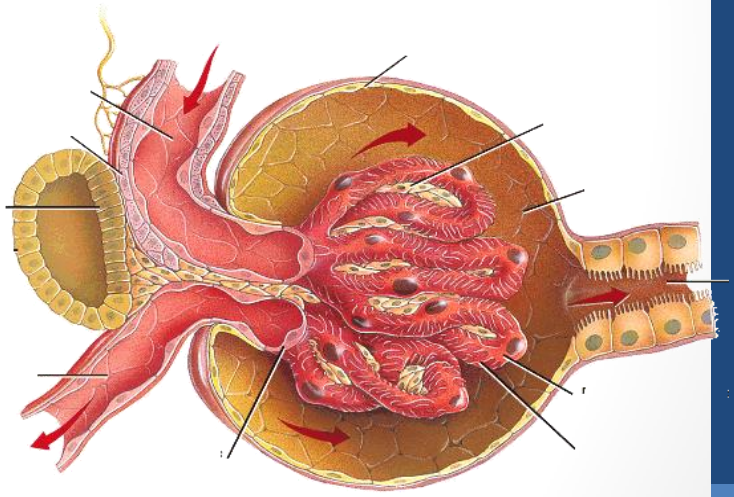
Infection Related Glumerulonephritis

PASHA,F. MD

Assistant Proffesor of Nephrology

Tehran Islamic Azad University

of Medical Sciences



Introduction

- Postinfectious glomerulonephritis (PIGN) is an immunemediated glomerulonephritis caused by nonrenal bacterial infections.

- In the past, most cases occurred in childhood and followed streptococcal upper respiratory tract or skin infections, and hence were called ‘post-streptococcal glomerulonephritis (PSGN)

- The past 3 decades have witnessed a major shift in epidemiology and outcome.

PSGN

- One of the oldest recognized renal diseases.
- Now less commonly seen in industrialized nations, but in the underprivileged world, the burden remains high.
- Subclinical disease is 4-20 times more common.
- Gp A streptococci were assumed the only strain capable of causing GN, recently epidemics sec to Gp C streptococci, *S. zooepidemicus* have been seen.

Changing Trends

before

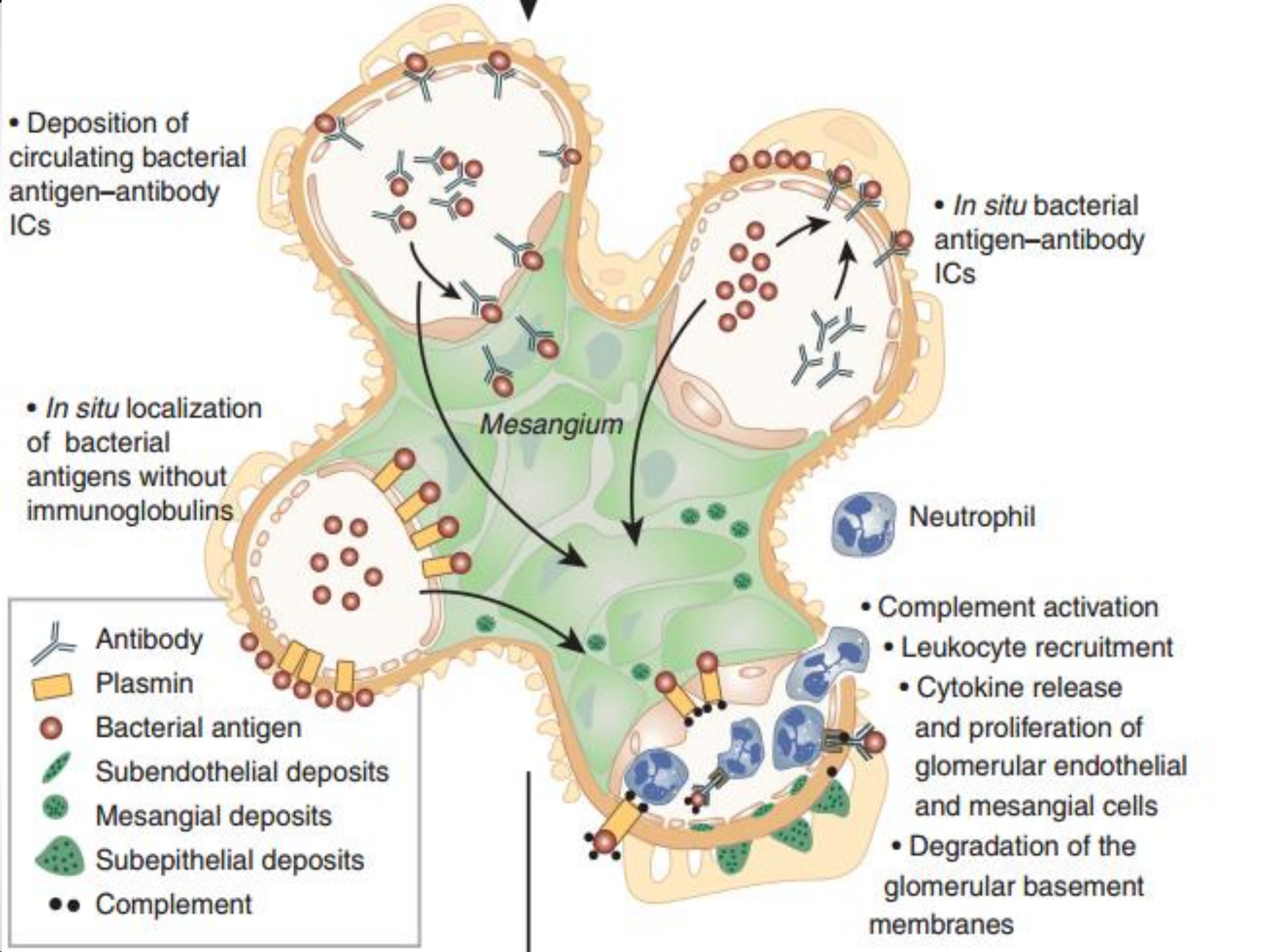
- Acute poststreptococcal glomerulonephritis (APSGN)
- Pathogeneic agents mainly group A streptococcus
- Age group - pediatric
- Prognosis- complete recovery >95% of patients

current

- In adults, staphylococcal infections are now as common as streptococcal infections and are 3fold more common PIGN
- Pathogeneic agent : includes staph and gram negative bacteria
- Age group – older
- Prognosis- complete recovery in 50-60% of patients

Pathogenesis: mechanisms for the immunologic glomerular injury

- Deposition of circulating immune complexes with streptococcal antigenic components.
- In situ immune complex formation resulting from deposition of streptococcal antigens within the glomerular basement membrane (GBM) and subsequent antibody binding.
- In situ glomerular immune complex formation promoted by antibodies to streptococcal antigens that cross-react with glomerular components (molecular mimicry).
- Autoimmune reactivity:
  -Anti- (IgG) (modifcation by streptococcal neuraminidase may modify immunoglobulins, rendering them autoantigenic).
  - Anti-DNA antibodies
  - anti-C1q antibodies,
  - antineutrophil cytoplasmic antibodies (ANCA)
  -RF

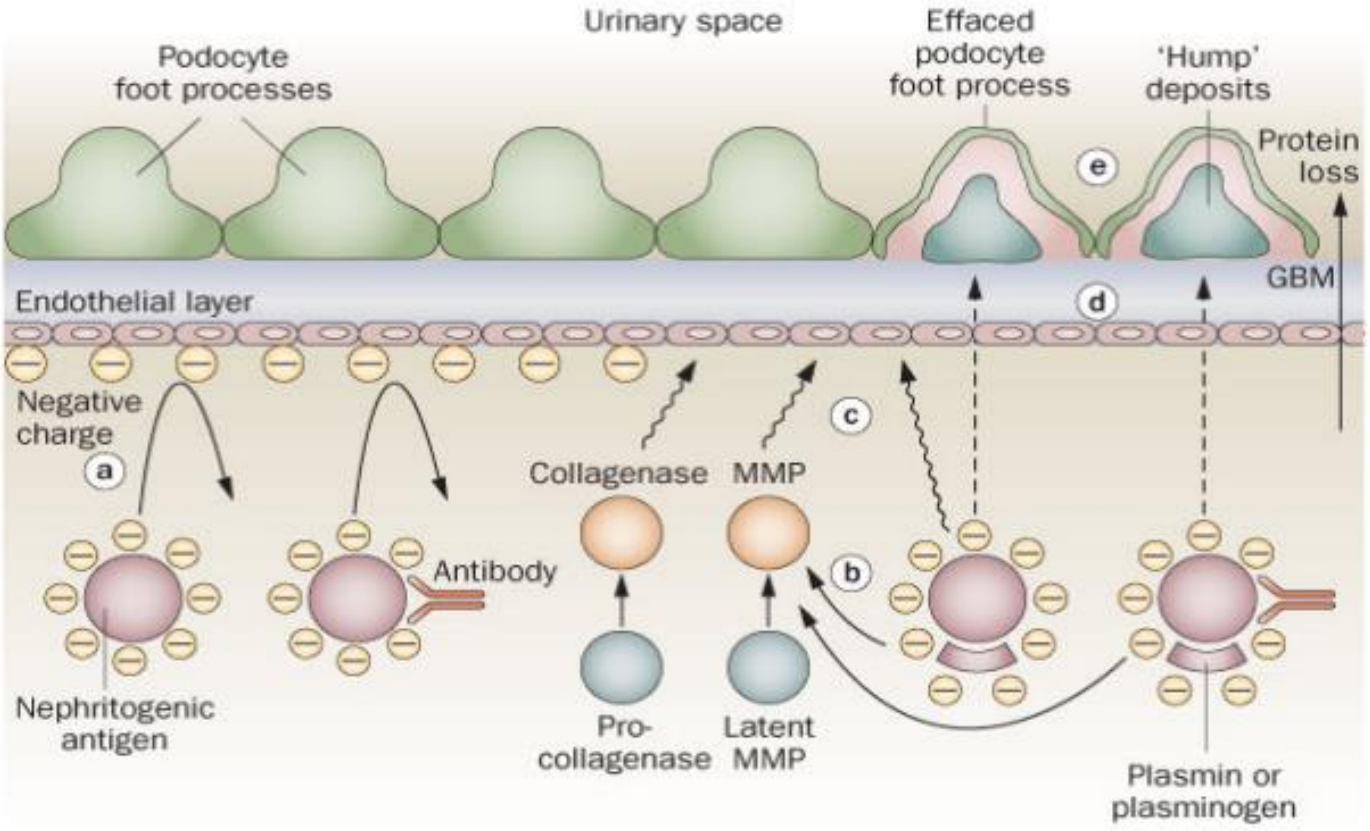

• Deposition of circulating bacterial antigen–antibody ICs
• *In situ* bacterial antigen–antibody ICs
• *In situ* localization of bacterial antigens without immunoglobulins
Mesangium
Neutrophil
• Complement activation
• Leukocyte recruitment
• Cytokine release and proliferation of glomerular endothelial and mesangial cells
• Degradation of the glomerular basement membranes
Antibody
Plasmin
Bacterial antigen
Subendothelial deposits
Mesangial deposits
Subepithelial deposits
Complement

streptococcal antigen(s) responsible for PSGN

- Nephritis-associated plasmin receptor (**NAPlr**), a glycolytic enzyme, which has glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity .NAPlr has a plasmin-like activity which may promote a local inflammatory reaction. An elevated urinary plasmin activity has been observed in patients with acute PSGN

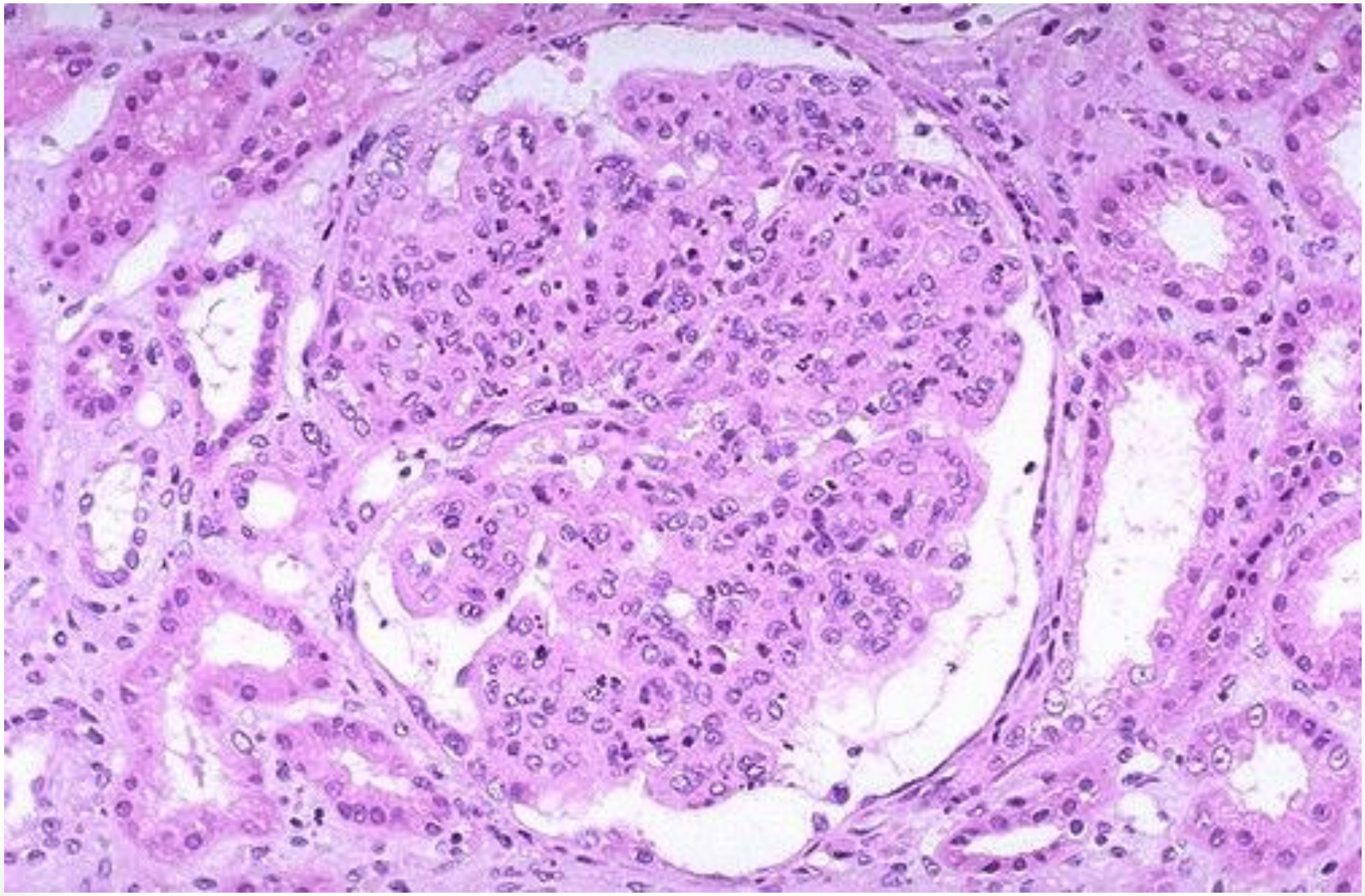
- Streptococcal pyrogenic exotoxin B (**SPE B**), a cationic cysteine proteinase, has been localized in the subepithelial deposit

Immune complex deposition



PATHOLOGY

- **Light microscopy**
- diffuse proliferative and exudative GN with prominent endocapillary proliferation and numerous neutrophils
- small subepithelial hump-shaped deposits.
- The severity of involvement varies and usually correlates with the clinical findings.
- Patients who are asymptomatic or have mild disease may have biopsies that show little glomerular involvement, whereas patients with diffuse endocapillary proliferative GN are more likely to have full-blown acute nephritic syndrome (ie, red to brown urine, proteinuria, edema,hypertension, and acute renal failure
- Crescent formation is uncommon and is associated with a poor prognosis.



The most common light microscopic patterns

- Of the 72 patients with ≥3 months of follow-up (mean, 29 months):
- Diffuse prolif (53%),
- focal (28%),
- mesangial (13%) proliferative glomerulonephritis.
- IgA-dominant PIGN occurred in 17%.
- 22% achieved complete recovery,
- 44% had persistent renal dysfunction,
- 33% progressed to ESRD.
- The presence of diabetes, higher creatinine at biopsy, dialysis at presentation, the presence of diabetic glomerulosclerosis, and greater tubular atrophy and interstitial fibrosis predicted ESRD.
- Prognosis for these older patients is poor, with fewer than 25% recovering full renal function.

PATHOLOGY

- **IF:**
- characteristic pattern of deposits of C3 and immunoglobulin G (IgG) distributed in a diffuse granular pattern within the mesangium and glomerular capillary walls

- The granular pattern of C3 deposition in the capillary walls (garland-type deposits) gives a "starry sky" pattern

- Other immune reactants (eg, immunoglobulin M [IgM], immunoglobulin A [IgA], fbrin, and other complement components) may also be detected

PSGN FLUORECENT MICROSCOPY

Post-infectious glomerulonephritis is immunologically mediated, and the immune deposits are widely distributed within the capillary loops.

The deposits are seen here with bright breen fluorescence in a granular, **bumpy pattern** because of the focal nature of the immune complex deposition process.

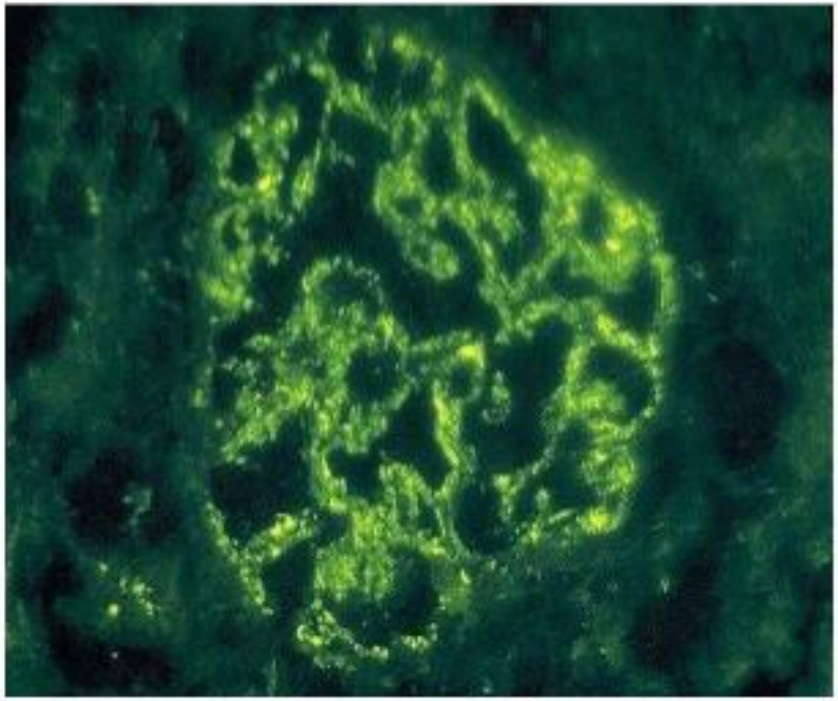
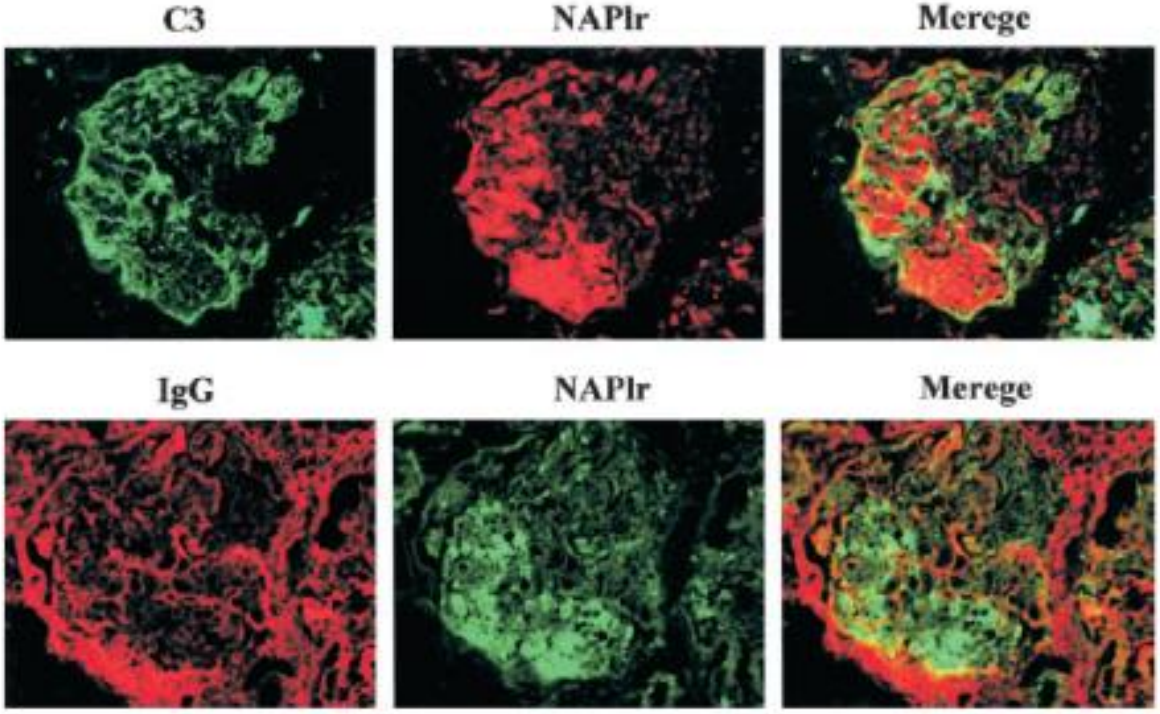


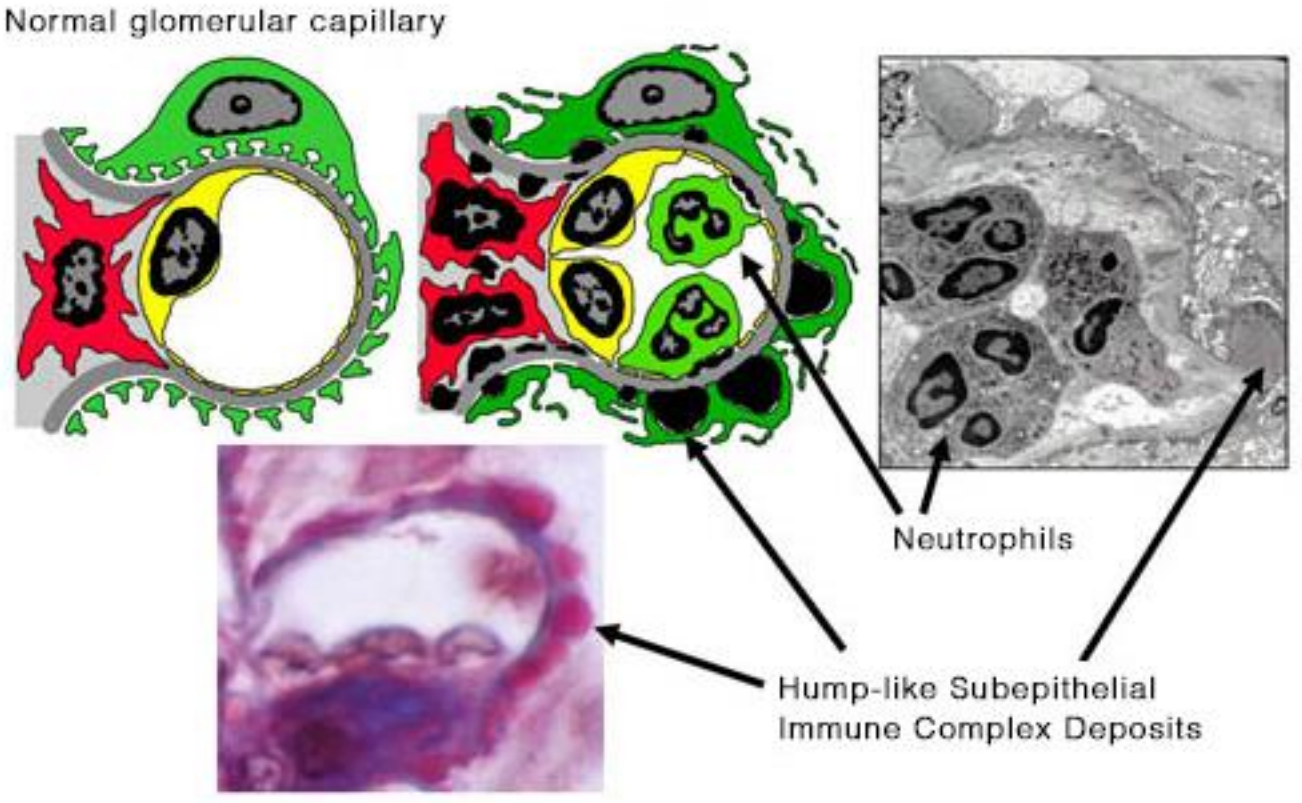
Table 4. Immunofluorescence studies in patients with APSGN[a]

Time from Onset to Biopsy	*n*	NAPlr	Plasminogen	Fibrinogen	C3	IgG	IgA
1–14 d	25	25/25 (100)	10/25 (40)	15/25 (60)	25/25 (100)	16/25 (64)	11/25 (44)
15–30 d	18	11/18 (61)	5/18 (28)	11/18 (61)	18/18 (100)	11/18 (61)	8/18 (44)
31–90 d	7	0/7 (0)	0/7 (0)	4/7 (57)	6/7 (86)	3/7 (43)	3/7 (43)
Total	50	36/50 (72)	15/50 (30)	30/50 (60)	49/50 (98)	30/50 (60)	22/50 (44)



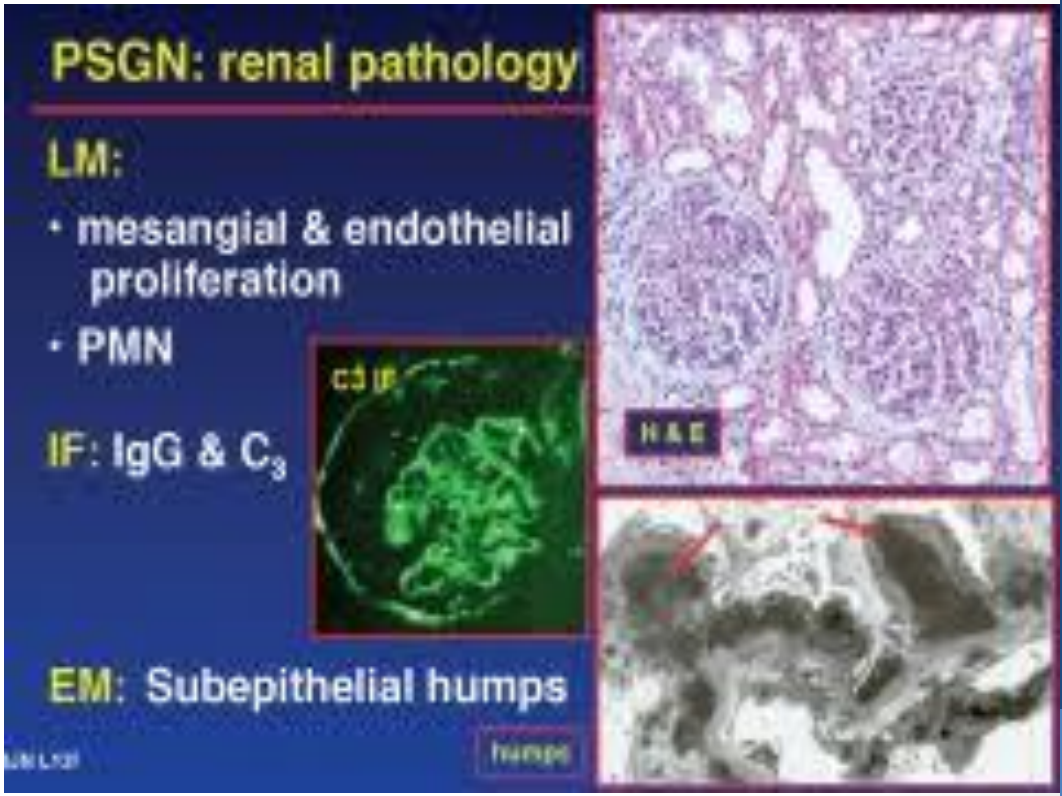
Pathology- EM

Postinfectious Glomerulonephritis Capillary Viewed by Electron Microscopy (top right) and High Magnification Light Microscopy (bottom)



Electron microscopy

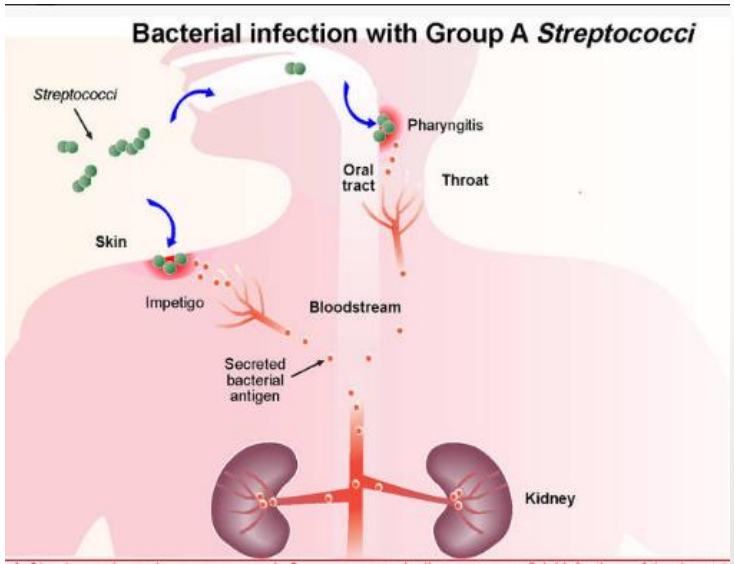
The dome-shaped subepithelial electron-dense deposits that are referred to as humps



Clinial presentation

- classic patient with APSGN :
- a child (the male:female ratio is 2:1) between the ages of 2 and 18.
- The latent period between URI and nephritis is 7–10 days and 2–4 weeks in cases that follow skin infection.
- Typical clinical presentation is:
  - acute nephritic syndrome (hematuria, edema, hypertension, and oliguria)
  - in a minority of cases, nephrotic syndrome
  -in rare cases,by a rapidly progressive (crescentic GN)

- clinical course: In a typical case improvement is observed after 2–7 days when the urine volume increases, followed rapidly by resolution of edema and HTN.



JASN Journal of the American Society of Nephrology

Clinical Research

Postinfectious Glomerulonephritis in the Elderly

Samih H. Nasr, Mary E. Fidler, Anthony M. Valeri, Lynn D. Cornell, Sanjeev Sethi, Amy Zoller, Michael B. Stokes, Glen S. Markowitz and Vivet

JASN January 2011, 22 (1) 187-195; DOI: https://doi.org/10.1681/ASN.2010060611

Abstract

Postinfectious glomerulonephritis (PIGN) is primarily a childhood disease that occurs after an upper respiratory tract infection or impetigo; its occurrence in older patients is not well characterized. Here, we report 109 cases of PIGN in patients ≥65 years old diagnosed by renal biopsy. The male to female ratio was 2.8:1. An immunocompromised background was present in 61%, most commonly diabetes or malignancy. The most common site of infection was skin, followed by pneumonia and urinary tract infection. The most common causative agent was staphylococcus (46%) followed by streptococcus (16%) and unusual gram-negative organisms. Hypocomplementemia was present in 72%. The mean peak serum creatinine was 5.1 mg/dl, and 46% of patients required acute dialysis.

In this issue

View Selected Citations (

Results

Infectious Agent[a]	No. of Patients (%)
Staphylococcus	50 (46)
Streptococcus[b]	17 (16)
E. coli	5 (5)
Pseudomonas	2 (2)
Actinetobacter	1 (1)
Serratia marcescens	1 (1)
Proteus	1 (1)
Klebsiella	1 (1)
Enterobacter cloacae	1 (1)
Candida	1 (1)
Unknown	37 (34)

Site of Infection[a]	No. of Patients (%)
Skin	31 (28)
Lung	17 (16)
Urinary tract	14 (13)
Upper respiratory tract	11 (10)
Osteomyelitis	8 (7)
Endocarditis	7 (6)
Deep-seated abscess	5 (5)
Empyema	2 (2)
Prostatitis	1 (1)
Infected pancreatic cyst	1 (1)
Phlebitis	1 (1)
Sepsis (source not identified)	3 (3)
No clinical evidence of infection	19 (17)

Postinfectious Glomerulonephritis in the Elderly

Table 1. Demographics and predisposing factors to infection (109 patients)

	No. of Patients (%)
Male/female	80/29 (73/27)
Age in years	
65 to 69	37 (34)
70 to 79	52 (48)
≥80	20 (18)
Race	
white	82 (75)
hispanic	7 (6)
African American	5 (5)
Native American	3 (3)
Asian	2 (2)
undisclosed	10 (9)
Predisposing factors for infection	67 (61)
DM	53 (49)
malignancies	15 (14) (six had DM)
alcoholism	4 (4) (three had DM)
severe malnutrition	1 (1)
myelofibrosis	1 (1)
cirrhosis	1 (1)
synthetic heart valve	1 (1)

DM, diabetes mellitus.

Table 4. Clinical characteristics at presentation

	No. of Patients (%)
New onset hypertension	13 (12)
Long-standing hypertension	78 (72)
Peripheral edema	72/106 (68)
New onset congestive heart failure	28/106 (26)
Proteinuria <1 g/24 h	19/72 (26)
Proteinuria 1 to 3 g/24 h	22/72 (31)
Proteinuria >3 g/24 h	31/72 (43)
Full nephrotic syndrome	23/87 (26)
Hypoalbuminemia	83/91 (91)
Hematuria	
microscopic or macroscopic	98/103 (95)
macroscopic hematuria	19 (17)
Leukocyturia	63/97 (65)
Creatinine ≤1.2 mg/dl	4/108 (4)
Creatinine 1.21 to 2.0 mg/dl	14/108 (13)
Creatinine >2.0 mg/dl	90/108 (83)
Dialysis at biopsy	48/105 (46)
Low C3	57/83 (69)
Low C4	29/83 (35)
Low C3 or C4	60/83 (72)
Low C3 and C4	26/83 (31)

Nasr et al: JASN 2011

Laboratory findings

—**variable decline GFR** detected by a rise in serum creatinine.

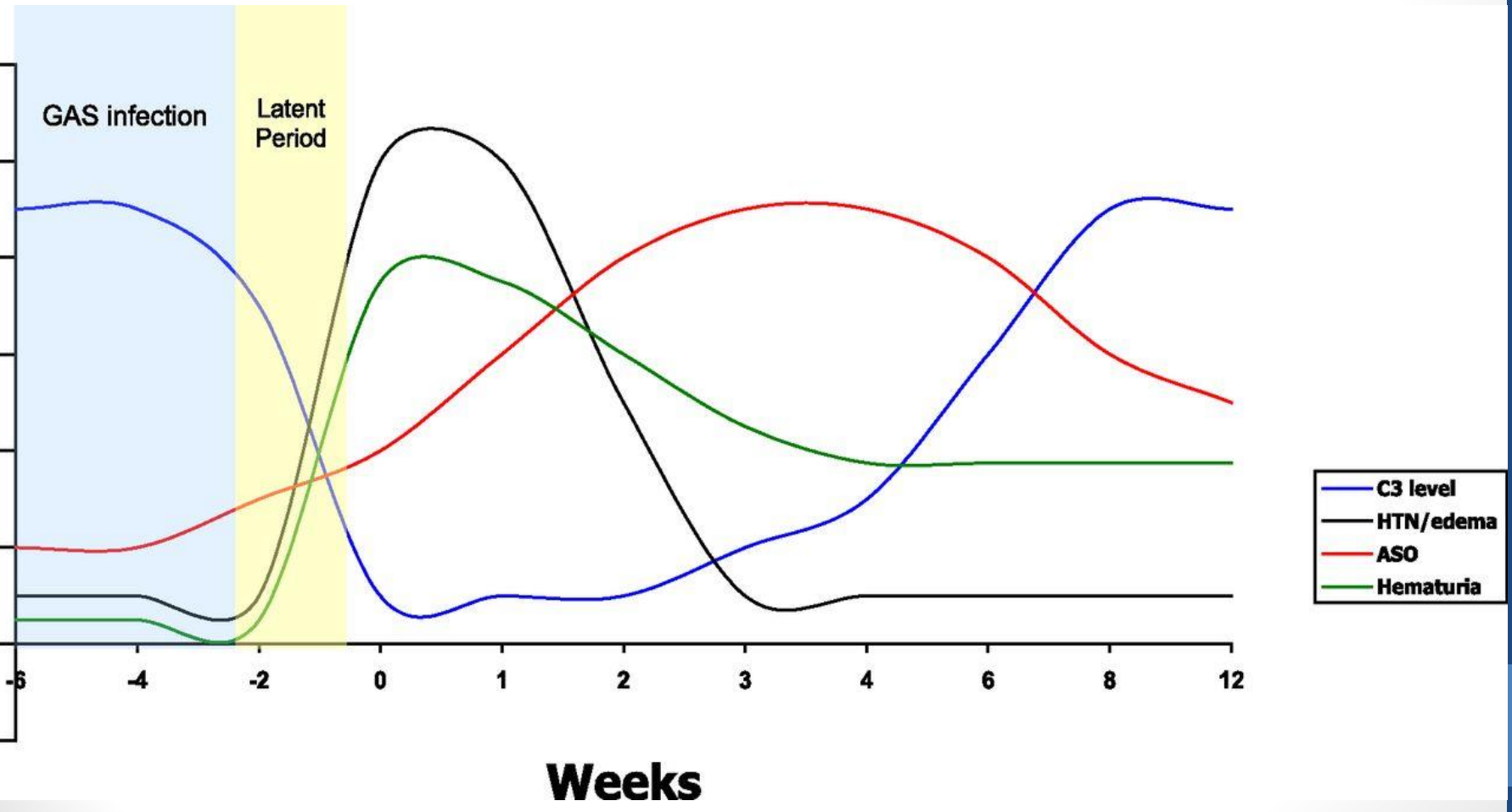
---proteinuria

—**hematuria** (dysmorphic) with or without RBC casts

— In approximately 90 percent of patients, **C3 and CH50** (total complement activity) are signiꞗcantly depressed in the first two weeks of the disease course C4 and C2 levels may be low The, C3 and CH50 return to normal within four to eight weeks after presentation.

—25 percent of patients will have either a **positive throat or skin culture**

Laboratory findings



Serology

- The best markers for PSGN are serum antibody levels to NALPr or SPEB/zSPEB, (rarely available).

- **The streptozyme test**, which measures five different streptococcal antibodies, is positive in more than 95% of patients due to pharyngitis and approximately 80 percent of those with skin infections
  includes

- Anti-streptolysin (ASO)
- Anti-hyaluronidase (AHase)
- Anti-streptokinase (ASKase)
- Anti-nicotinamide-adenine dinucleotidase (anti-NAD)
- Anti-DNase B antibodies

DIAGNOSIS

— PSGN is usually diagnosed based upon clinical findings of acute nephritis and demonstration of a recent group A beta-hemolytic streptococcal (GAS) infection.

-Although a low C3 and/or CH50 (total complement) level are consistent with a diagnosis of PSGN, these complement components may also be decreased in other forms of glomerulonephritis, including membranoproliferative glomerulonephritis

DDx

- Membranoproliferative glomerulonephritis (MPGN)
- IgA nephropathy .
- Secondary causes of glomerulonephritis - Lupus nephritis and IgA vasculitis (IgAV; HenochSchönlein purpura [HSP]) nephritis
- Postinfectious GN due to other microbial agents - Acute nephritis due to viral and other bacterial agents
- hepatitis B and endocarditis-associated glomerulonephritis

ACUTE MANAGEMENT

- **Antibiotic therapy**
  early treatment of streptococcal infection has been reported to prevent or reduce the severity of glomerulonephritis

  Preventive antibiotic treatment may be indicated in case of an epidemic situation or for household members of index cases

- **Supportive care**
  treating the clinical manifestations of the disease, particularly complications due to volume overload. These include hypertension and, less commonly, pulmonary edema. General measures include sodium and water restriction and loop diuretics.
  Loop diuretics generally provide a prompt diuresis with reduction of blood pressure and edema. Infrequently, patients have hypertensive encephalopathy due to severe hypertension. These patients should be treated emergently to reduce their blood pressure. Oral nifedipine or parenteral nicardipine are effective, while angiotensin-converting enzyme (ACE) inhibitors should be used with caution due to the risk of hyperkalemia.

Poststreptococcal Glomerulonephritis Treatment & Management

Updated: Dec 15, 2018 | Author: Duvuru Geetha, MD, MRCP; Chief Editor: Vecihi Batuman, MD, FASN more...

Medical Care

Symptomatic therapy is recommended for patients with acute poststreptococcal glomerulonephritis (APSGN), and it should be based on the clinical severity of the illness. The major goal is to control edema and blood pressure. Those sequelae are most likely to arise in the first 7 to 10 days of APSGN. [14]

During the acute phase of the disease, restrict salt and water. If significant edema or hypertension develops, administer diuretics. Loop diuretics increase urinary output and consequently improve cardiovascular congestion and hypertension.

For hypertension not controlled by diuretics, usually calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) are useful, although ACEIs and ARBs carry the risk of hyperkalemia and temporarily impairing recovery of renal function. [14] For malignant hypertension, intravenous nitroprusside or other parenteral agents are used.

Other features of therapy are as follows:

- Indications for dialysis include life-threatening hyperkalemia and clinical manifestations of uremia

De Novo Postinfectious Glomerulonephritis Secondary to Nephritogenic Streptococci as the Cause of Transplant Acute Kidney Injury: A Case Report and Review of the Literature

Alexander Bullen and Mita M. Shah

Division of Nephrology-Hypertension, University of California San Diego, San Diego, CA, USA

Correspondence should be addressed to Mita M. Shah; mshah@ucsd.edu

Received 22 December 2017; Accepted 26 April 2018; Published 31 May 2018

Academic Editor: Ryszard Grenda

Acute kidney injury is common among kidney transplant recipients. Postinfectious glomerulonephritis secondary to nephritogenic streptococci is one of the oldest known etiologies of acute kidney injury in native kidneys but rarely reported among kidney transplant recipients. This report is of a biopsy-proven case of acute kidney injury in a renal allograft recipient caused by de novo poststreptococcal glomerulonephritis.

Case Presentation

- Presentation of a biopsy-proven rare cause of AKI in a KTR as PIGN secondary to nephritogenic streptococci.

- The patient was a 45-year-old Hispanic male who had ESRD of unknown etiology, hypertension, and hyperlipidemia
- Two years afer transplant he presented to the renal transplant clinic with complaints of lower extremity edema that had appeared over the previous three days. He stated he had experienced a fu-like illness a week prior

- Due to acute kidney injury, proteinuria, and hematuria in the setting of suboptimal immunosuppression, there was a high concern for acute rejection versus rapidly progressive glomerulonephritis perhaps due to recurrence of the unknown primary disease

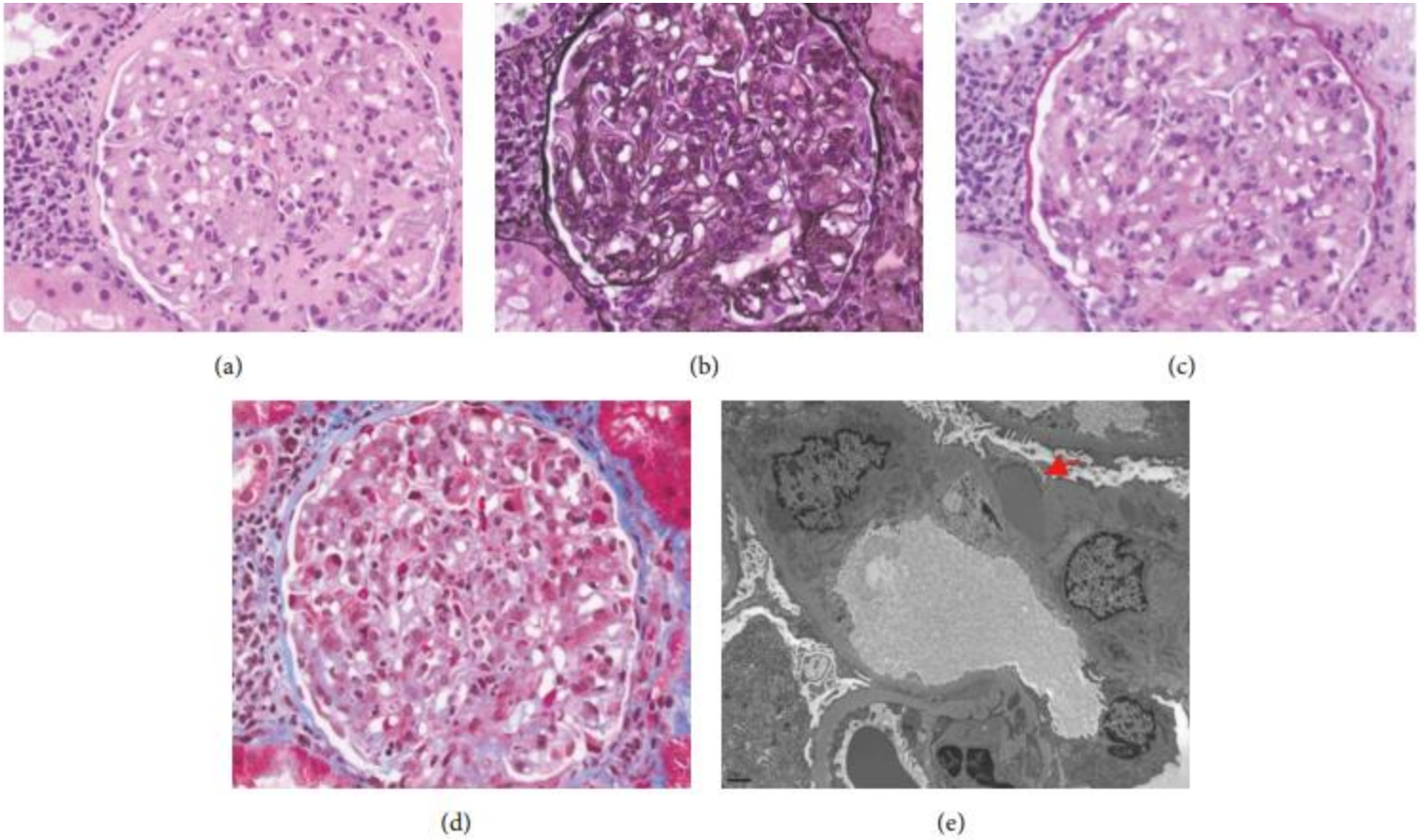
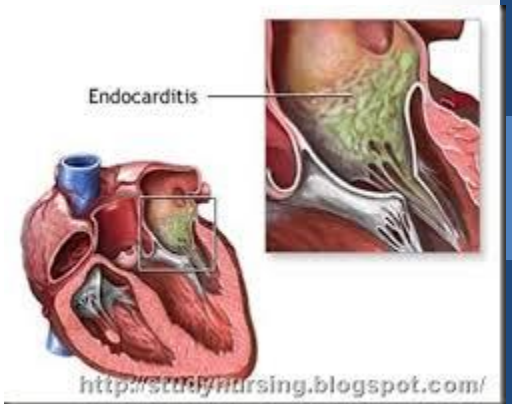


FIGURE 1: (a) Light microscopy. Hematoxylin and stain. Significant endocapillary proliferation with neutrophils and swollen endothelial cells. (b) Jones stain with occasional double contour. No evidence of significant crescents noted. (c) Periodic acid-Schiff stain revealed mild mixed interstitial inflammation with lymphocytes, plasma cells, and neutrophils. (d) Trichrome stain with focal mild interstitial fibrosis and tubular atrophy. (e) Electron microscopy. Large subepithelial electron dense deposits (arrow) consistent with "humps".

IE related GN

Patients with infective endocarditis (IE) can develop several forms of kidney disease:

1. a bacterial infection-related immune complex-mediated glomerulonephritis (GN)
2. renal infarction from septic emboli
3. renal cortical necrosis
4. drug-induced acute interstitial nephritis
5. aminoglycosides acute kidney injury (due to acute tubular necrosis)



Etiology

- The most common organism in IE-associated GN is *S. aureus*, (56 percent of cases)
- *Streptococcus* species are the next most common.
- Less common organisms include *Bartonella henselae*, *Coxiella burnetii*, *Cardiobacterium hominis*, and *Gemella*.
- In 9 percent of patients with IE-associated GN, no organism could be cultured.

Risk factors and comorbidities

- One-half of affected patients do not have a known risk factor
- in the remainder, common comorbidities included :

1. cardiac valve disease (30 percent)
2. intravenous drug use (29 percent)
3. hepatitis C (20 percent)
4. diabetes (18 percent) The cardiac valve infected was tricuspid in 43 percent, mitral in 33 percent, and aortic in 29 percent of patients in the largest series described [5]. There are a few case reports of patients with IE and GN who developed pulmonary hemorrhage, potentially mimicking other systemic diseases such as antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis and antiglomerular basement membrane (anti-GBM) autoantibody disease

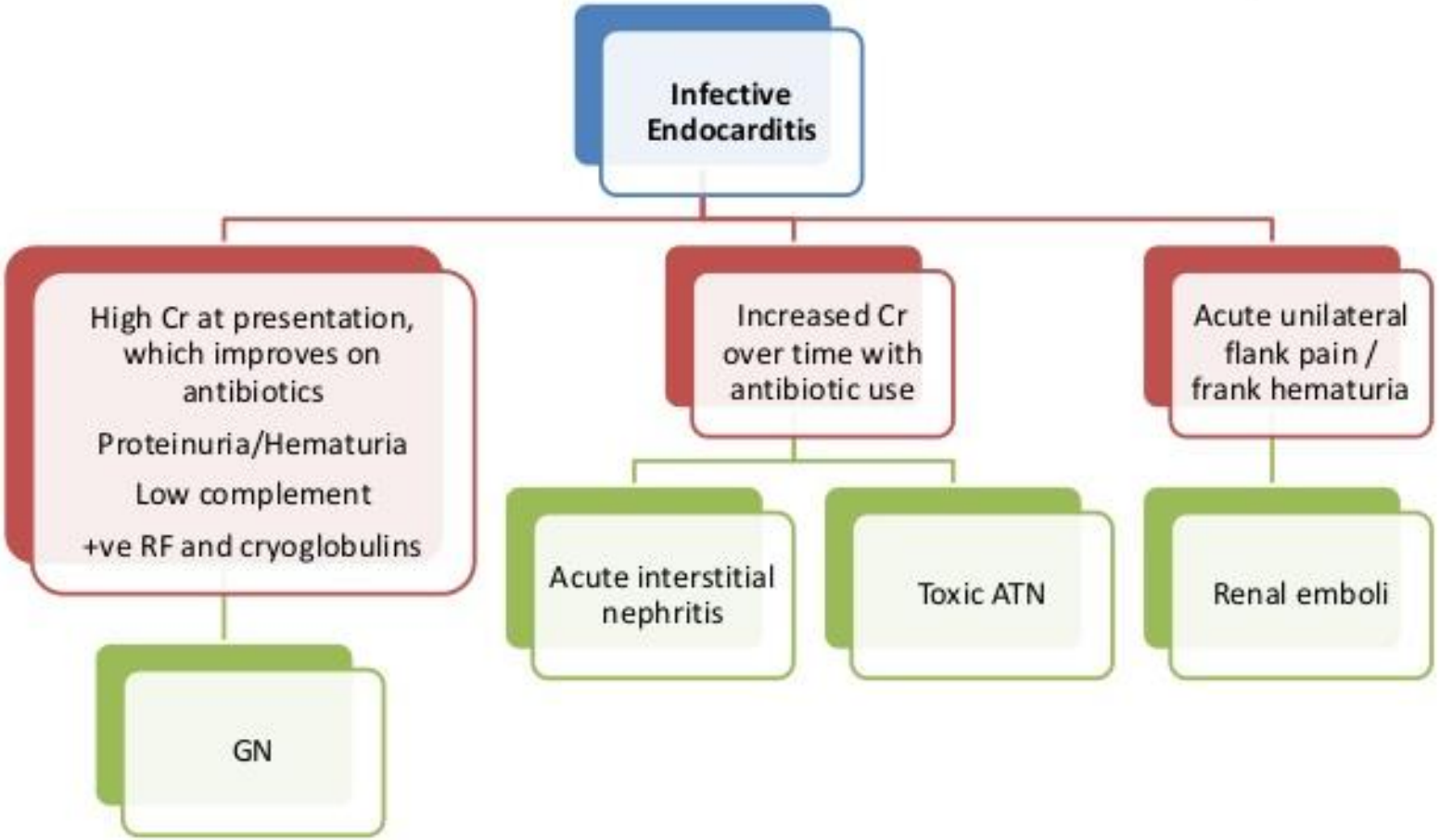
- The cardiac valve infected was :
- tricuspid in 43 percent
- mitral in 33 percent
- and aortic in 29 percent of patients There are a few case reports of patients with IE and GN who developed pulmonary hemorrhage, potentially mimicking other systemic diseases such as antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis and antiglomerular basement membrane (anti-GBM) autoantibody disease

Clinical presentation

- Acute kidney injury is the most common (79 percent)
- almost all patients have hematuria (97 percent)
- Features of the acute nephritic syndrome were seen in a minority (10 percent),
- nephrotic syndrome (6 percent)
- 53 percent of patients had reduced C3 complement
- and 19 percent had reductions in C4 complement, suggesting activation of the alternative complement pathway.
- ANCA pos in up to one-third of patients
- some patients also have a positive rheumatoid factor,
- rare patients are positive for anti-GBM autoantibodies.

Endocarditis

Renal Presentation (other than GN)



Viruses associated with GN

Acute	
Dengue	ICGN, MsPGN
Hantavirus	HFRS-MsPGN
Varicella-zoster	DPGN
Parvovirus	ICGN, PAN, MPA, TMA, IgA
HAV	ICGN, MsPGN
HBV	DPGN
CMV	cFSGS, MN, IgA, HSP, ICGN, MPGN, TMA
EBV	ICGN, MN, MsPGN
Coxsackie B	RPGN
Subacute	
Parvovirus	cFSGS
EBV	cFSGS, MN
HBV	PAN
HCV	PAN
Chronic	
HBV	MN, Type I MPGN, MPGN+MC, PAN, IgA, FSGS
HIV	HIVAN, HIVICK, TMA
HCV	Type I MPGN+MC, Type I MPGN, PAN, IgA, MN
HEV	MN

Clin J Am Soc Nephrol. 2017 Aug 7; 12(8): 1337–1342.
Published online 2016 Oct 24.

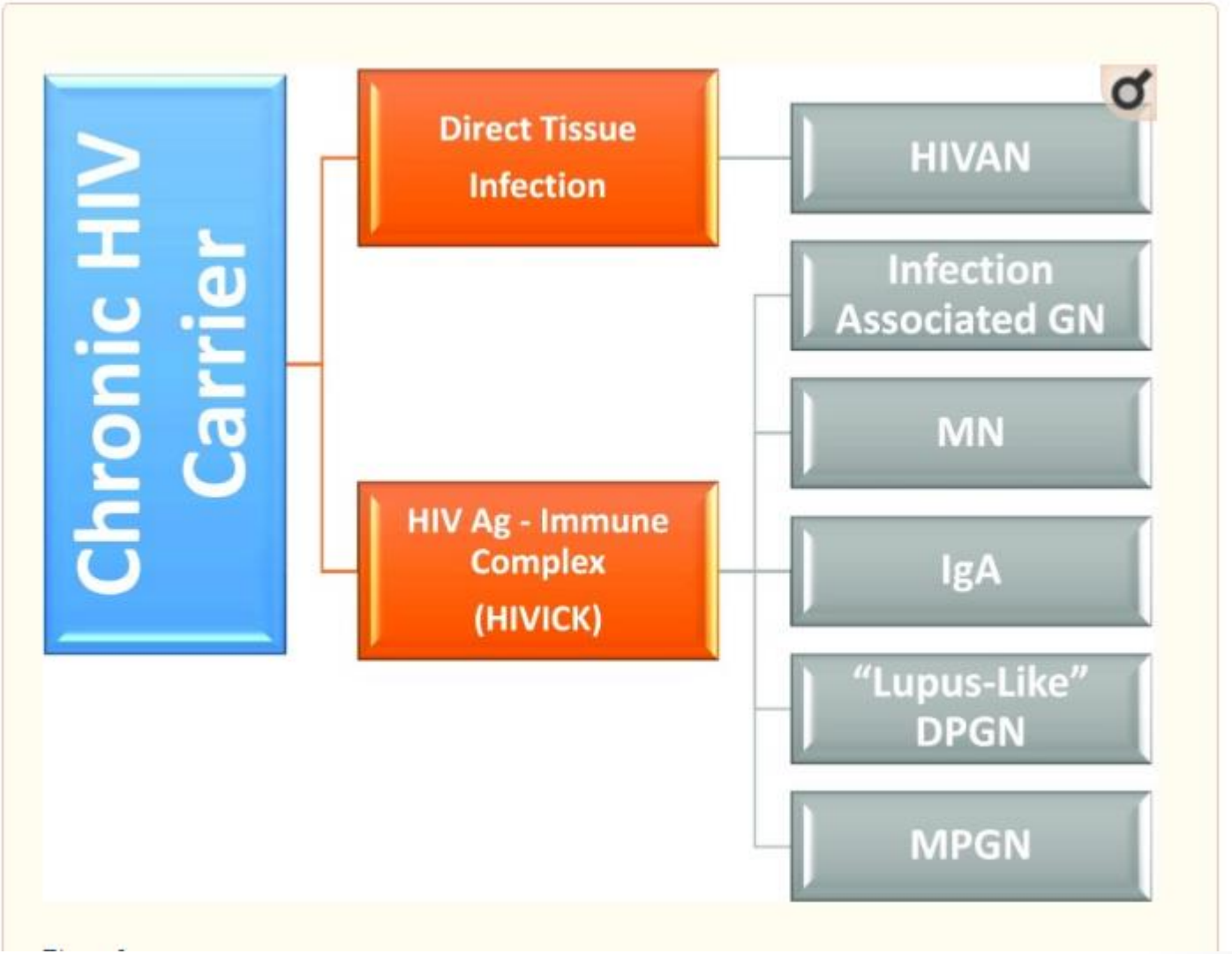
link a viral illness with a specific form of GN

- certain supporting criteria must be met:
- (*1*) demonstration of the presence of active quantifiable viremia primarily through serologic PCR testing,
- (*2*) the identification of viral proteins/nucleic acid residues within renal tissue and/or within immune complexes deposited in the glomerular basement membrane
- (*3*) resolution/regression of the glomerular lesion concomitant with the host immune clearance of viremia or eradication of viremia through antiviral therapy.

- Recent emerging data has proposed a new relationship of GN associated with occult viral disease which is defined as the presence of viral nucleic acid in renal tissue and in peripheral blood mononuclear cells but with complete absence of detectable systemic viremia by standard PCR amplification techniques.

- Occult hepatitis C (HCV) has been detected in 30%–50% of patients with idiopathic membranous nephropathy, IgA, FSGS, ANCA positive vasculitis, and membranoproliferative GN (MPGN)

- Similarly, occult hepatitis B (HBV) infection has been described with documented HBV antigens found in renal tissue but with absent viremia in selected cases of idiopathic membranous nephropathy and IgA

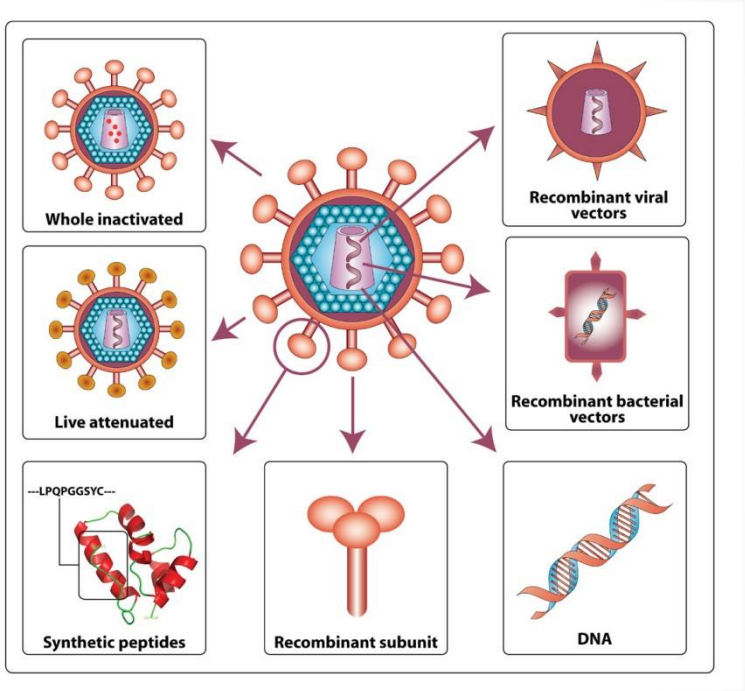

Chronic HIV Carrier
Direct Tissue Infection
HIV Ag - Immune Complex (HIVICK)
HIVAN
Infection Associated GN
MN
IgA
"Lupus-Like" DPGN
MPGN

HIVAN

- collapsing FSGS (cFSGS)
- , microcystic dilation of the tubules,
- interstitial nephritis,
- and the presence of intracytoplasmic tubulo-reticular inclusions (“TRI-IFN footprints”).

- By definition, the only specific requirement to fulfill the diagnosis of HIVAN is the presence of cFSGS in the setting of HIV infection with the remaining lesions found in variable frequencies

- The pathogenic mechanisms of glomerular disease in HCV and HIV patients exemplify the wide spectrum of immunologic and microbiologic pathways utilized by viruses in general to cause renal disease.




Thank you