Staphylococcal-associated Glomerulonephritis

دکتر فرشاد درّی
نفرولوژیست

Box 1. Proposed Nomenclature for Glomerulonephritis Associated With Infection

Postinfectious GN

Criteria

- The GN is preceded by an infection that resolves or is resolving with or without antimicrobial therapy
- A latent period of a few days to 4 weeks follows in which there is no clinical evidence of GN
- The latent period ends with the acute onset of GN

Cause

- Poststreptococcal GN is the only well-documented cause of postinfectious GN (see text)

Infection-Related GN

Criteria

- The infection is mechanistically related to the GN (see Table 1)
- The GN is a manifestation of an ongoing infection (ie, it is not a postinfectious GN)

Cause

- There are many different bacterial, viral, fungal, and parasitic infections that can cause infection-related GN (see text)

Comment: "Poststaphylococcal GN" is not a postinfectious GN. It is the result of an ongoing infection (there is no latent period). It has been suggested that postinfectious GN means that the infection preceded the GN. That would be logical only if there was a form of GN that precedes infection (preinfectious GN), which, of course, there is not. See text for additional arguments that "poststaphylococcal infection" is a misnomer.

Thus, poststaphylococcal GN should be referred to as staphylococcus-related GN.

Abbreviation: GN, glomerulonephritis.

Table 1. Overview of Infection-Related Glomerulonephritis According to Clinical Features and Glomerular Histology

	Infection		
GN Type	**Duration**	**Type**	**Onset of GN[a]**
IgA nephropathy (acute flare of the established GN)	Few days	Typically viral pharyngitis or upper respiratory tract infection	1-3 d
C3 nephritis (acute flare of established GN)	Few days	Typically viral pharyngitis or upper respiratory tract infection	1-3 d
Poststreptococcal GN (de novo GN)	1 to a few weeks	β-Hemolytic streptococcus pharyngitis, sinusitis, otitis media, cellulitis, or other sites	A few days to 4 wk (after resolution of infection and onset of GN)
Staphylococcus-related GN (de novo GN)	Weeks	Cellulitis in an ischemic extremity, osteomyelitis, endocarditis, and other sites	Weeks to months
Other forms of de novo GN during subacute to chronic bacterial, viral, fungal, or parasitic infection	Weeks to months	Many different sites	Weeks to months

Note: Most forms of bacterial infection–related GN are proliferative immune complex–mediated GN. However, the GN associated with chronic viral, fungal or parasitic infection is often a membranous nephropathy. Also, some of the proliferative GNs associated with subacute infection are pauci immune (no evidence of glomerular antibody or immune complex deposition).[60]

Abbreviations: GN, glomerulonephritis; IgA, immunoglobulin A.

[a]After the onset of infection.

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 codominant or dominant)

Glomerulonephritis with other persistent infections

- Endocarditis
- Deep seated abscesses
- Shunt nephritis

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 (frequently mild) 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

TABLE 1. Demographic and Clinical Features of Patients with *Staphylococcus* Infection-associated Glomerulonephritis

No. of patients	83
Sex (M/F)	64/19
Age, years, mean ± SD	58 ± 17 (13–90)
Region (Asians/Americans/others), fraction of patients, %	41/40/2 (49.4/48.2/2.4)
Proteinuria, fraction of patients, %	78/83 (94)
Proteinuria, g/24 h, mean ± SD	3.85 ± 3.44g/d (0.15–15 g/d)
Hematuria, fraction of patients, %	82/83 (98.8)
AKI at presentation, fraction of patients, %	75/83 (90.4)
Scr at onset, mg/dL, mean ± SD	2.29 ± 2.16 mg/dL, (0.50–9.90 mg/dL)
Peak Scr, mg/dL, mean ± SD	5.67 ± 3.23 mg/dl, (1.30–12.29 mg/dl)
Hypocomplementemia, fraction of patients, %	45/83 (54.2)
Hypertension, fraction of patients, %	15/83 (18.1)
DM, fraction of patients, %	20/83 (24.1)
Heart diseases, fraction of patients, %	18/83 (21.7)
Malignancy, fraction of patients, %	14/83 (16.9)
Cultures: MRSA/MSSA/SE/*Streptococcus*/ fraction of patients, %	55/21/4/3 (66.3/25.3/4.8/3.6)
Origin of infection: visceral abscess/skin infection/ joint infection/respiratory infection/blood/ genitourinary system/digestive system/unknown, fraction of patients, %	26/24/12/8/7/3/1/2 (31.3/28.9/14.5/9.6/8.4/3.6/1.2/2.4)
Therapy: antibiotics alone/antibiotics plus steroids or immunosuppressants/steroids or immunosuppressants/unknown (fraction of patients, %)	45/14/4/20 (54.2/16.9/4.8/24.1)
Outcomes: R/PRD/ESRD/death/unknown, (fraction of patients, %)	36/15/19/12/1 (43.4/18.1/22.9/14.5/1.2)

AKI = acute kidney injury, DM = diabetes mellitus, ESRD = end-stage renal disease, F = female, M = male, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-sensitive *Staphylococcus aureus*, PRD = persistent renal dysfunction, R = remission, Scr = serum creatinine, SD = standard deviation, SE = *Staphylococcus epidermidis*.

Table 1. Clinical characteristics of the 48 cases reported in the literature from 1980–2010[a]

Number of patients	$N = 48$(%)
Age (mean)	21–89 (59.1)
Sex (M/F)	40/8
Creatinine at presentation (mean)	0.5–9.9 (2.53 mg/dL)
Proteinuria	
>3 g/day	25 (52%)
<3 g/day	19 (40%)
None specified	4 (8%)
Hematuria	
Gross	8 (17%)
Microscopic	40 (83%)
Complement level	
Normal	35 (72%)
Low	12 (25%)
NA	1 (3%)
Purpuric lesion	13 (27%)
Hypertension	7 (14%)
Diabetic	11 (22%)
Onset after infection (week)	1–16 (4.5)
Steroids use	9 (18%)
Type of infection	
MRSA	33 (68%)
MSSA	9 (18%)
Other	6 (14%)
Outcome	
RRT	16
Death	7

[a]NA, non available.

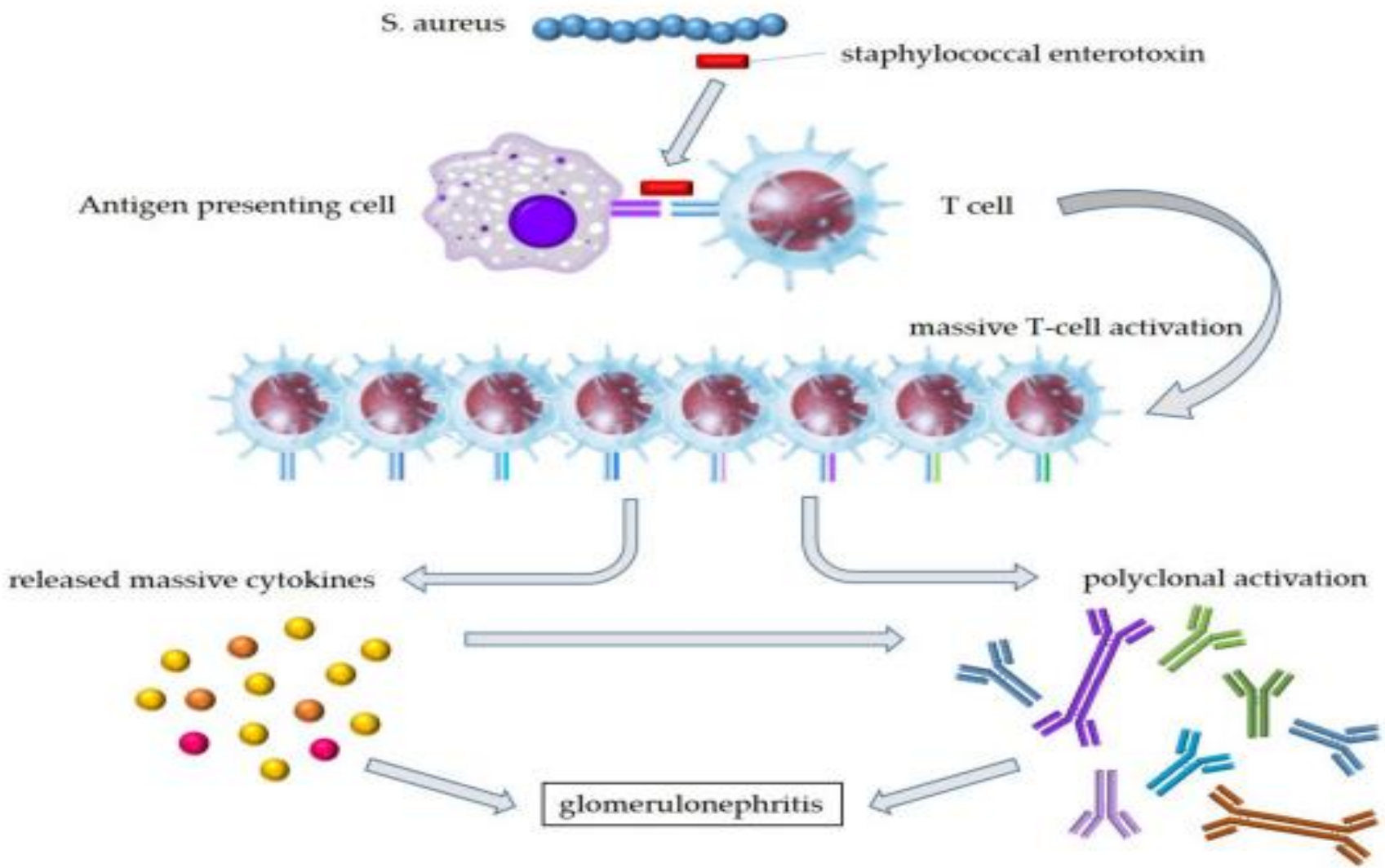


Figure 4. Hypothesis of pathogenesis in SAGN with IgA-dominant deposition. Staphylococcal enterotoxins produced by *S. aureus* bind to specific TCR-Vβ on T cells and the outer part of the MHC molecules without being processed. Bacterial superantigens lead the MHC-unrestricted huge T-cell activation. The subsequent excessive release of cytokines activates not only T cells but also B cells; the polyclonal immunoglobulin production leads to the formation of immune complexes, resulting in the onset of SAGN. *S. aureus*—*Staphylococcus aureus*.

TABLE 2. Histopathology Features of Patients with *Staphylococcus* Infection-associated Glomerulonephritis

Light microscopy	
EPGN, %	19 (22.9)
DPGN, %	24 (28.9)
MsPGN, %	24 (28.9)
Crescents, %	30 (36.1)
ATN, %	25 (30.1)
DGS, %	13 (15.7)
Tubular atrophy, %	22 (26.5)
Inflammation, %	53 (63.9)
Interstitial fibrosis, %	14 (16.9)
Fibrinoid necrosis, %	5 (6.0)
Immunofluorescence	
IgA, fraction of patients, %	76/83 (91.6)
IgG, fraction of patients, %	54/83 (65.1)
IgM, fraction of patients, %	32/83 (38.6)
C3, fraction of patients, %	77/83 (92.8)
κ light-chain, fraction of patients, %	23/83 (27.7)
λ light chain, fraction of patients, %	25/83 (30.1)
C1q	14/83 (16.9)
Fibrin	6/83 (7.2)
Electron microscopy: location of immune complex deposits	
Subepithelial, fraction of patients, %	38/71 (54.3)
Subepithelial deposits including "humps," %	32/71 (45.1)
Subendothelial, fraction of patients, %	21/71 (29.5)
Mesangium, fraction of patients, %	56/71 (78.9)
GBM or TBM thickening	12/71 (16.9)

ATN = acute tubular necrosis, DGS = diabetic glomerulosclerosis, DPGN = diffuse proliferative (both mesangial and endocapillary) glomerulonephritis, EM = electron microscopy, EPGN = endocapillary proliferative glomerulonephritis, GBM = glomerular basement membrane, IF = immunofluorescence, LM = light microscopy, MsPGN = mesangial proliferative glomerulonephritis, TBM = tubular basement membrane.

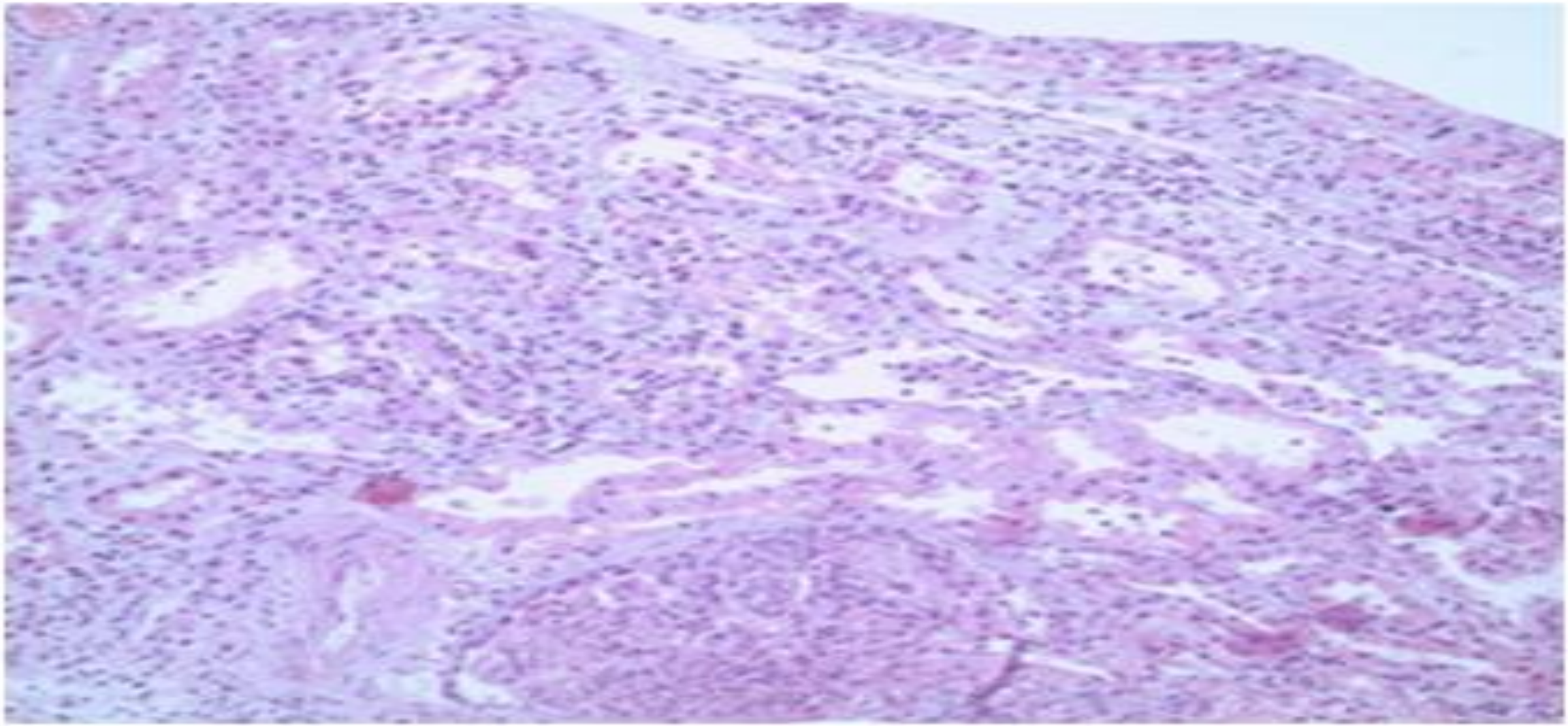
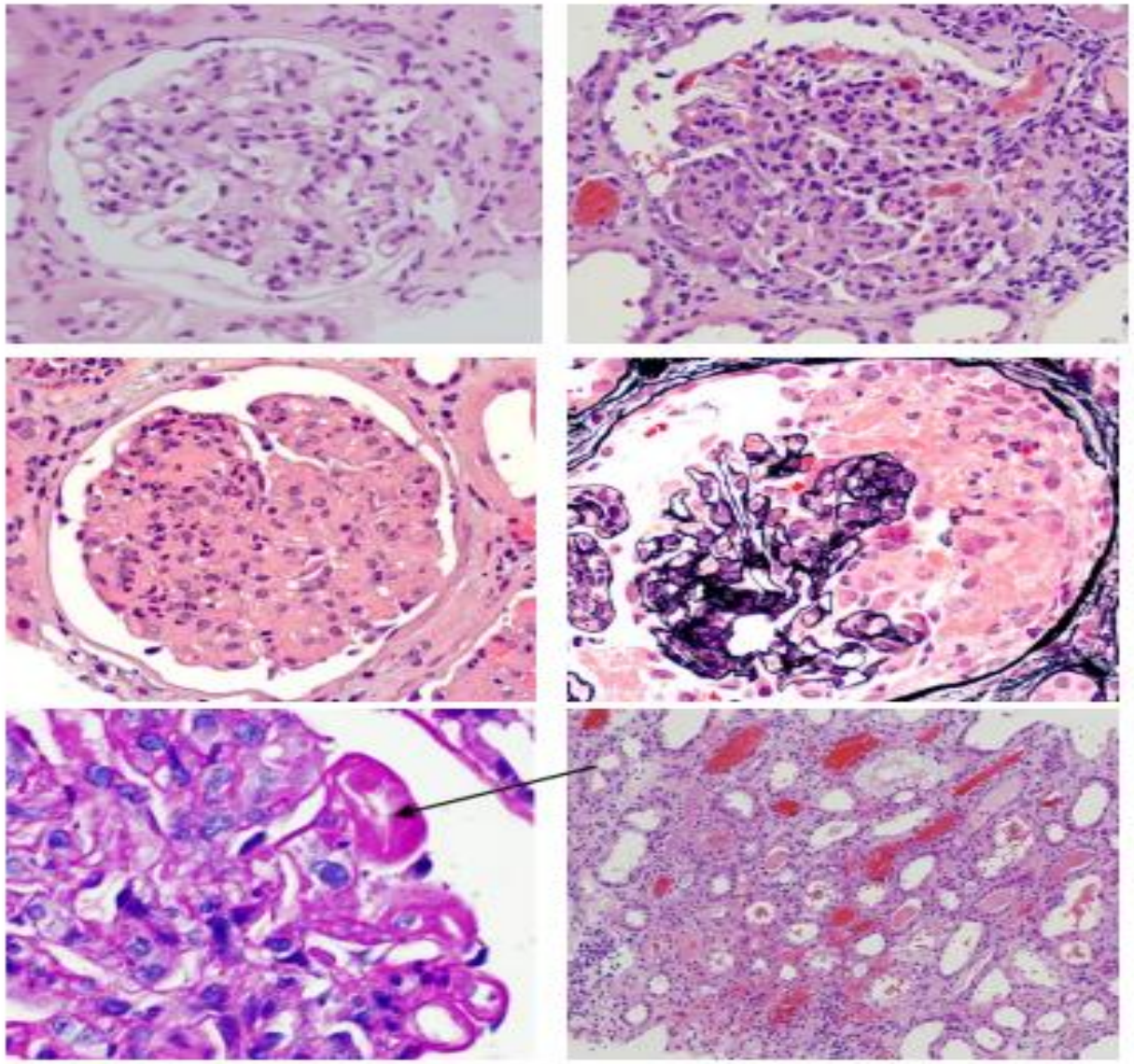


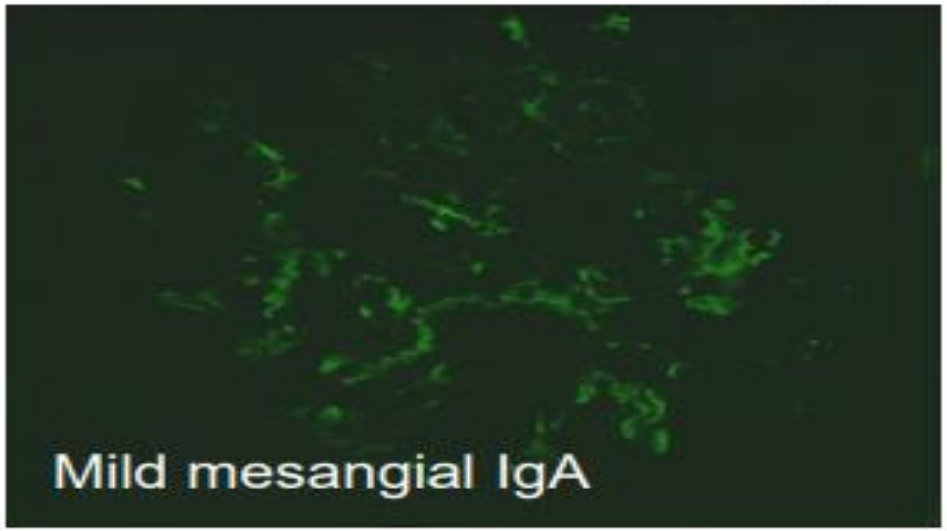
Figure 1. Diffuse exudative endocapillary and extracapillary glomerulonephritis. Note accompanying tubulitis and acute interstitial inflammation.

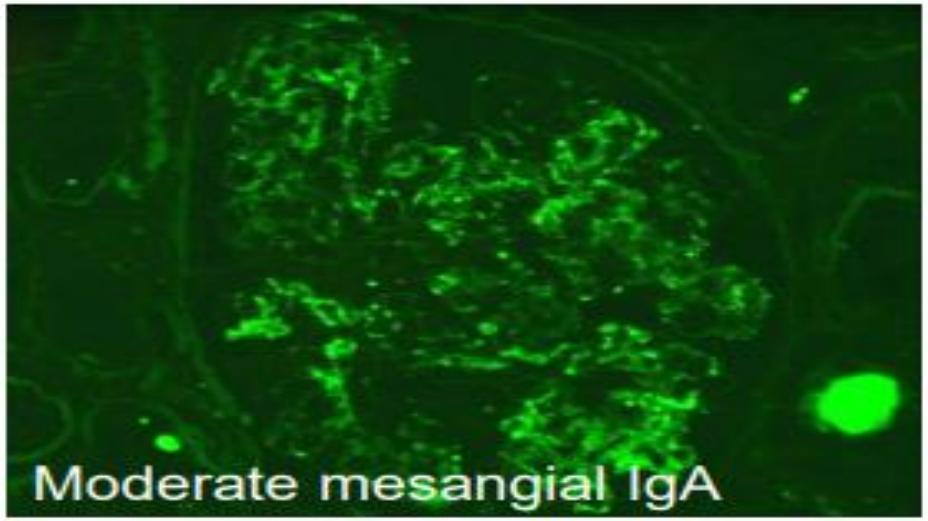
Morphology of SIAGN: Light Microscopy

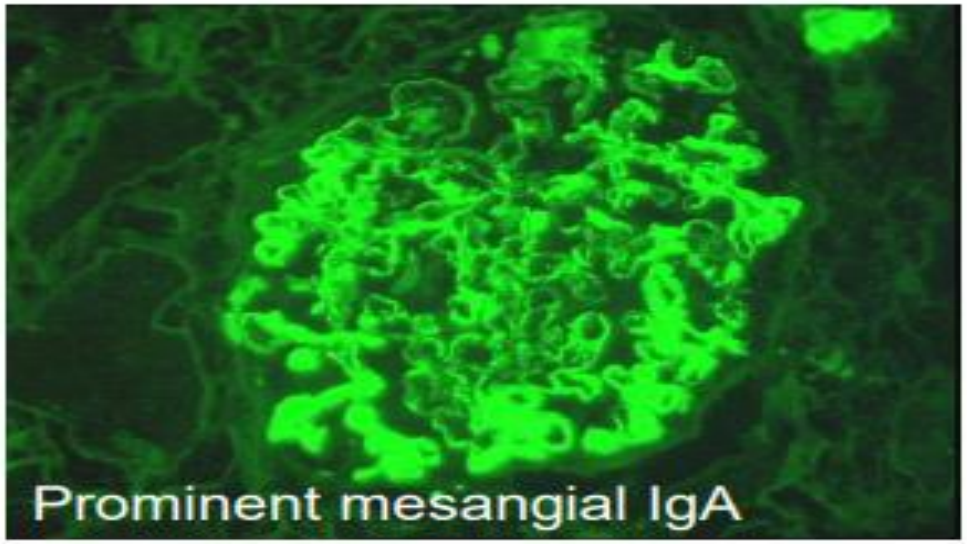
- Spectrum of glomerular changes.
- ATN
- RBC casts

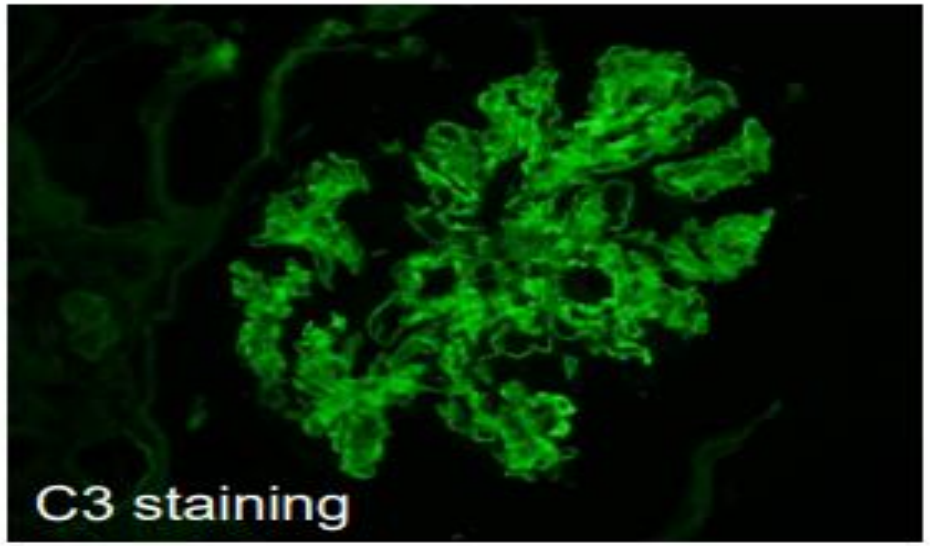


Immunofluorescence: IgA of variable intensity. C3 usually bright









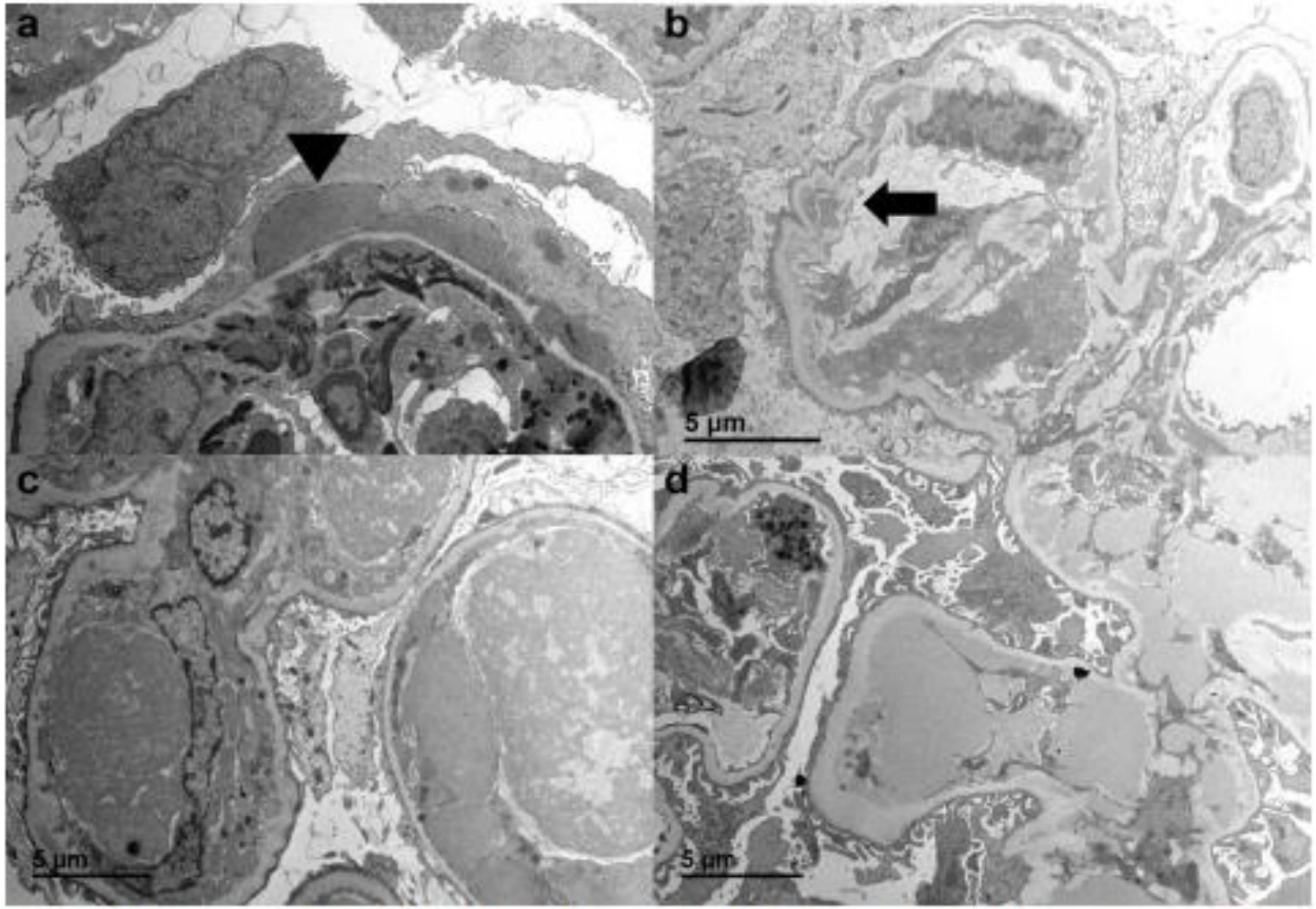
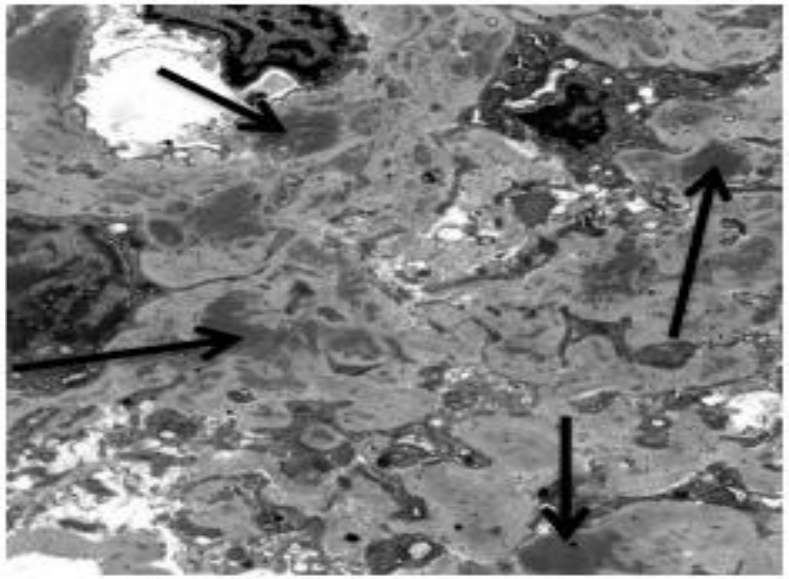


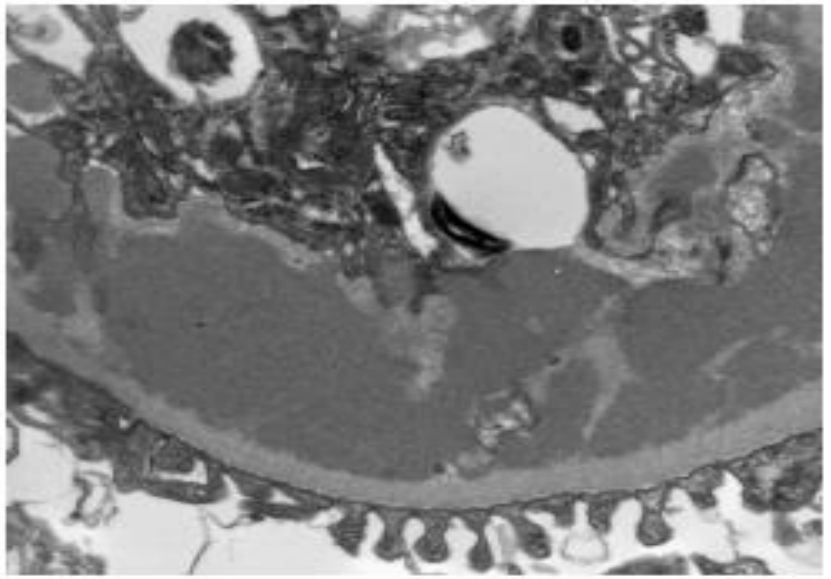
Figure 3. By electron microscopy, all patients had subendothelial and mesangial immune-type electron-dense deposits. One patient (patient #1) had subepithelial hump-like deposits (a) (arrowhead) and 1 patient (patient #2) had abundant subendothelial deposits with segmental duplication of the glomerular basement membrane (b; arrow). One patient (patient #3) had prominent intraluminal deposits on the sample for electron microscopy (c), and one (patient #4) demonstrated large subendothelial deposits corresponding to wireloop deposits on light microscopy (d).

Electron microscopy

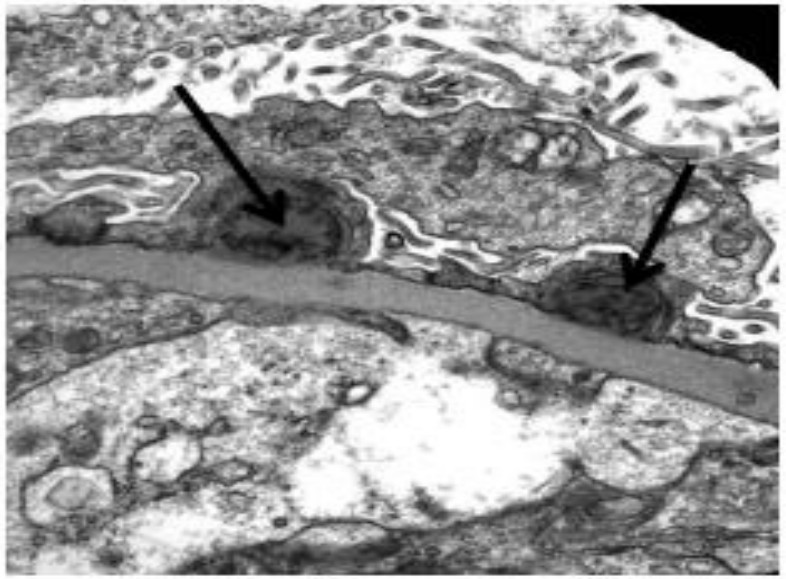
"Humps" may or may not be seen.



Mesangial deposits
(always present)



Subendothelial deposits
(sometimes large)



Subepithelial "humps"
(24% of cases at OSU)

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

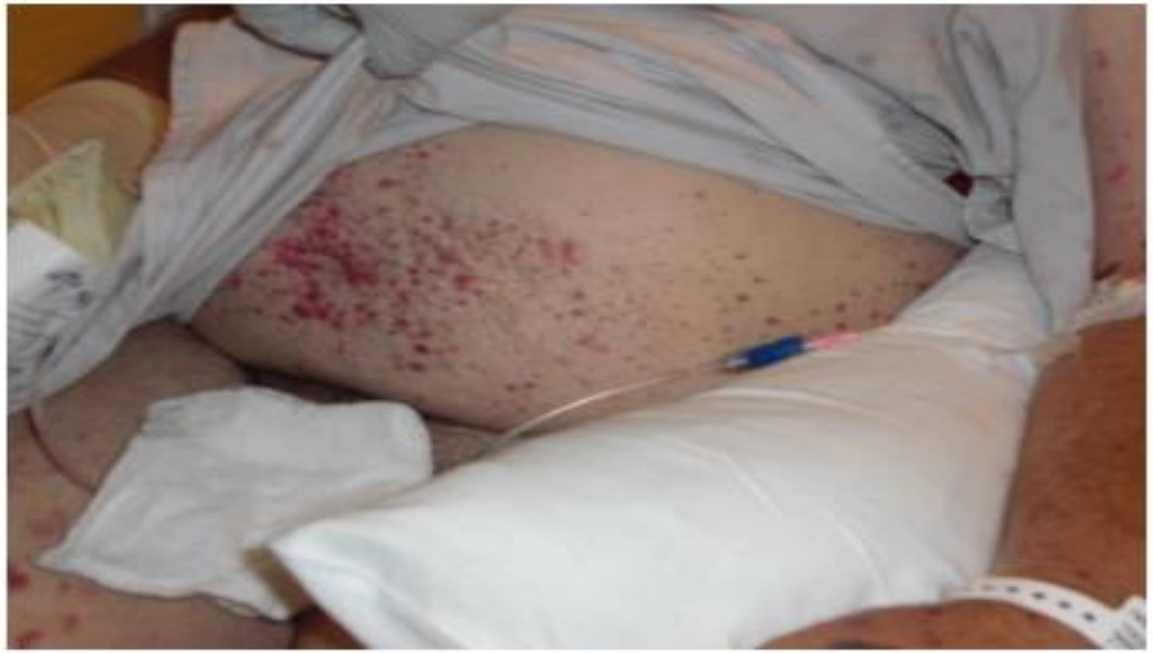
Clinical Differential diagnosis of SIAGN and IgA nephropathy

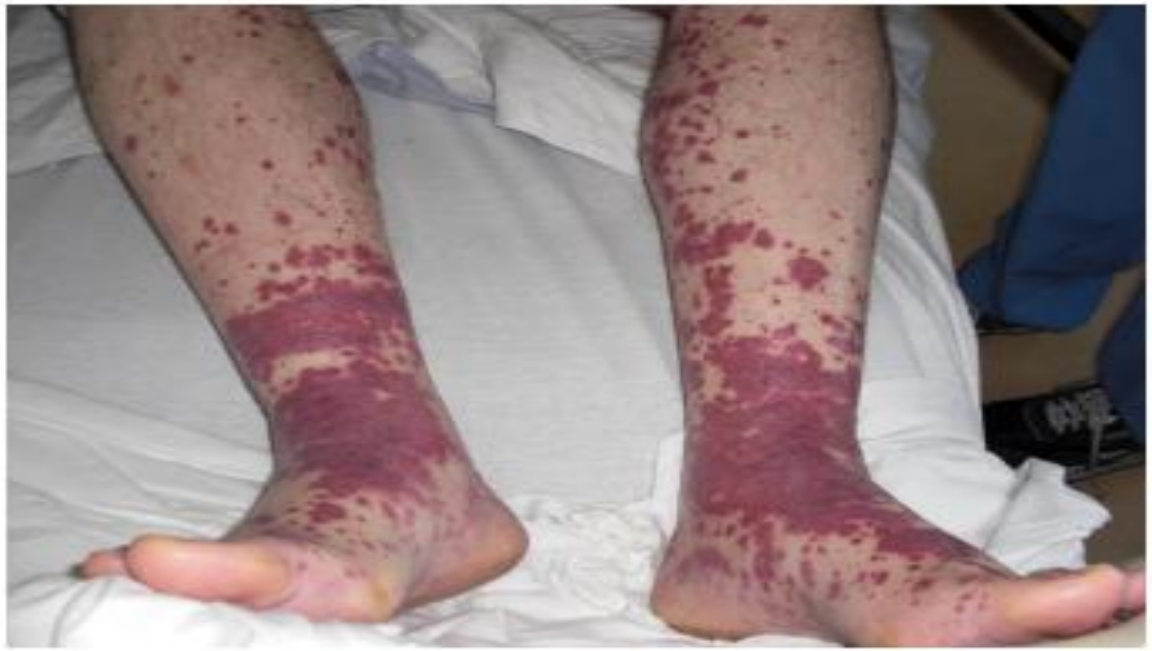
Patient Characteristic	SIAGN	Primary IgA nephropathy
Age	Usually older (50-80 years)	Usually younger (20-30 years)
History of infection	antecedent or coexistent	Occasionally (30 to 40% after URI)
Latent period	Several weeks, ongoing infection	May be "Synpharyngitic" 1 to 2 days
Microbes	Staphylococcus, 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, drug addiction, chronic devastating diseases, obesity)	Uncommon

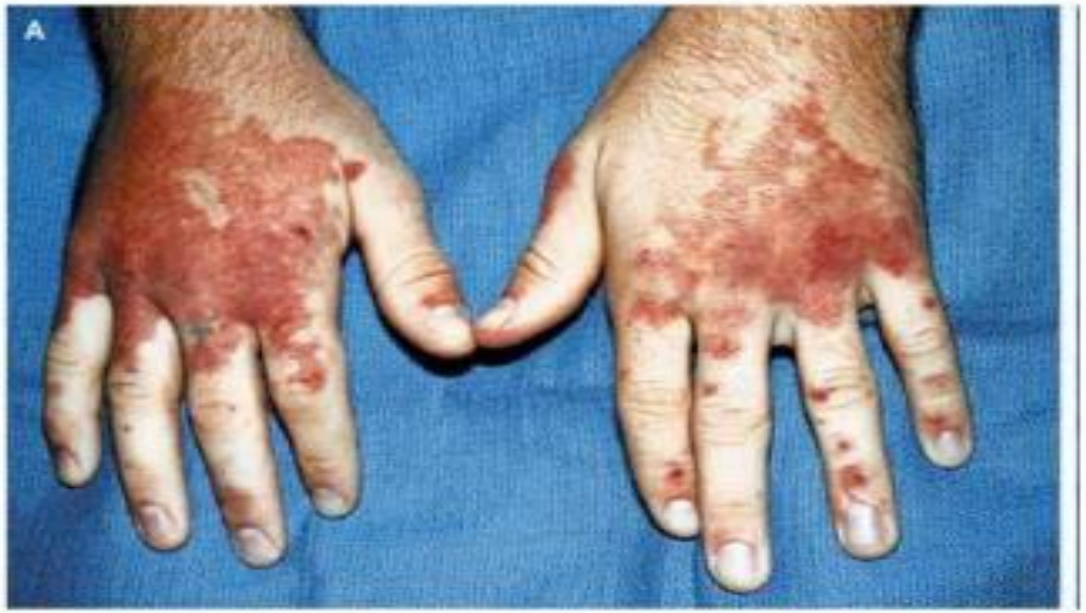
Morphologic Differential Diagnosis of IgA Nephropathy and SIAGN

		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







Rash - Palpable Purpura

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

	Idiopathic Henoch-Schönlein Purpura (HSP)	HSP-like presentation in Staphylococcus infection associated glomerulonephritis
Age	Predominantly affecting children, uncommon in adults	Predominantly affects the elderly population
Other associated co-morbidities	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 Staphylococcus aureus (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.

Satoskar A et al: Clin Nephrol 79:302-312, 2013

HSP-like presentation in an elderly or adult

Always consider underlying staphylococcus infection before starting immunosuppression

If you have a patient with AKI, heavy 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


ماهنشان