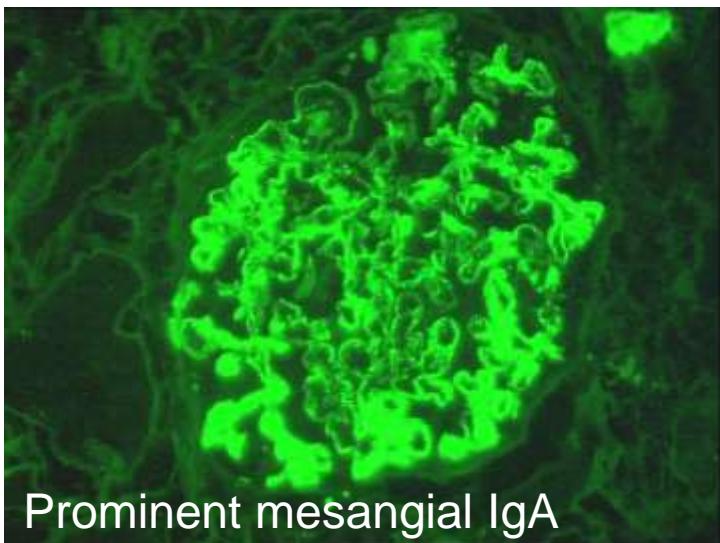
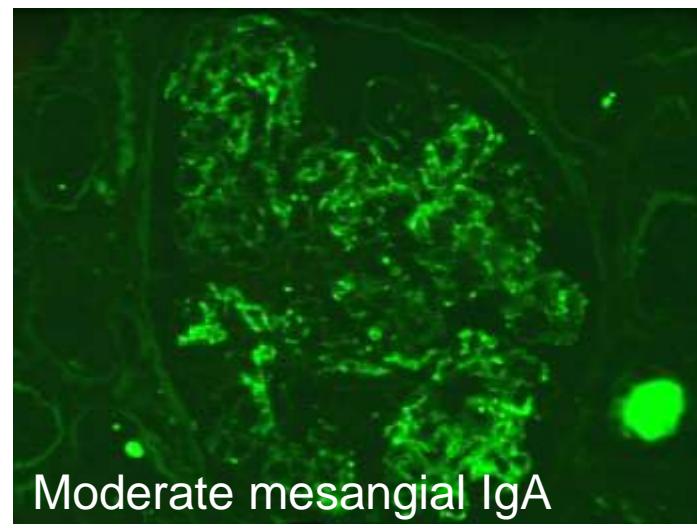
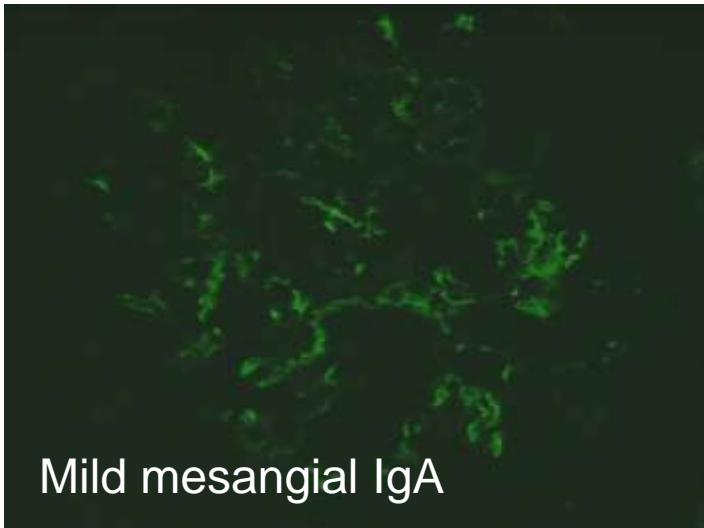
Clinicopathologic features	n	%
Age (years)	58 +/- 15 (31-91)	
Ethnicity		
Caucasian	62	92%
African American	3	4.40%
Asian	2	2.90%
Gender		
Males	52	76%
Females	16	23%
Diabetes mellitus	29	43%
Hypertension	25	37%
Staphylococcal strain		
MRSA	40	
MRSE	1	
MSSA	17	
Staph strain unknown	10	
Mixed bacterial infection	6	
Blood culture positive	31	46%
Local wound culture positive	43	64%
Both cultures positive	7	10%
Low C3	17 of 49	35%
Low C4	6 of 49	
Both C3 and C4 low	6 of 49	
Purpuric lower extremity skin rash	14	20%
Nephrotic range proteinuria	32 of 53	60%
Type and site of infection		
Endocarditis	12	18%
Osteomyelitis	9	13%
Cellulitis; leg ulcers	14	21%
Pneumonia	8	12%
Motor vehicle accident, multiple wounds	2	3%
Septic arthritis	3	4%
Post-surgical site infection	5	7%
Visceral abscess	5	7%
Urinary tract infection	2	3%
Bacteremia	6	9%
Multiple sites of infection	7	10%

# Morphology of SIAGN: Light Microscopy

- Spectrum of glomerular changes.
- ATN
- RBC casts

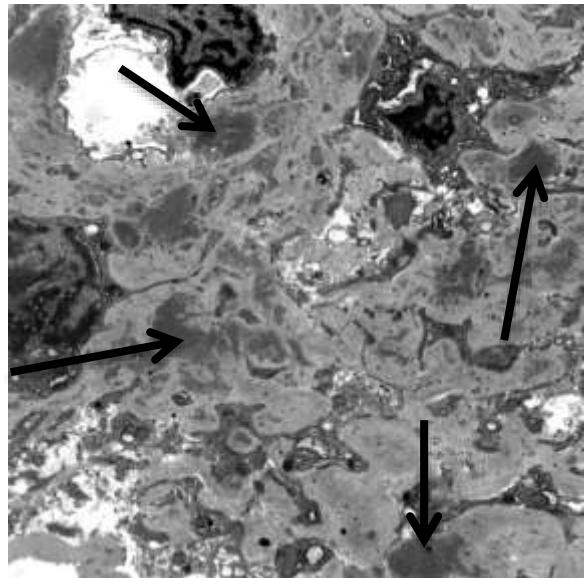


# Immunofluorescence: IgA of variable intensity. C3 usually bright

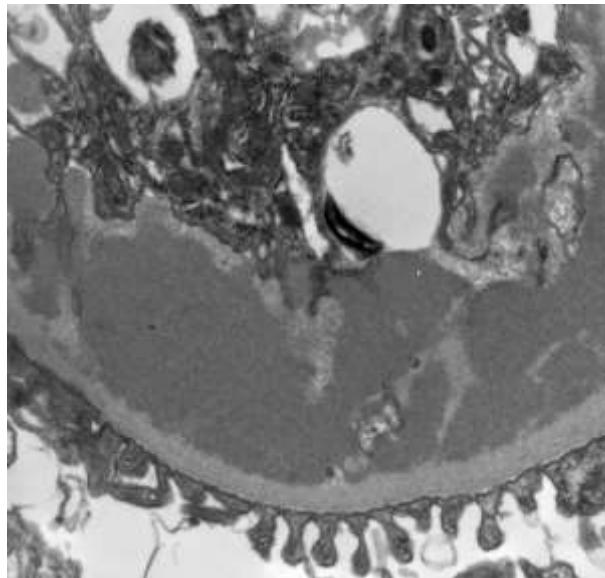


## Electron microscopy

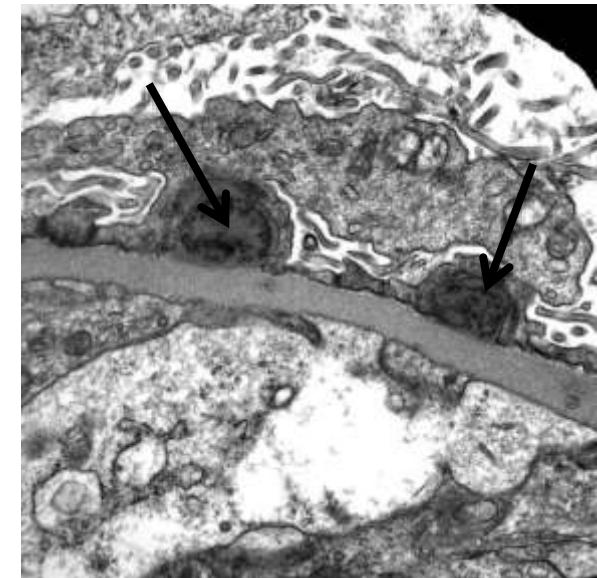
“Humps” may or may not be seen.



Mesangial deposits  
(always present)



Subendothelial deposits  
(sometimes large)



Subepithelial “humps”  
(35% of cases)

**Based on morphology alone, differentiating SIAGN from IgA nephropathy is difficult**

## Morphologic Differential Diagnosis of IgA Nephropathy and SIAGN

		IgAN	SIAGN
LM	Mesangial Hypercellularity	0-3+	0-3+
	Endocapillary Hypercellularity	0-2+	0-3+
	Crescents	0-2+	0-2+
IF	IgA	2-3+	1-3+ (rarely absent)
	C3	0-2+	1-3+
	C1q	0	0-1+
	IgG	0-2+	0-1+
EM	Mesangial Deposits	2-3+	2-3+
	Subendothelial Deposits	0-2+	0-3+
	Subepithelial “Humps”	0	0-2+

Unreliable: Renal biopsy findings are quite similar

# Clinical Differential diagnosis of SIAGN and IgA nephropathy

Patient Characteristic	SIAGN	Primary IgA nephropathy
Age	Usually older (50-80 years)	Usually younger (20-30 years)
History of infection	antecedent or coexistent	Occasionally (30 to 40% after URI)
Latent period	5 to 10 weeks, ongoing infection	May be “Synpharyngitic” 1 to 2 days
Microbes	Staphylococcus, about 70% MRSA	May be bacterial or viral
Site of infection	Skin infection, infected leg ulcers in diabetic patients, deep –seated abscesses, post-surgical infections	Upper respiratory tract infections (URI)
Gross hematuria at presentation	50 to 60% of cases	40% (more frequent in children)
Proteinuria	Frequently nephrotic range	Usually mild <1 g/24 hours
Serum complement	Normal or low end of normal range	Normal
Acute kidney injury	Common	Uncommon
Comorbidities	Common (diabetes, chronic devastating diseases, obesity)	Uncommon

If you have a patient with AKI, proteinuria, hematuria and some evidence of infection (other than upper respiratory tract) and particularly if the patient has comorbidities, such as diabetes, morbid obesity, cancer, etc. and the renal biopsy diagnosis is IgA nephropathy, seriously consider **staphylococcus infection** in the background

# Case History (Case #2)

- 51-year-old Caucasian male
  - Right wrist pain and swelling
  - MRI 2 weeks prior to presentation: tenosynovitis.
  - Purpura on legs progressed to burning erythematous rash on legs, thighs, buttocks, lower abdomen, arms.
  - Abdominal pain – X-ray – Colonic distention
  - Patient was started on steroid (Medrol Dosepak – methylprednisolone)

**IV methyl prednisolone (125 mg) with 2 g ceftriaxone on day of transfer to OSU medical Center.**

**Temporary relief only.**

# Laboratory Data on Admission

Serum creatinine: 0.9 mg/dl on admission

Urinalysis: Trace blood, no protein, no WBCs, no RBCs, few granular casts

WBC count: 9,200/ $\mu$ l

Differential: 85% PMNs, 7.2% Lymphs, 5.9% Monos ESR: 43 mm

Blood cultures negative

Arthrocentesis

Unfortunately, only scant fluid obtained, no cell count available

No crystals by polarized light

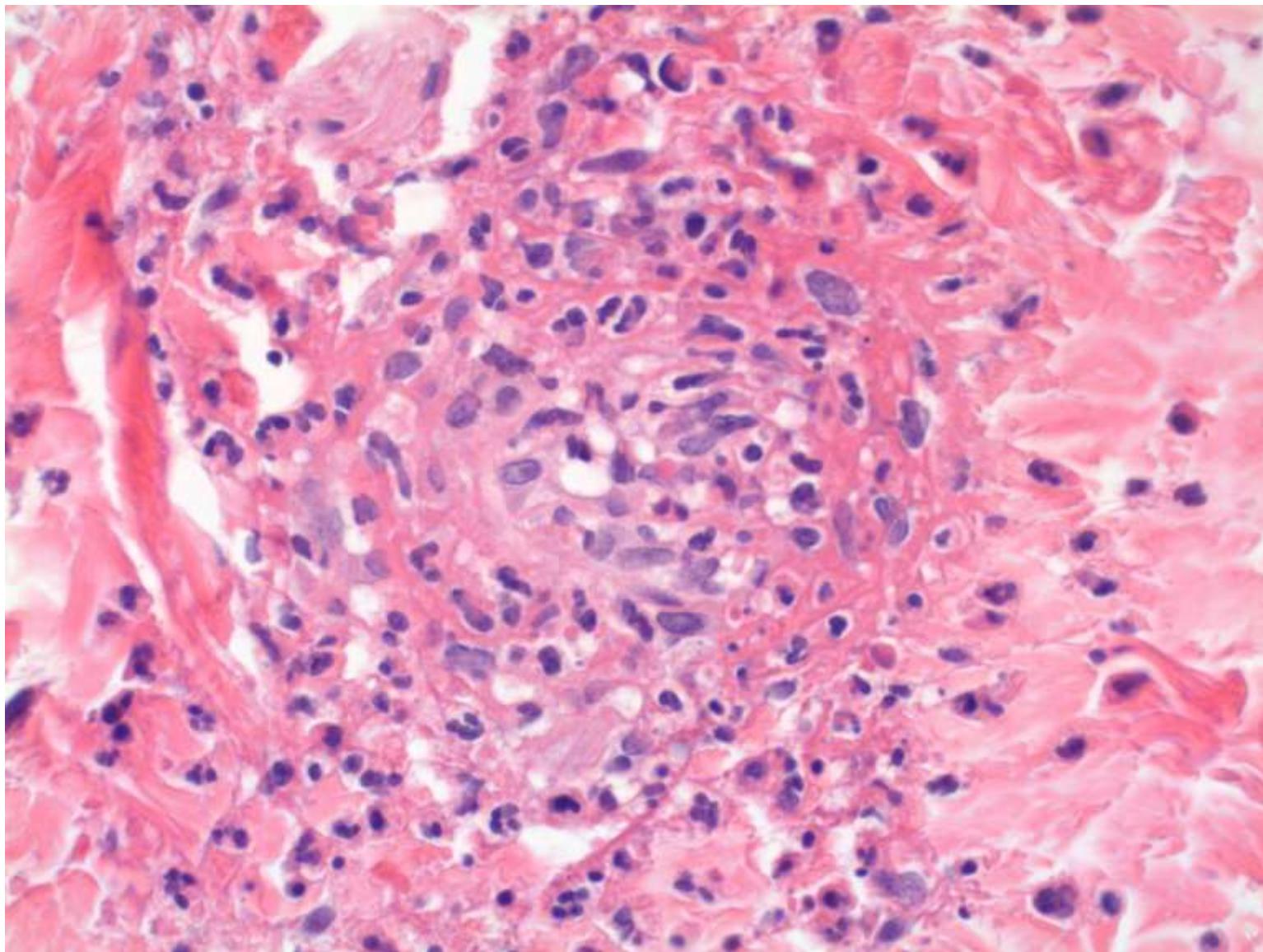
# Additional Labs

- ANCA – Negative
- ANA – Negative
- RF – < 20
- Total IgG – 452
- Total IgA – 302
- Hepatitis B, C – Negative
- Lyme Abs - Negative
- Serum immunofixation - negative

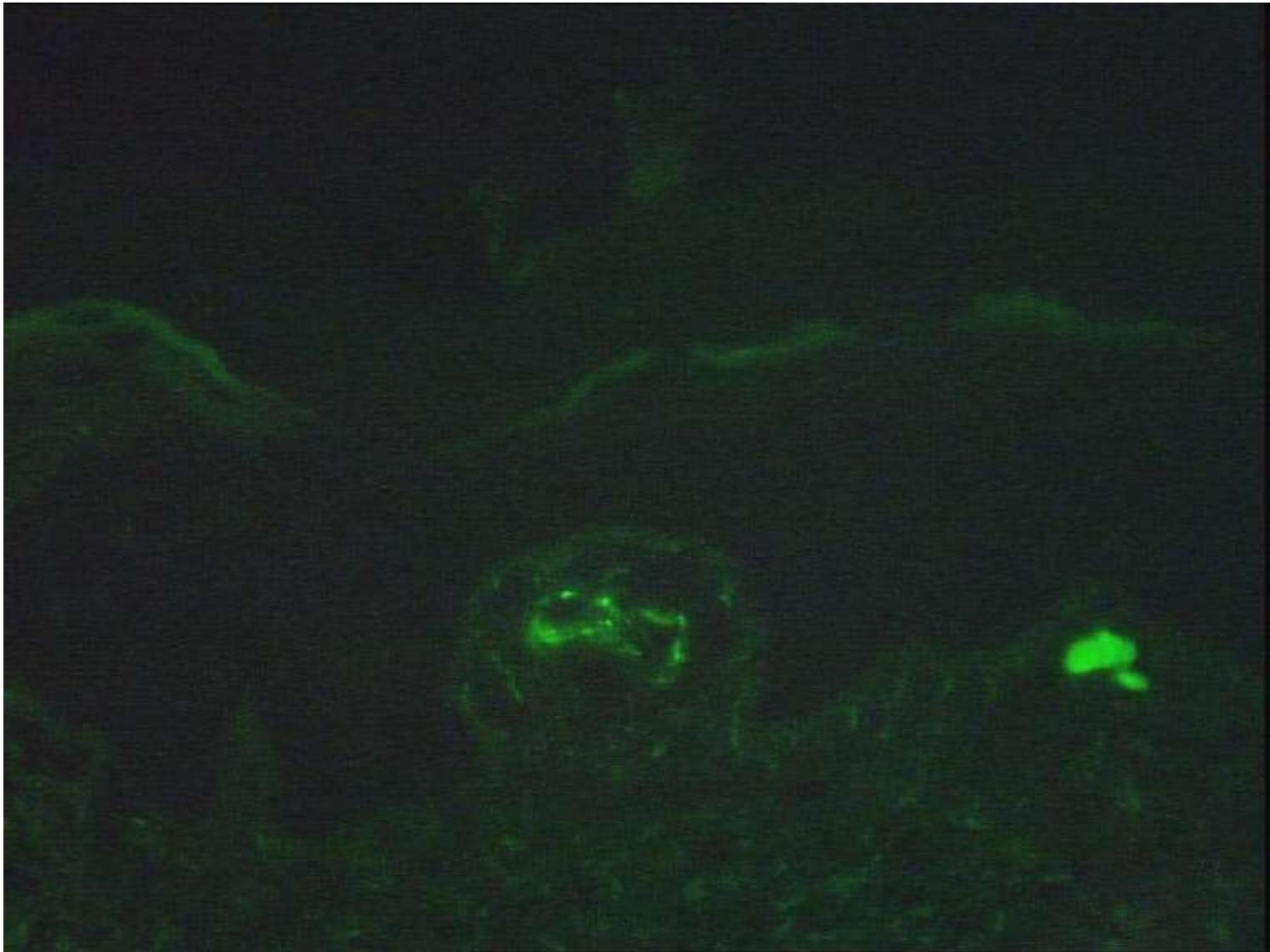


Rash - Palpable  
Purpura

# Skin Bx - Leukocytoclastic vasculitis



# Skin Bx immunofluorescence staining – IgA in arteriolar walls



Presumptive Diagnosis:  
Henoch Schönlein Purpura  
(IgA vasculitis)

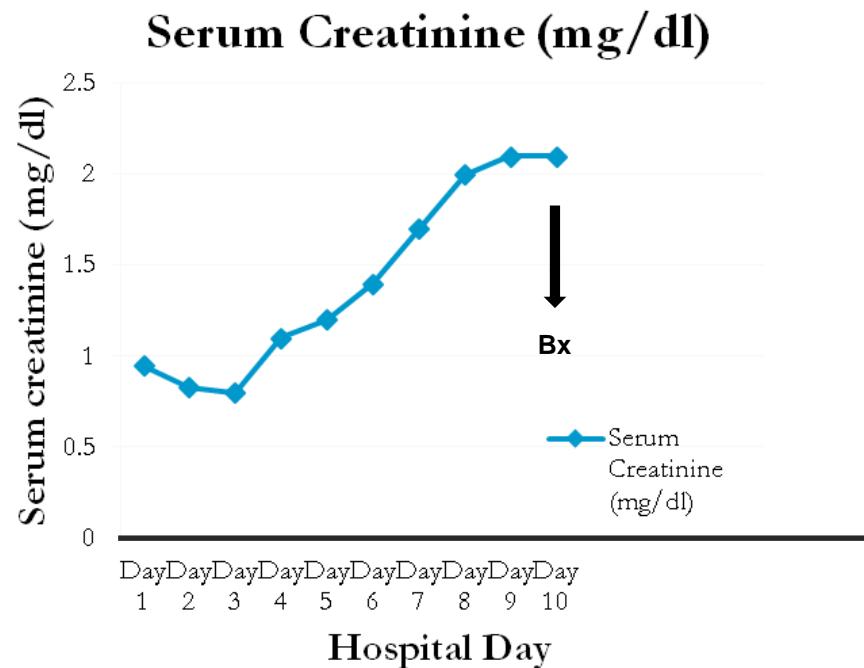
- Findings not in favor of HSP:
  - **Monoarticular arthritis**
  - Persistence and worsening of symptoms despite high dose steroids
  - Joint pain preceded skin rash
  - Adult onset presentation

# Hospital Day 4

- Progression of rash to multiple bullous lesions on upper and lower extremities



# Renal function worsened



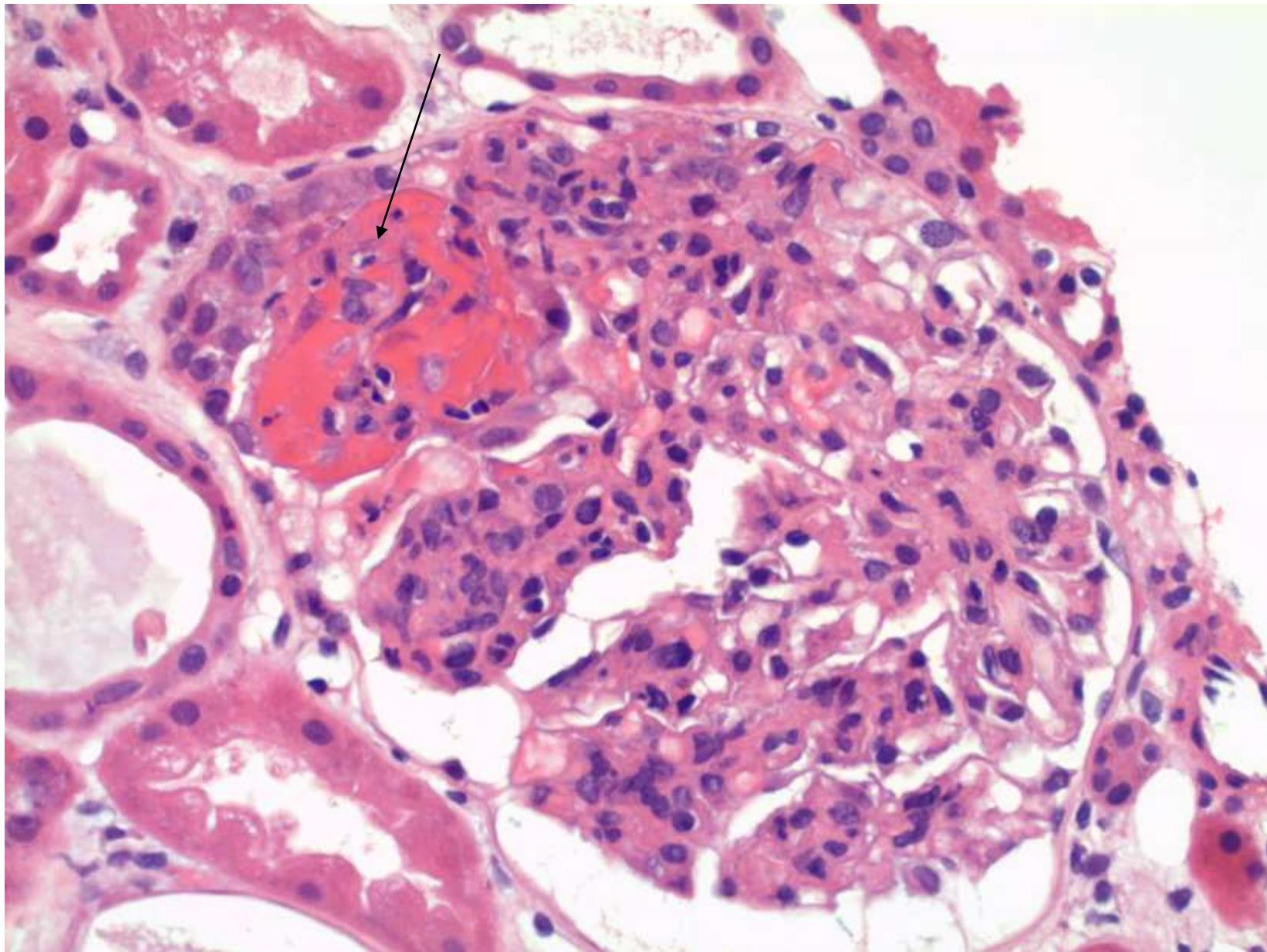
Urine output fell.

Patient became febrile.

Systolic blood pressure less than 100 mm Hg.

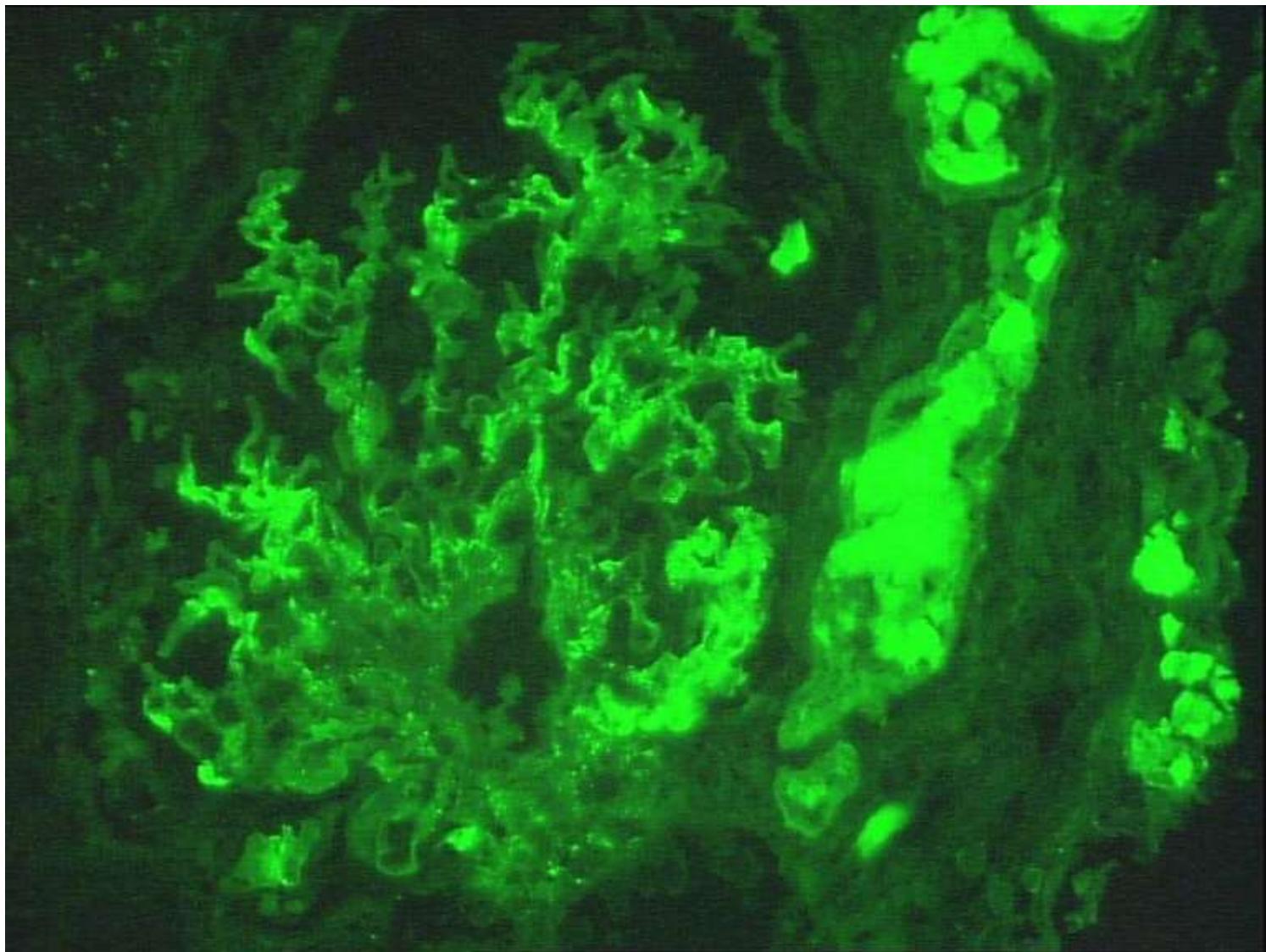
Leukocytosis – WBC 17,900/ $\mu$ l

## Segmental necrosis with early crescent formation

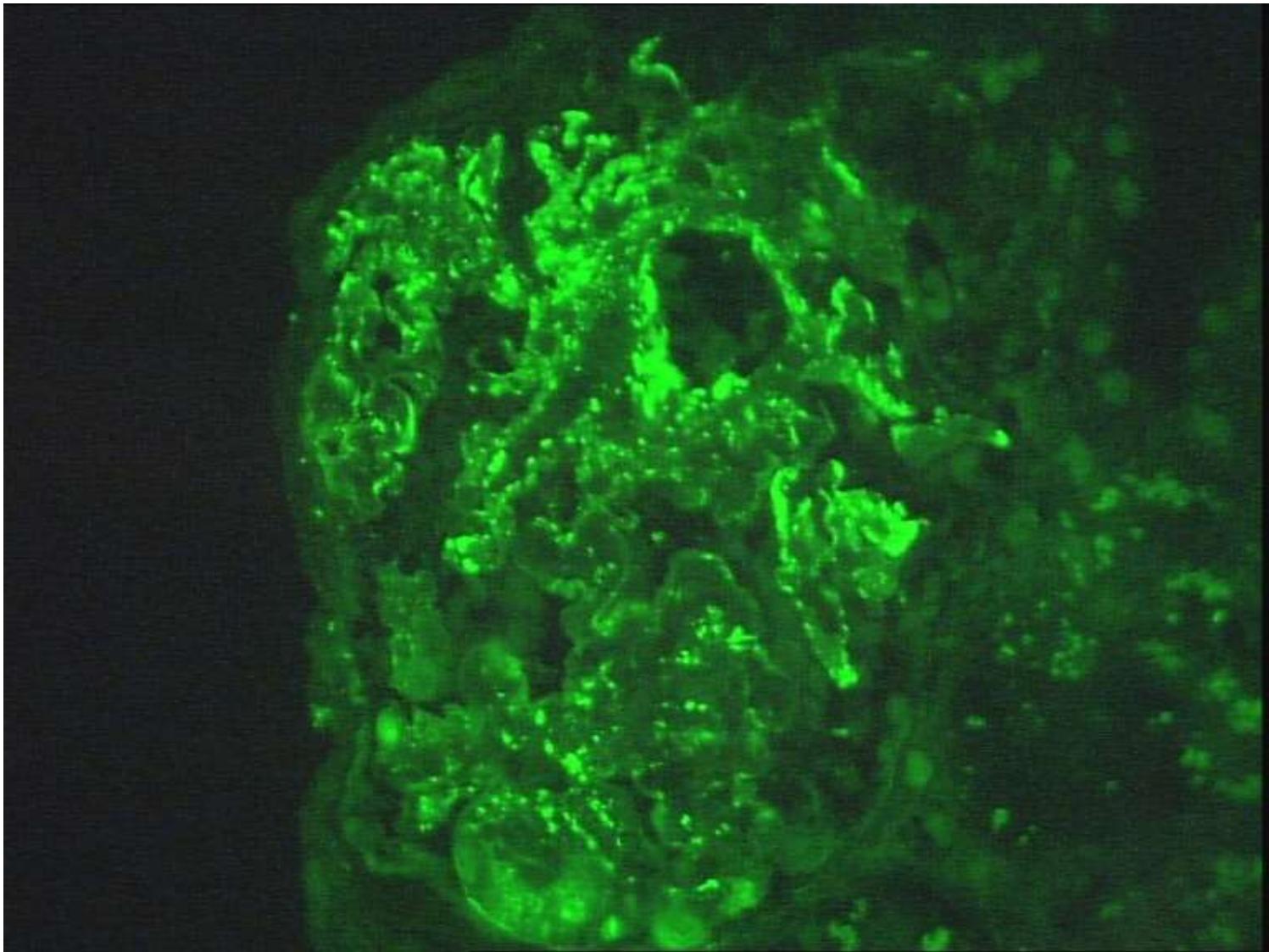


Immunofluorescence panel alb, IgG, IgA, IgM, C1q, C3, Fibrinogen, kappa and lambda

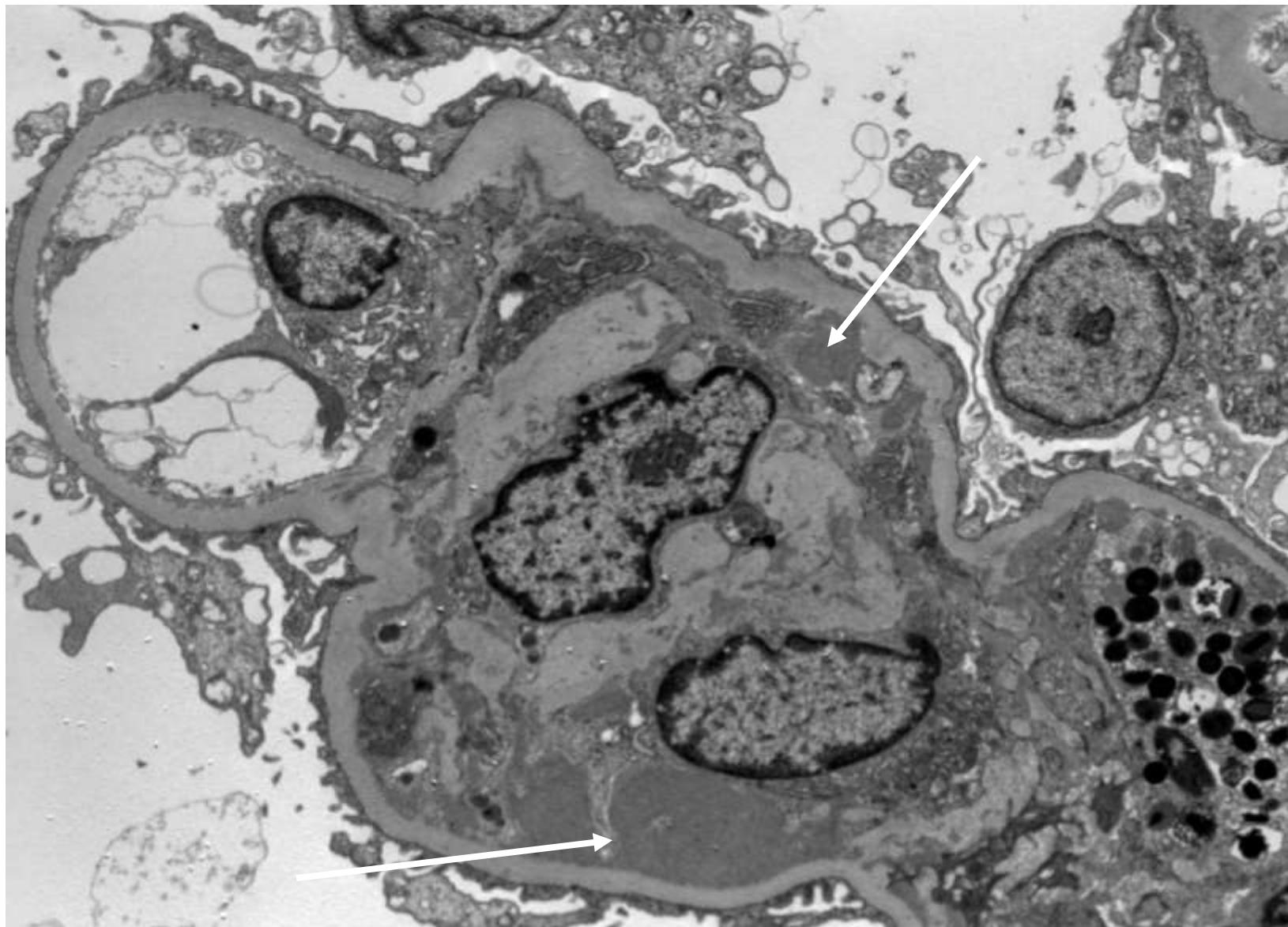
IgA (granular mesangial staining)



# C3 (coarse granular mesangial staining)



# Electron dense immune-type mesangial deposits



## Biopsy Diagnosis

**Diffuse proliferative glomerulonephritis with IgA and C3 containing immune complex deposits.**

*Note: The biopsy findings raise the possibility of IgA-dominant Staphylococcus infection-associated acute glomerulonephritis.*

**(PROBABLY NOT HENOCH-SCHÖNLEIN PURPURA OR IgA NEPHROPATHY)**

- Repeat MRI of the wrist

MRI Results - Extensive osteomyelitis of the distal radius, all carpal bones and 2nd and 3rd proximal metacarpals. Extensive overlying cellulitis, myositis, and fasciitis.

Blood cultures: still negative

# Further management and follow-up

- Debridement of the wrist wound
- Cultures from synovium and bone: Methicillin-Sensitive Staphylococcus aureus (MSSA)
- Started on Nafcillin infusion for MSSA – 6 weeks
- Renal function stabilized at serum creatinine of 2.0mg/dl.
- Follow up after completion of antibiotics
  - Serum creatinine decreased to 1.3mg/dl
  - Urinalysis – negative for blood and protein

# One of the most common diagnostic pitfalls in renal pathology

Clinically very important

IgA nephropathy

Henoch-Schönlein purpura

IgA-dominant  
Staphylococcus infection  
associated GN

Carefully differentiate between these diseases, all  
show IgA immune complex deposits – treatments  
significantly different

Biopsy findings alone are not sufficient to distinguish between these.

Clinical history is very important.

Blood cultures often negative, local wound cultures required.

Need to have a high level of suspicion and alert your nephrology colleagues, to look for possible infection.

Table 4. Comparison of idiopathic HSP and Staphylococcus infection associated glomerulonephritis presenting with HSP-like symptoms.

	<b>Idiopathic Henoch-Schönlein Purpura (HSP)</b>	<b>HSP-like presentation in Staphylococcus infection associated glomerulonephritis</b>
Age	Predominantly affecting children, uncommon in adults	Predominantly affects the elderly population 
Other associated comorbidities	No other co-morbid conditions seen	Patients commonly diabetic, have post-surgical wound complications, alcoholic, history of malignancy, endocarditis, intravenous catheters.
Associated infections	May have recent history of upper respiratory tract infection (bacterial or viral), but usually cleared before onset of HSP vasculitis.	Ongoing infections such as infected diabetic ulcers, infected surgical sites or trauma wounds, endocarditis, pneumonia, visceral abscess, infected intravenous catheters. Infection may be undiagnosed before the onset of ARF. Usually methicillin resistant or sensitive <i>Staphylococcus aureus</i> (MRSA/MSSA), mixed bacterial infections.
Findings on skin biopsy	Leukocytoclastic vasculitis with mild IgA deposits	Leukocytoclastic vasculitis with mild IgA deposits
Findings on kidney biopsy	Focal or diffuse mesangial and intracapillary proliferative glomerulonephritis with or without crescents. Mesangial IgA, C3	Focal or diffuse mesangial and intracapillary proliferative glomerulonephritis with or without crescents. Crescents are usually small and segmental. Mesangial IgA and C3 with/without mild IgG.
Therapy	Supportive management in children. Glucocorticoid treatment only if needed for persistent renal dysfunction.	Active treatment of the infection. Immunosuppression should be avoided. 
Outcome	In children, usually self-limited disease and favorable renal outcome. In adults, renal outcome can be poor.	Usually poor renal outcome.

# Conclusions

- Staphylococcus infection became the most common cause of infection-associated GN in the US (and probably in most developed countries), particularly in adults and in the elderly
- AKI + Proliferative GN with IgA deposits (frequently with severe proteinuria): Consider infection, in particular staphylococcus infection
- Infection may not be clinically obvious – needs to be carefully looked for.
- Blood cultures may be negative. Local wound cultures important.
- SAIGN should be clearly distinguished from IgA nephropathy/HSP.
- Infection is active, ongoing; therefore avoid the term “post-infectious” (post-staphylococcal) glomerulonephritis
- Treatment of the infection is most important. Immunosuppression should be avoided

# Suggested Reading

- Satoskar AA, Nadasdy T, Silva FG: Acute Postinfectious Glomerulonephritis and Glomerulonephritis Caused by Persistent Bacterial Infection. In: Jennette JC, Olson JL, Silva FG, D'Agati VD (eds.): Heptinstall's Pathology of the Kidney, Seventh Edition. Wolters Kluwer, Philadelphia, 2015, pp. 367-436.
- Nast CC. Infection-related glomerulonephritis: changing demographics and outcomes. *Adv Chronic Kidney Dis.* 2012; 19:68-75.
- Satoskar AA, Molenda M, Scipio P, et al. Henoch-Schönlein purpura-like presentation in IgA-dominant *Staphylococcus* infection-associated glomerulonephritis – a diagnostic pitfall. *Clin Nephrol.* 2013; 79:302-12.
- Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. *Kidney Int.* 2013; 83:792-803.
- Nadasdy T, Hebert LA. Infection-related glomerulonephritis: understanding mechanisms. *Semin Nephrol.* 2011; 31:369-75.
- Glassock RJ, Alvarado A, Prosek J, et al. *Staphylococcus*-related glomerulonephritis and poststreptococcal glomerulonephritis: why defining “post” is important in understanding and treating infection-related glomerulonephritis. *Am J Kidney Dis.* 2015; 65:826-32.

