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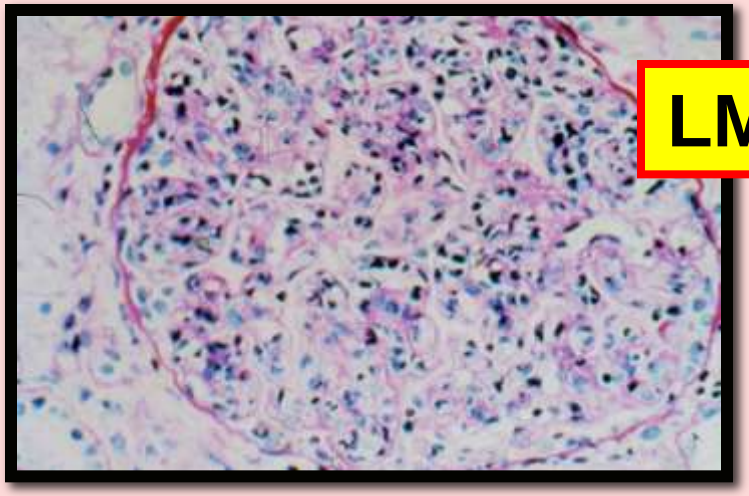
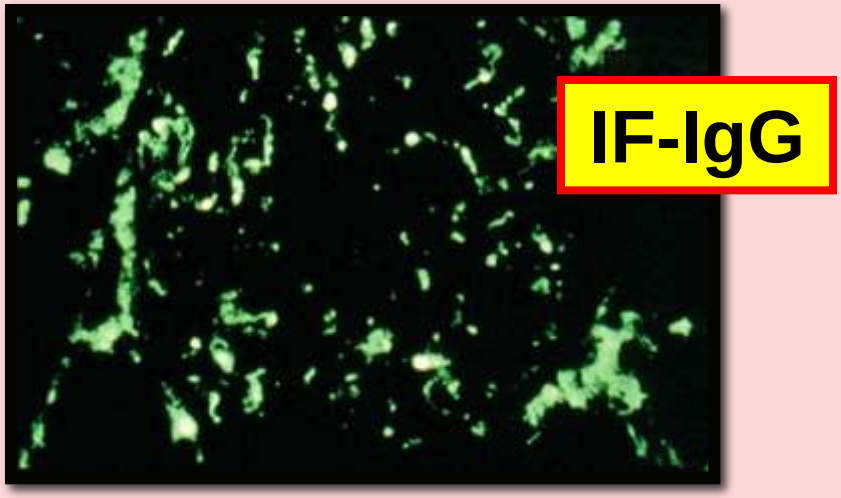
Post-infectious (bacterial) Glomerulonephritis

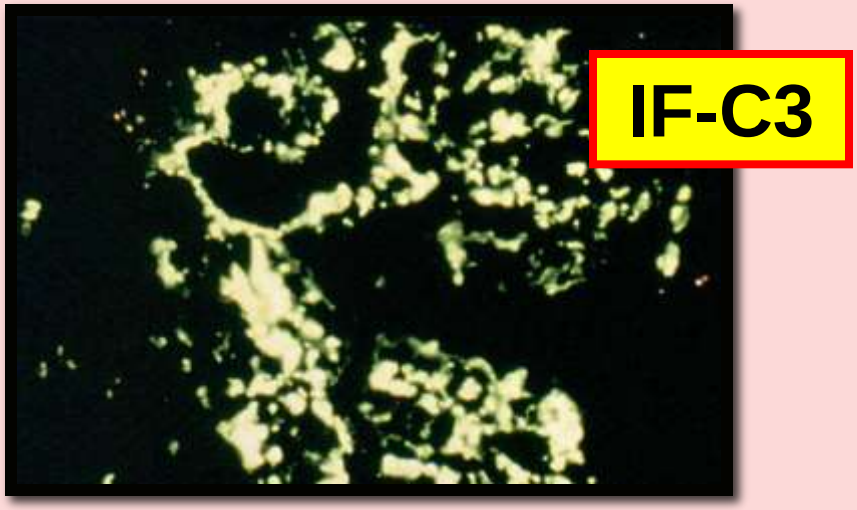
(An Update)

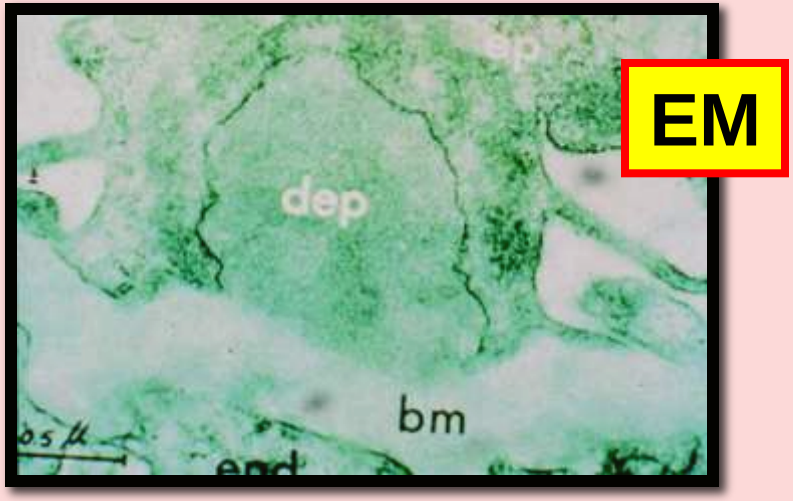
William Couser, MD
Affiliate Professor of Medicine
University of Washington
Seattle, WA USA

Post-streptococcal GN (PSGN)

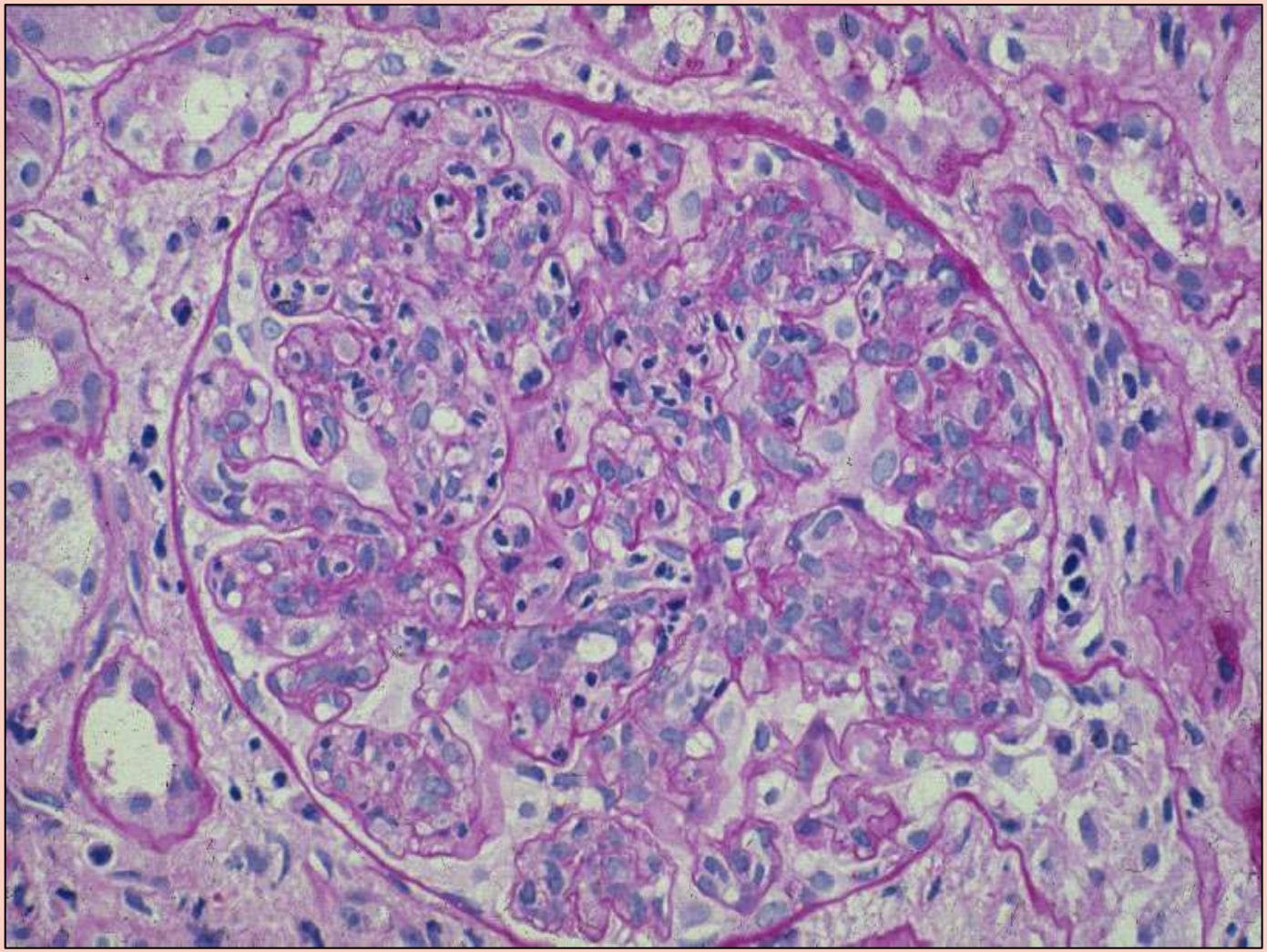








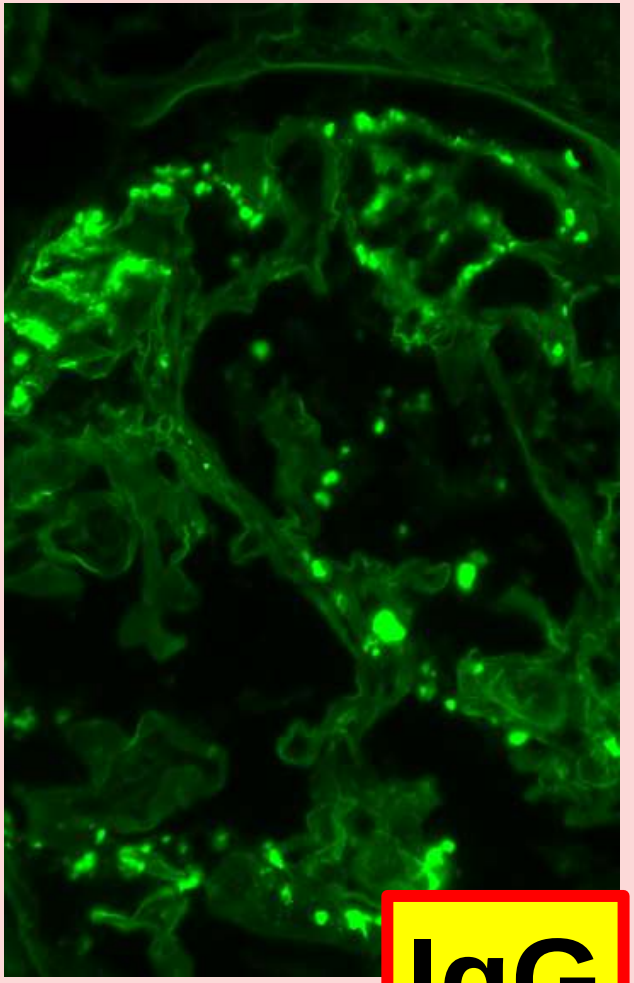
PSGN – diffuse proliferative and exudative GN

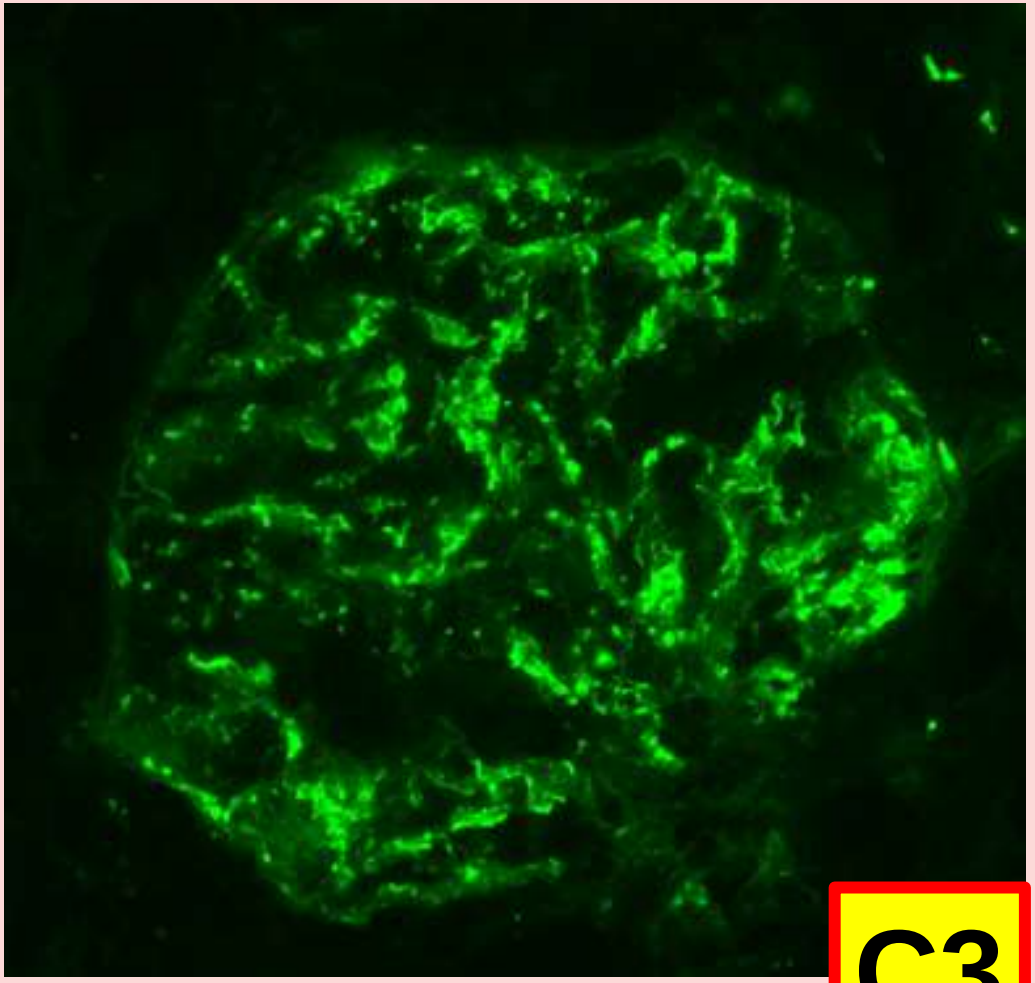


From Rennke ASN BRC 2011

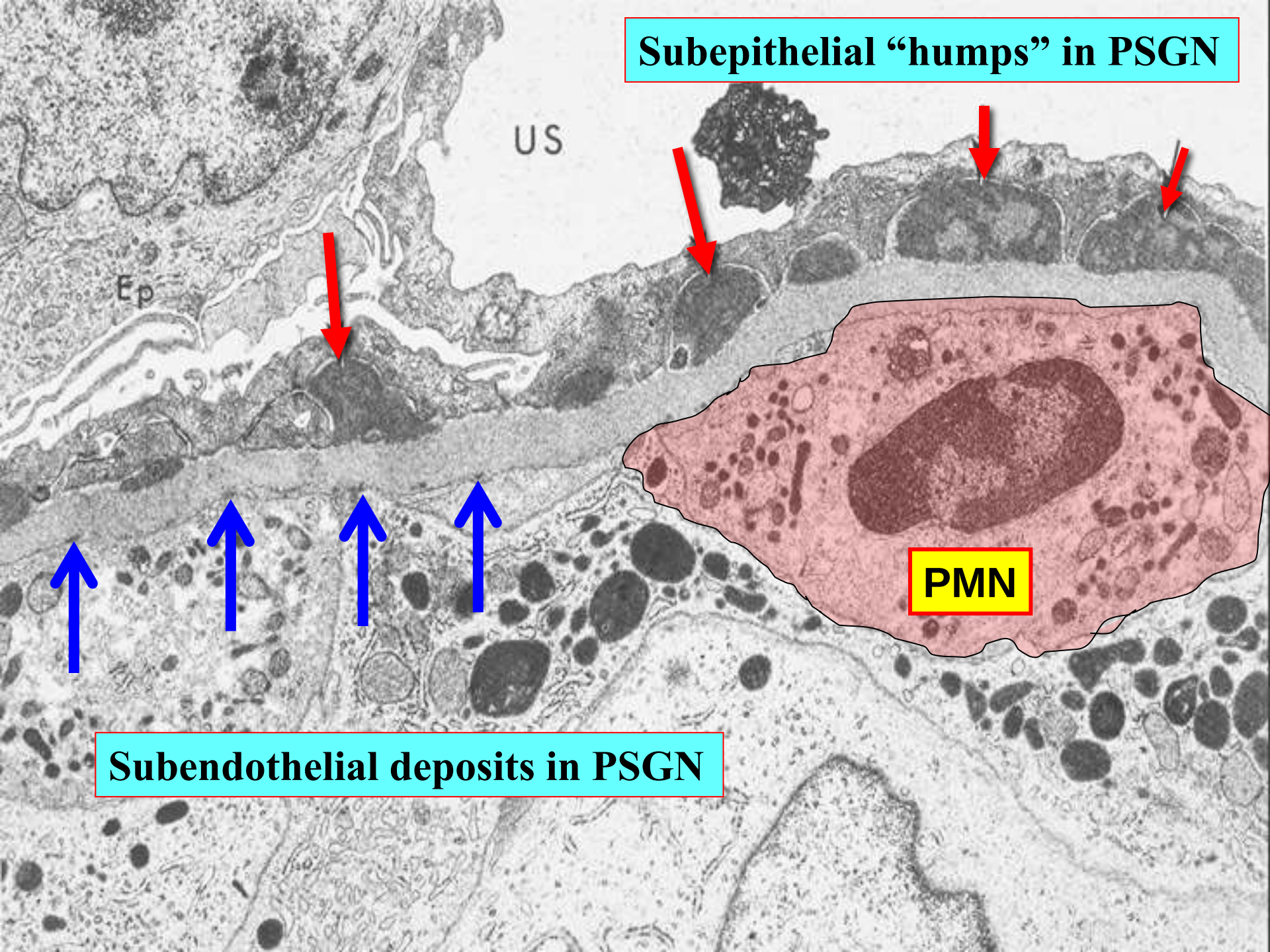
PSGN IF: 1+ IgG, 3+ C3

A “C3 nephropathy”

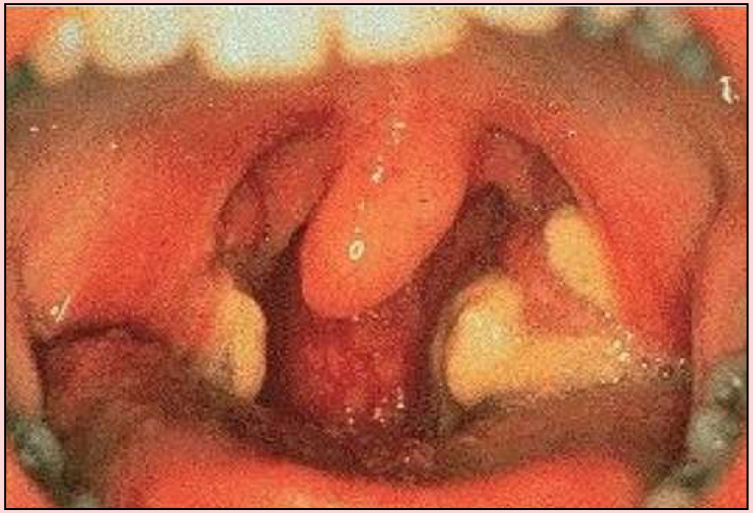




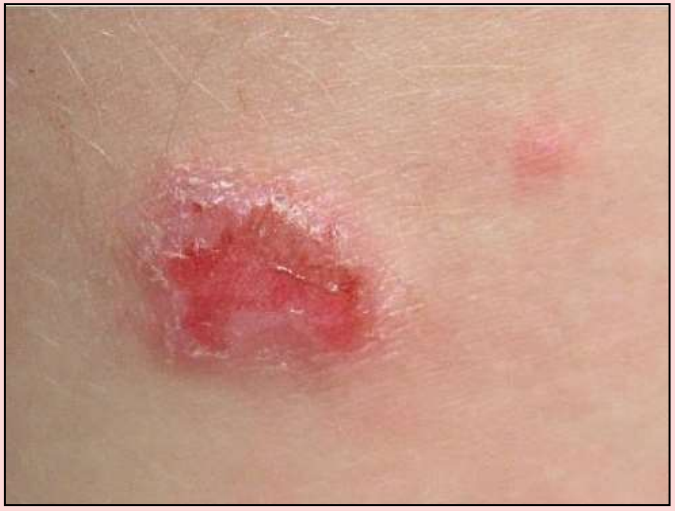
Modified from Nephpath.com


Subepithelial “humps” in PSGN
US
Ep
PMN
Subendothelial deposits in PSGN

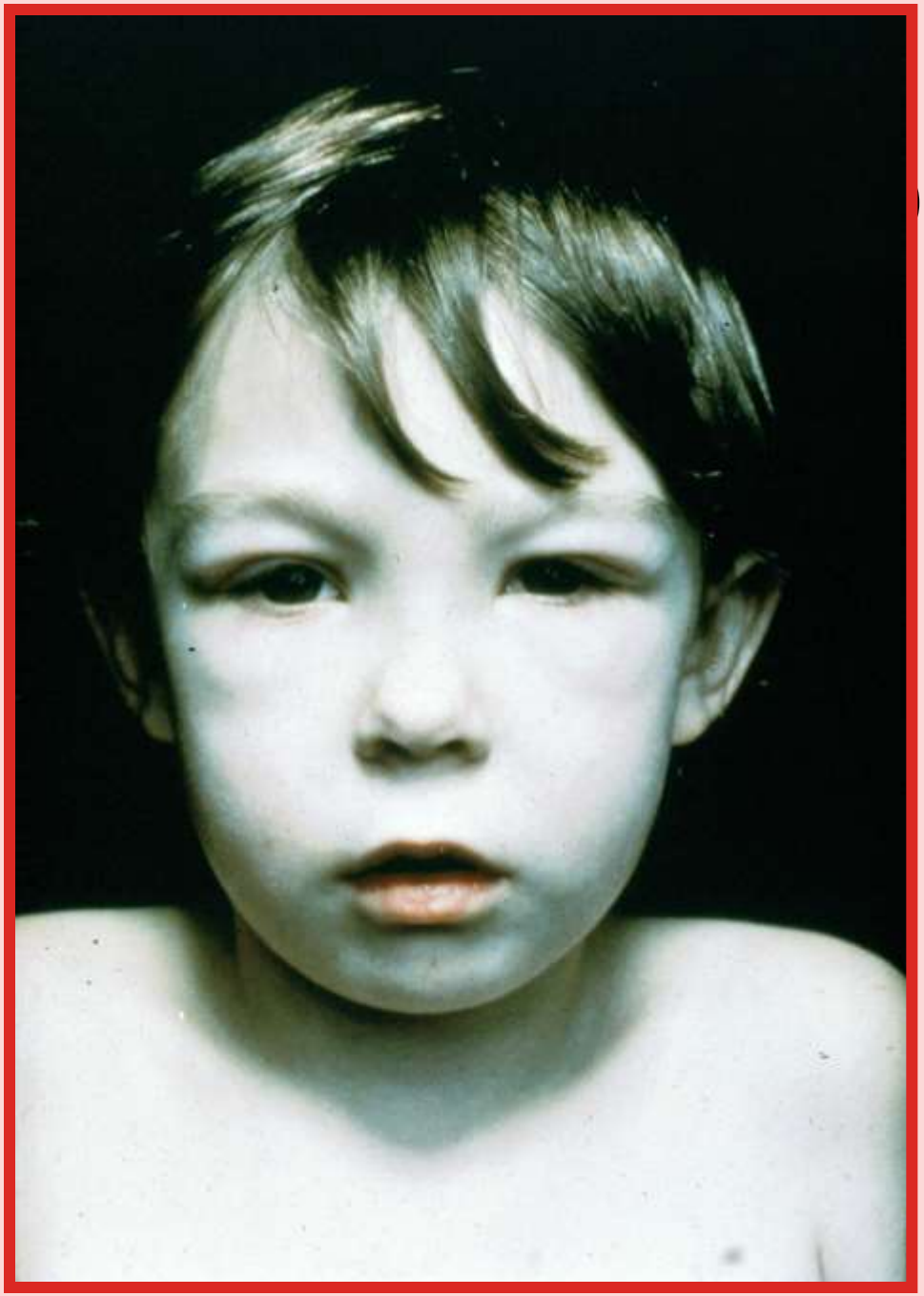
ETIOLOGY OF PSGN



Strep pharyngitis (40%)

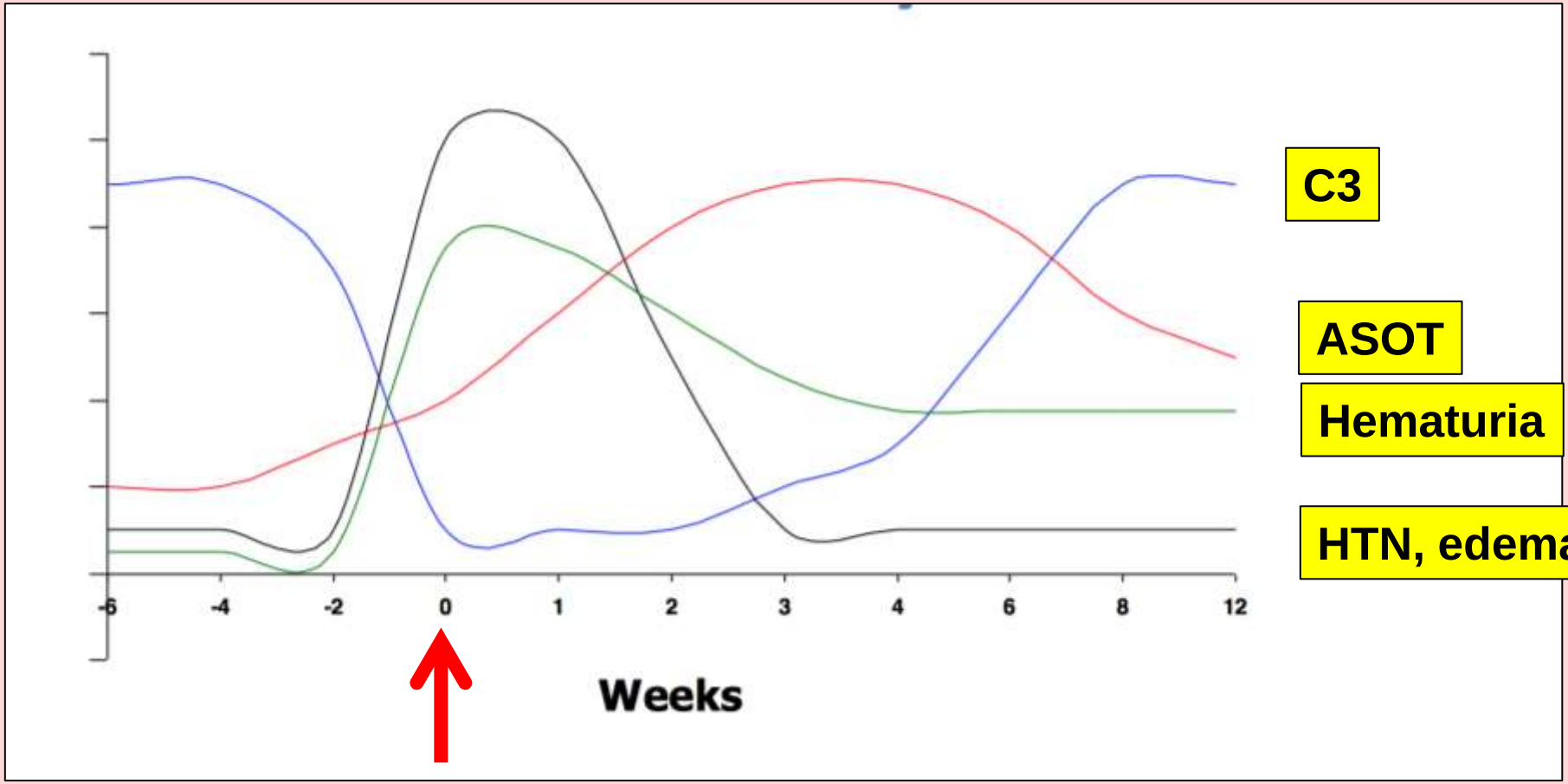


Strep pyoderma (60%)



Peri-orbital edema in 10 yo boy with acute, post-streptoccocal GN

Typical time course of symptoms and lab values in PSGN



Post-strep GN in adults today (109 cases)
Changing epidemiology and outcomes

- **Incidence**
  - About 12% of exposed people get clinical GN
  - 25% of exposed people or family members get subclinical GN

Bottom line:

As the population ages and epidemic cases decrease with improved hygiene, PSGN in adults is becoming a disease of greater severity, worse prognosis and often affecting older, mostly immunocompromised men.

  - Anuria > 24 hrs
  - Oliguria > 7 days
  - Atypical laboratory results or clinical picture.

- **Recovery (3 months)**
  - **Complete: 22%**
  - **Partial-CKD 44%**
  - **ESRD 33%**

Kanjanabuch, Nat Rev Nephrol 5:259, 2009; Nasr et al, JASN 22: 187, 2011

Post-streptococcal nephritis

Can you make the diagnosis serologically?

Test	Sensitivity	Specificity	Duration
Increased ASO Titer	75%	Only for infection	6-8 weeks
Increased Streptozyme	>90%	Only for infection	6-8 weeks
Low complement (alternate or MBL pathway)	>90% (First 2 weeks)	No (C3 nephropathies)	4-8 weeks
Cryoglobulins	20%	Any chronic inflammation	4 weeks
Rheumatoid factor	20%	Several collagen vascular diseases	4 weeks

Differential diagnosis of renal diseases with **fluid phase C activation** (**low** serum complement levels)

Disease	Pathway	Serum C' levels	Other
SLE	Classical	Low C1,C4,C2,C3, CH_{50}	ANA, anti-dsDNA
MPGN I	Classical	Low C1,C4,C3, CH_{50}	Anti-HCV, cryos, rheumatoid factor
Chronic infection (SBE, shunt nephritis, IgA dominant PIGN	Classical	Low C1,C4,C3, CH_{50}	Bacterial infection Cryoglobulins Rheumatoid factors
Post-strep GN	Alternative	Normal C1,C4,C2 Very low C3, CH_{50}	ASOT, streptozyme
C3 GN	Alternative	Normal C1,C4,C2 Low C3, CH_{50}	C3-nephritic factors, Abnormal C regulatory proteins

Post-streptococcal GN:
Typical clinical course derived mostly from pediatric studies

Sign	***Resolution***
• Diuresis	1 week
• Hypertension	2 weeks
• Cr to normal – longest on HD=38 days	3-4 weeks
• Low C3	6-8 weeks, longest 9 mos
• EM humps	6-7 weeks
• Hematuria	3-6 weeks
• Proteinuria	3 years: 15%, 10 years: 2%

Acute renal failure 5%

CKD: up to 20% (Sinha et al NDT 10-13-08)

ESRD: 2.5%

Outcomes of PSGN with >50% crescents and AKI in children

Although it is a reasonable clinical option, there is no data to demonstrate that steroid pulse therapy given to patients with acute, crescentic PSGN accelerates recovery, improves recovery rate or alters long term outcome.

– Only outcome predictor: Need for dialysis

Jellouli et al. Nephrol Ther (Epub 7-20-15)

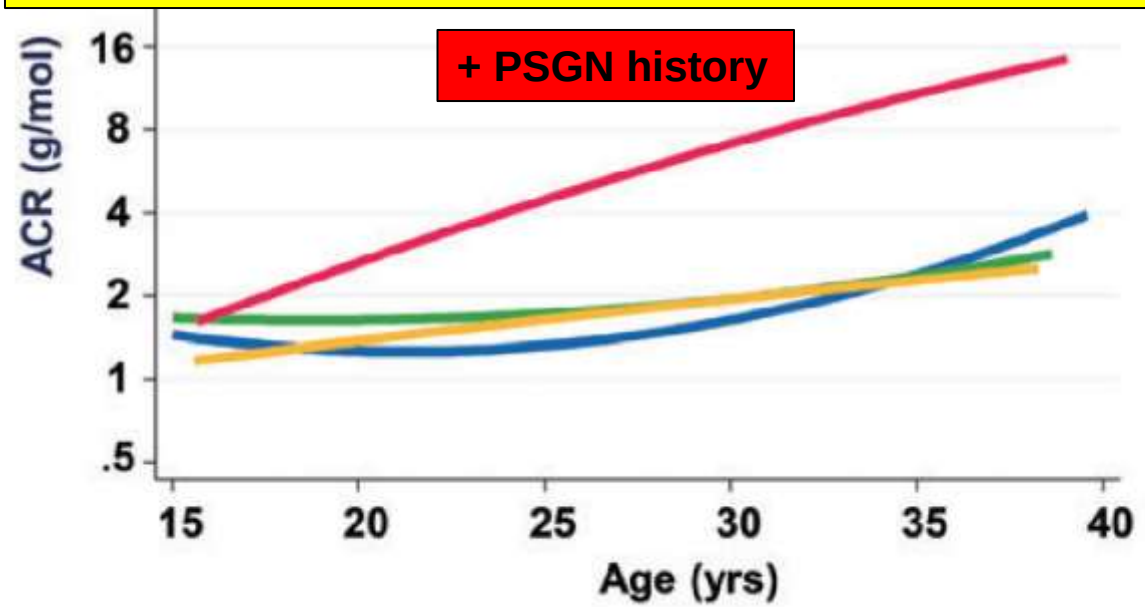
Long term prognosis in PSGN (4021 patients, **5-18 yr FU**) ESRD is an uncommon outcome

• Any abnormality	17%
• Proteinuria	14%
• Hypertension	14-45%
• Reduced GFR	1.3%

From Rodriguez-Iturbe et al JASN 19:1855, 2008;
Pinto et al. PLOS 1 (Epub 5-11-15)

History of PSGN > 5 yrs ago increases CKD later in life

Hazard ratios of a history of PSGN from impetigo for developing ACR >34 (overt albuminuria):
Males: 4.1
Females: 3.1



Hoy W et al. NDT (Epub 7-24-14); Hoy et al Kidney int 81:1026, 2012

What are the major risk factors for CKD and ESRD due to PSGN?

- Epidemic (low) vs sporadic (higher)
  - Children (low, 1%) vs adults (10-35%)
  - Age (>60, 75% have CKD)
  - Severity (Crescents, AKI) (50%)
  - Proteinuria after 12 mos
  - Persistent low C3 beyond 6 weeks

“Atypical” post-infectious GN

- Acute onset of nephritic syndrome with persistent

Bottom line:

- **Some (? many) cases of GN following infectious episodes have C3 nephropathies rather than immune complex GN.**
- **These patients do not fully recover.**
- **Examples of complement regulatory protein abnormalities associated with more severe disease have now been reported in SLE and IgA nephropathy as well.**

Sethi et al. Kidney Int 83:293, 2013

Treatment of PSGN

- There is no KDIGO guideline for treating acute PSGN because most patients recover spontaneously and need only supportive care.
- Steroid pulse therapy can be considered in patients with persistent AKI and a crescentic lesion on biopsy.
- There is one case report of a dramatic and immeadiate response to Eculizumab in a 10 yo girl with classical acute PSGN, elevated ASOT, oliguric ARF (Scr 6.4) and crescents who did not respond to pulse steroids. (Sharma et al. ASN abstract 2014)

Non-streptococcal post-infectious GN is now called "Infection-related GN" (IRGN)

Clinical features

- **Now 34% age >65**
- **35% have a co-morbid condition:**
  - **Diabetes (15%), cancer, alcoholism, cirrhosis, immunosuppression, HIV, IVDA, malnutrition**
- **50% of cases are subclinical**
- **20-40% nephrotic at the outset**
- **Increasing incidence of IgA-dominant PIGN**
  - **Older males**
  - **Diabetic or other co-morbid conditions**
  - **Acute renal failure**
  - **Only 30-70% low C3**
- **30-70% CKD (60% if sporadic)**
- **Overall ESRD 10-20%, 50% if diabetic**

Nasr et al: Medicine 87:21, 2008; Nast: Am J CKD 12:68, 2012

Infection-related GN in adults (109 cases)
Changing demographics

- **Risk factors (61% immunocompromised)**
  - Age >64 64%
  - Diabetes 29%
  - Cancer 5%
  - HIV 2%
  - IVDU 1%
- **Sites of infection (Diverse)**
  - Upper respiratory 23%
  - Skin 18%
  - Lung 18%
  - Endocarditis 12%
- **Organisms (Mostly Staph)**
  - Staph 46%
  - Strep 16%
  - Gram negatives % 10%

Nasr S et al: JASN 22:187, 2011

Infection-related GN

Sites of infection

Site of Infection	%
Upper respiratory	23
Pneumonia	17
Skin Endocarditis	17 10
Osteomyelitis	5
Urinary Tract	5
Abscess	2
Vertriculo-peritoneal shunt	1
Phlebitis	1
Unknown	16

Nasr et al. Medicine 87: 21, 2008

Infection-related GN

Clinical features

Clinical features	Without diabetes (N=70)	With diabetes (N=16)
Serum Cr at biopsy Mg/dl	3.89	6.44
Mean Proteinuria G/day	3.6	4.1
Nephrotic Syndrome (%)	30	23
Hematuria	90	100
Low C3 or C4	67	100

Nasr et al. Medicine 87:21, 2008

Infection-related GN

Outcomes (52 pts, mean FU 25 mos

Outcome	DM -	DM +
Complete recovery	56%	0%
CKD	27%	18%
ESRD	17%	82%

Nasr et al, Medicine 87:21, 2008

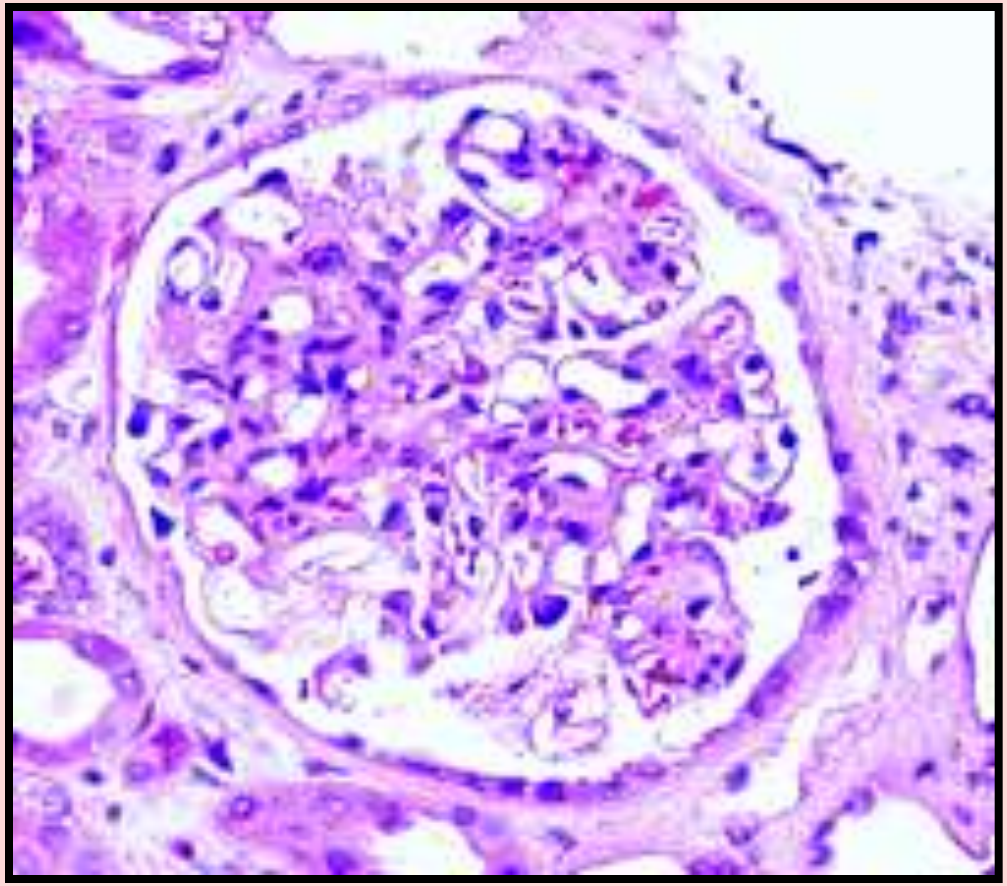
Acute infection-related GN

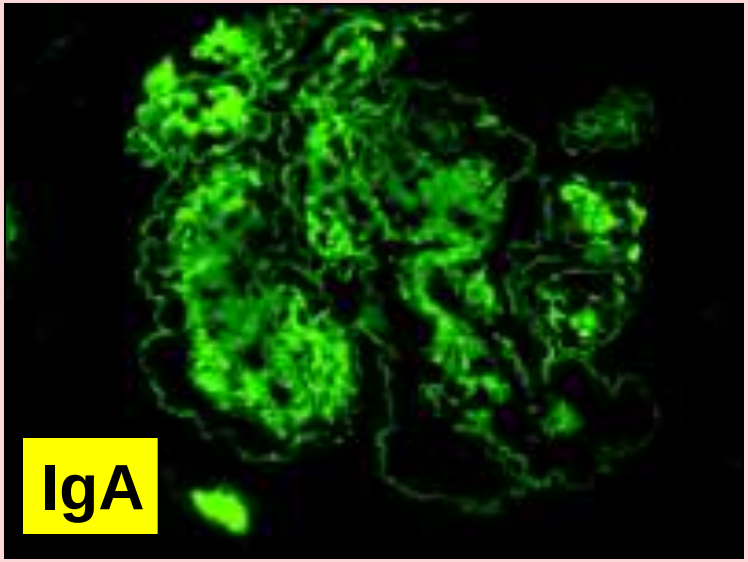
Also think of:

- IgA-dominant post-infectious GN
- Bacterial endocarditis
- Shunt nephritis
- Nephritis with visceral abscesses

Post-staphlococcal IgA-dominant infection-related GN

Older male, MRSA, diabetic, AKI





From Haas et al, Human Path 39, 1309, 2008

IgA- dominant infection-related GN

- RPGN, AKI, nephrotic syndrome (30%)
- Usually Staph infection, esp. MRSA (68%)
- Often older diabetics, usually male
- 50% have low C3
- IgA/C3 by IF, deposits at all 3 sites by EM, usually include humps
- Differentiate from IgA by risk factors, infection history, humps, and usually more severe disease.
- **Treatment: Antibiotics**

Satoskar et al, CJASN 1:1179, 2006; Wehbe et al NDT Plus 4:181, 2011

Clinical features of IgA-dominant post-infectious GN
(78 patients, 28 reports)

- **Clinical features**
  - Pathology: humps 100%
  - Hematuria 97%
  - Proteinuria 96%
  - AKI 85%
  - Active infection 100%
- **Outcomes (after antibiotic therapy)**
  - GFR improved: 55%
  - Persistent CKD: 12%
  - ESRD 20%
  - Died 14%
- **Risk Factors for death/ESRD**:
  - Age, diabetes

Bu et al. Am J Nephrol. 41:98, 2015

Can/should IgA-dominant post-infectious GN be treated with steroids?

Recommendation: Consider steroids (with antibiotics) if:

1. **>30% crescents, acute interstial nephritis or diffuse proliferative GN with progression.**

2. **No improvement after 6 weeks of antibiotics.**

3. **Nephrotic-range proteinuria.**

Eswarappa, et al. Use of steroid therapy in immunoglobulin A-dominant poststaphylococcal glomerulonephritis (Review). Hong Kong J Nephrol 24:336, 2014

Bacterial endocarditis-related GN (1)

- **Demographics:**
  - 49 adult cases, 4:1 male, Mean age 48, 30% over 60
- **Presentation**
  - AKI (80%), acute GN (20%)
- **Co-morbidities**
  - Cardiac valve disease (26%) (TC>MV>AV)
    - 50% of infected valves are prosthetic
  - IV drug abuse (18%)
  - HCV (20%), Diabetes (18%)
- **Organisms**
  - Staph 55% (MRSA 39%)
  - Strep (24%)

Boils, Couser et al. Renal Disease in Infective Endocarditis. An Update on Clinical and Pathologic Features. Kidney Int 87:1241, 2015

Bacterial endocarditis-related GN (2)

- **Labs**
  - Hypocomplementemia (56%) (low C3, normal C4 = AP)
  - Positive ANCA 28%
  - Positive ANA 15%

- **Pathology**
  - Focal necrotizing GN (78%) with crescents (55%)
  - Diffuse proliferative GN (33%)
  - C3 (100%); IgG (26%), IgA (29%)
  - EM: 14% classical humps

Boils, Couser et al. Renal Disease in Infective Endocarditis. An Update on Clinical and Pathologic Features. Kidney Int 87:1241, 2015

Shunt nephritis

- Chronic infection on ventriculoatrial or ventriculojugular shunts for hydrocephalus
- About 30% of shunts get infected, 0.7-2.0% of infected shunts get GN over 2 mos to many years
- *Staph epidermidis, Staph aureus* most common
- Chronic fever with hematuria and sometimes nephrotic syndrome (30%)
- May also develop AKI, allergic interstitial nephritis, TMA
- Biopsy: MPGN type I
- C-ANCA can be positive and justify steroids
- **Treatment: Shunt removal, 4-6 weeks of antibiotics**

Iwata et al. Am J Kidney Dis. 43: e11-6, 2004

GN with occult visceral abscess

- Crescentic RPGN with AKI
- Abscess usually intra- abdominal or intra-thoracic
- Serologies negative, C' low in 40%, cryos may be positive.
- No glomerular immune deposits by IF or EM
- Blood cultures negative
- **Treatment: May respond to steroids if no resolution with antibiotics**

Beaufils et al, NEJM 295:185, 1976, Clin Nephrol; 70:344, 2008

Many forms of GN may be "post-infectious"

(Reviewed in Couser W, Johnson RJ. The etiology of glomerulonephritis: Roles of infection and autoimmunity Kidney Int 86:905-14, 2014)

- **Post-streptococcal GN**
  - Nephritogenic streptococcal antigen (SpeB) activates complement directly through the MBL pathway.
- **IgA nephropathy**
  - IgA dominant post-staph GN in older male diabetics
  - Enteric microbiome activates TLR4 to induce abnormally glycosylated IgA_1 and anti-glycan antibodies.
- **Anti-GBM disease**
  - Molecular mimicry between anti-GBM T cell epitope $Pcol_{28-40}$ on gram negative organisms, esp. C bolinulum, induces autoimmunity to GBM antigen

Many forms of GN may be post-infectious

(Reviewed in Couser W, Johnson RJ. The etiology of glomerulonephritis: Roles of infection and autoimmunity Kidney Int 86:905-14, 2014 and Expanding the domain of post-infectious GN, Amer J Kidney Dis 66:725, 2015)

- **ANCA-positive vasculitis**
  - Staph or viral infections commonly precede MPA and GPA and molecular mimicry has been shown to lead to anti-complementary PR3 antibody linked to pathogenesis
  - Molecular mimicry with fimbrial antigen on gram negative bacteria (FimH) induces HLAMP2 antibody that has ANCA and anti-endothelial reactivity and induces “pauci-immune” GN.
- ***Idiopathic minimal change/focal sclerosis***
  - Pathogen- associated molecular patterns (PAMPS) via TLR4 upregulate podocyte CD80 and induce T cells to release “permeability factors”
- ***Membranoproliferative glomerulonephritis, Type I***
  - HCV antigen-C1q form TLR4 agonist that activates mesangial cells to proliferate and B cells to make cryoglobulins with rheumatoid factor activity

Thank you!

спасибо

spasibo