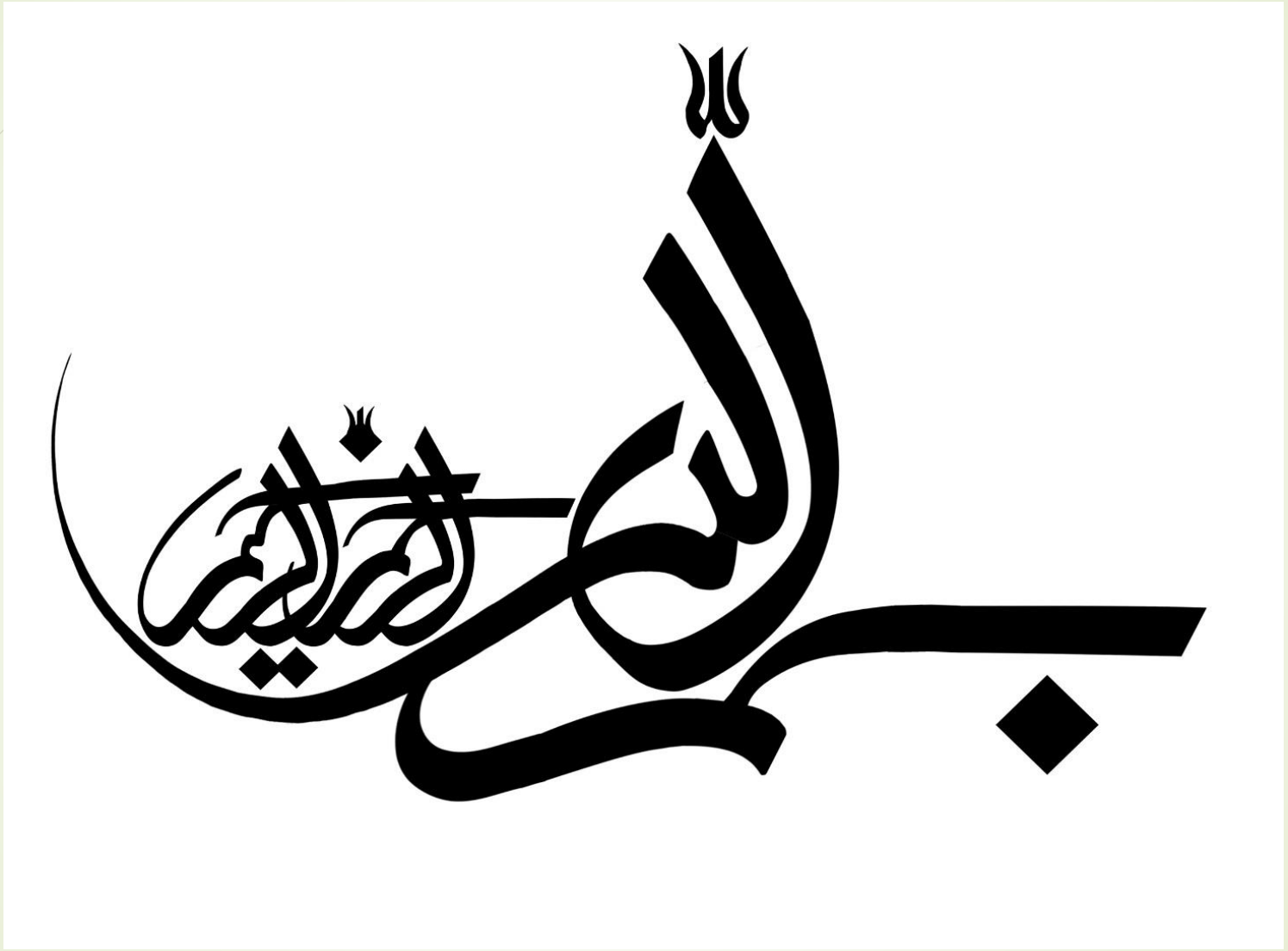
بسم الله الرحمن الرحيم

Acute Post-Streptococcal Glomerulonephritis

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Introduction

- Acute post-streptococcal glomerulonephritis (APSGN) is the prototypical postinfectious immune-mediated glomerulonephritis.
- It is associated with a previous skin or throat infection, most often caused by group A streptococcus (Streptococcus pyogenes) and occasionally by streptococcus group C or G.
- APSGN is the most common form of glomerulonephritis in children.
- APSGN is seen classically between 2 years of age and late adolescence.
- The latent period between infection onset and nephritis has often been reported as shorter with respiratory illness (7–10 days) than skin infection (2–6 weeks).
- The typical clinical presentation for ASPGN is a classic nephritic syndrome characterized by hematuria, edema, hypertension, and oliguria.

Pathogenesis

- Nephritogenic Antigens(NAPlr, SPEB, streptokinase, others)
- Autoimmunity (anti-IgG, other)
- Humoral and Cellular Immunity
- Activation of the complement system is a consequence of the glomerular antigen/antibody reactivity.
- The alternative complement pathway is usually most active in APSGN, with depression of C3 complement levels.
- some may also have a reduction in C1 and C4 levels. In these patients, Protein H, a surface streptococcal protein, in combination with IgG may activate the classical complement cascade.
- In some patients there may also be complement activation by the lectin pathway.

- In addition to humoral immune initiation, cellular immune mechanisms are also activated in APSGN.
- It has long been known that there is cellular adhesion molecule (ICAM-1, LFA-1) overexpression with infiltration of lymphocyte and macrophages in the glomeruli of these patients.
- Higher numbers of CD4-positive lymphocytes are present in renal biopsies obtained in the first 3–4 weeks of disease and decrease in frequency afterwards.
- Increased glomerular expression of IL-8 has been found to correlate with neutrophil infiltration.
- A genetic aspect to disease susceptibility has been suggested by a higher rate of disease in siblings.
- APSGN has also been associated with HLA-DR4 and DR-1.
- genetic mutations in the complement factor H (CFH) gene have been suggested as a cause for inducing dense deposit disease after an episode of PSGN as well as a chronic glomerulonephritis triggered initially by streptococcal infection.

Serological Findings

- With APSGN the most constant serological finding is a reduction in serum complement levels that occurs in more than 90% of cases.
- Complement levels return to normal usually within 1 to 3 months after the development of acute glomerulonephritis, reflecting the tendency for a rapid spontaneous improvement in disease activity.
- IgG and IgM serum levels are elevated in 80– 90% of patients with APSGN.
- An elevated antistreptococcal antibody titer is the usual laboratory confirmation of a preceding streptococcal infection since positive cultures are obtained in only 20–25% of cases.
- AntizSPEB/SPEB serum titers have been found to be the best markers of nephritogenic streptococcal infections.
- anti-streptolysin O and anti-DNAse B titers are most frequently assayed.
- Two-thirds of ASPGN patients in the first week of disease may also manifest cryoglobulins and elevated IgG-anti-IgG rheumatoid factor titers.

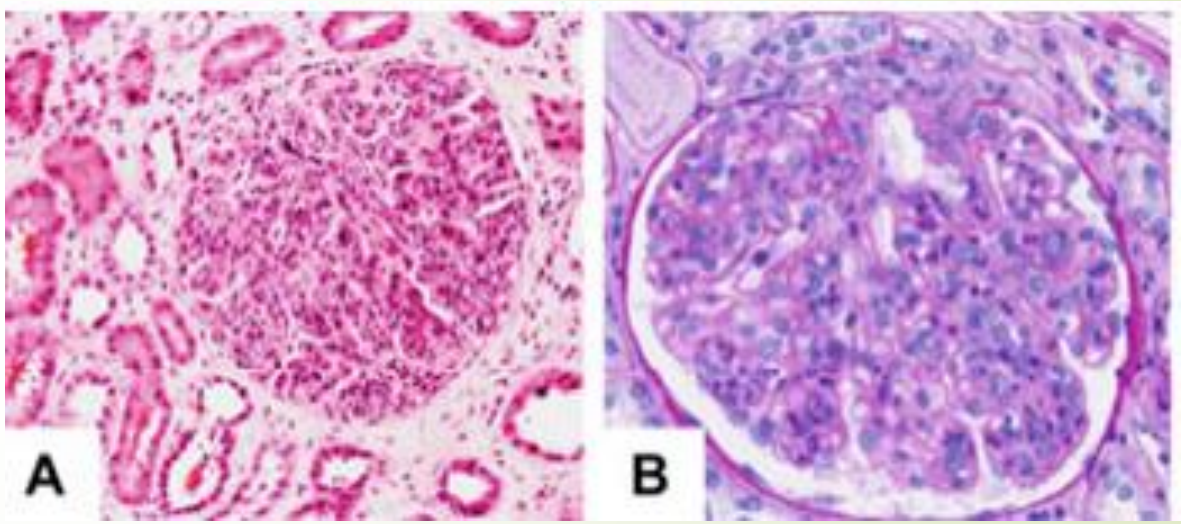
Pathology

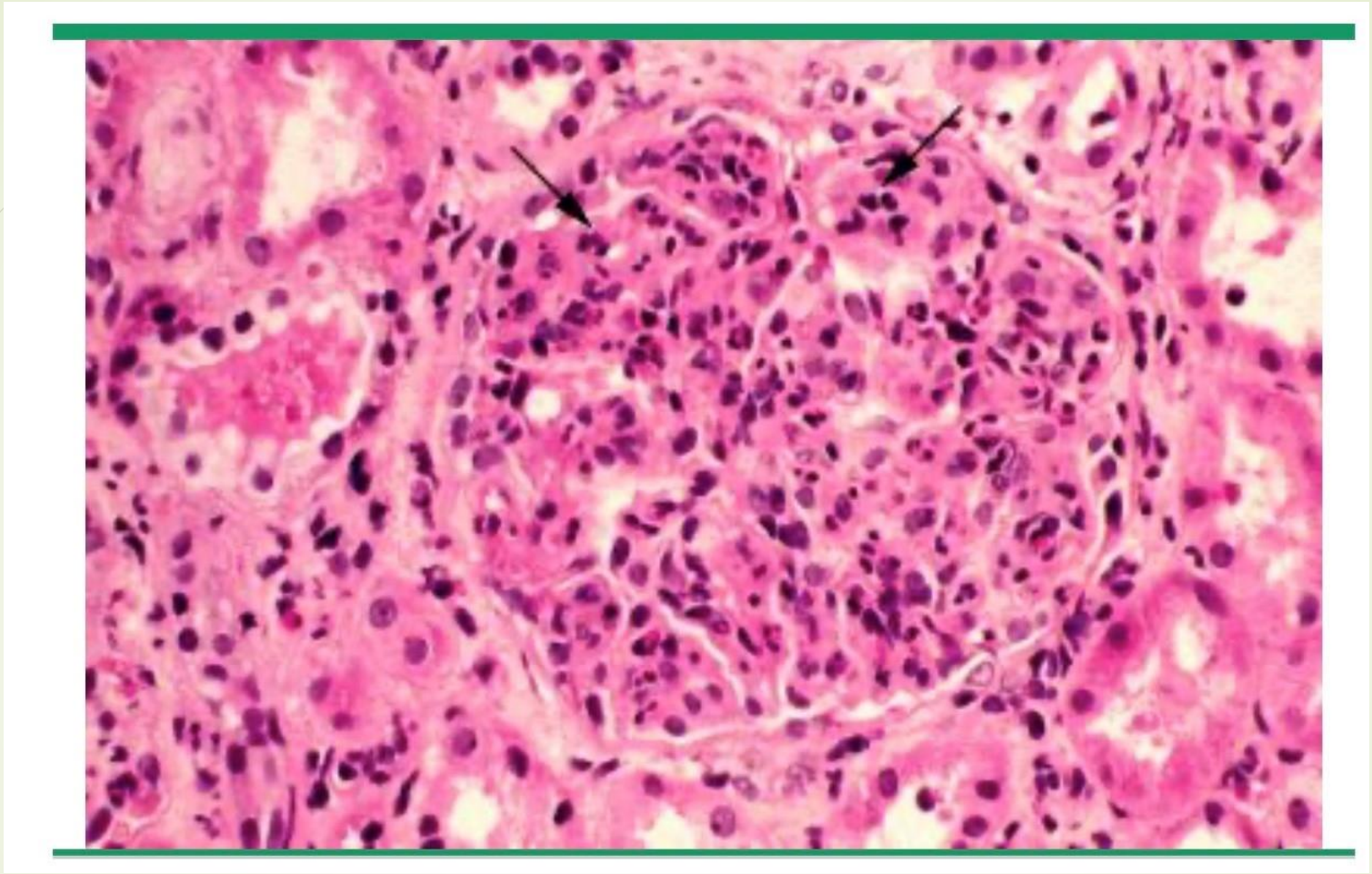
- Renal biopsy is seldom done in patients with APSGN.

- Biopsy is indicated :
- if the serum complement is normal at presentation
- stays persistently depressed several months after diagnosis
- In the setting of rapid progression of kidney failure
- concern for crescentic glomerulonephritis

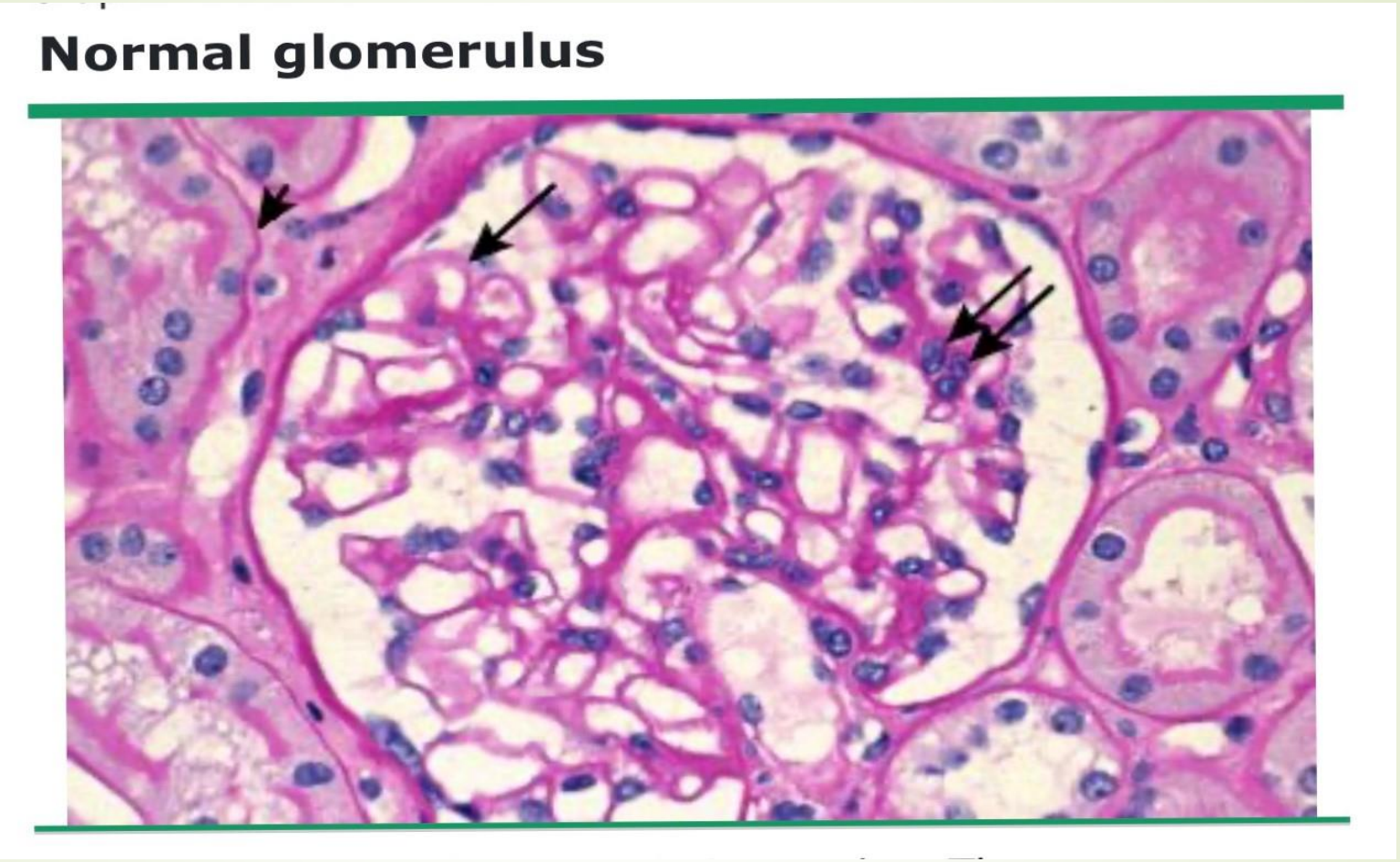
Light Microscopic Findings

- diffuse proliferative glomerulonephritis (GN)
- glomeruli are often enlarged and show global endocapillary hypercellularity
- Some cases will show focal endocapillary proliferation or just mesangial proliferation
- acute phase ,tends to be exudative with large number of neutrophils
- After the first few weeks of disease, there is a progressive decline in cellularity, initially from the loss of the neutrophils, and a predominant mesangial proliferation persists



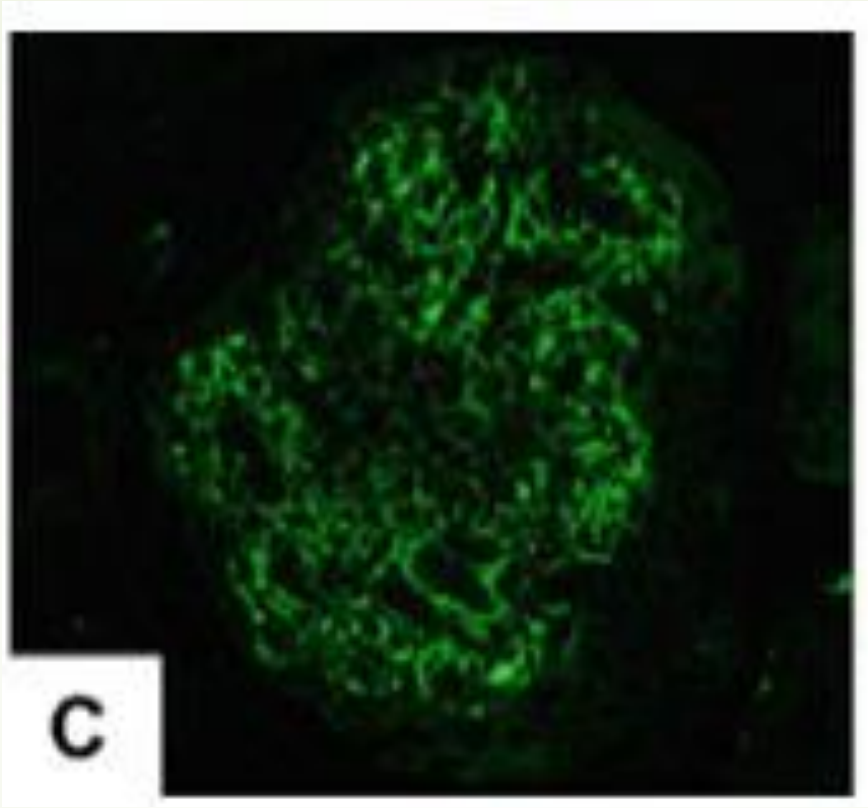


- High power light micrograph showing marked cellular proliferation and neutrophilic infiltration (arrows) within the glomerular tuft in postinfectious glomerulonephritis.few open capillary lumens can be seen.



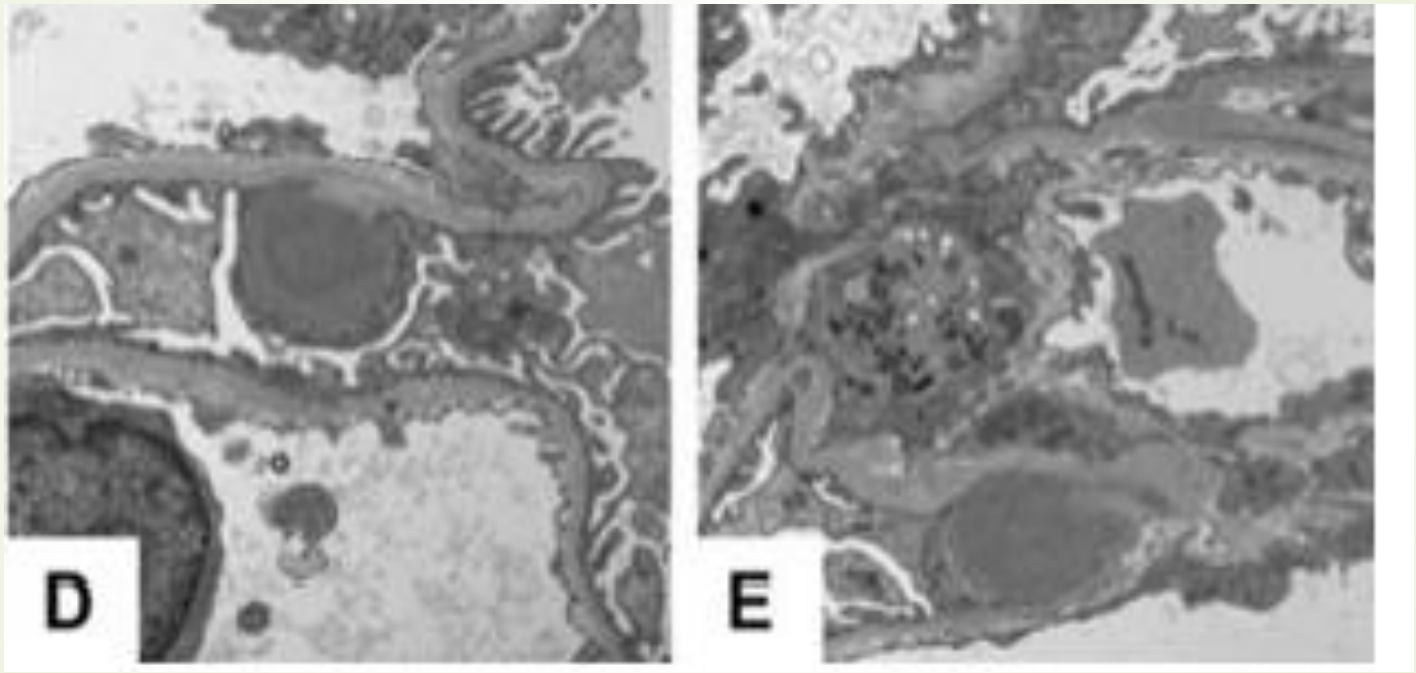
- Light micrograph of a normal glomerulus.there are only one or two cells per capillary tuft,the capillary lumens are open,the thickness of the glomerular capillary wall(long arrow) is similar to that of the tubular basement membranes(short arrow),and the mesangial matrix are located in the central or stalk regions of the tuft(arrows)

Immunofluorescence Microscopy



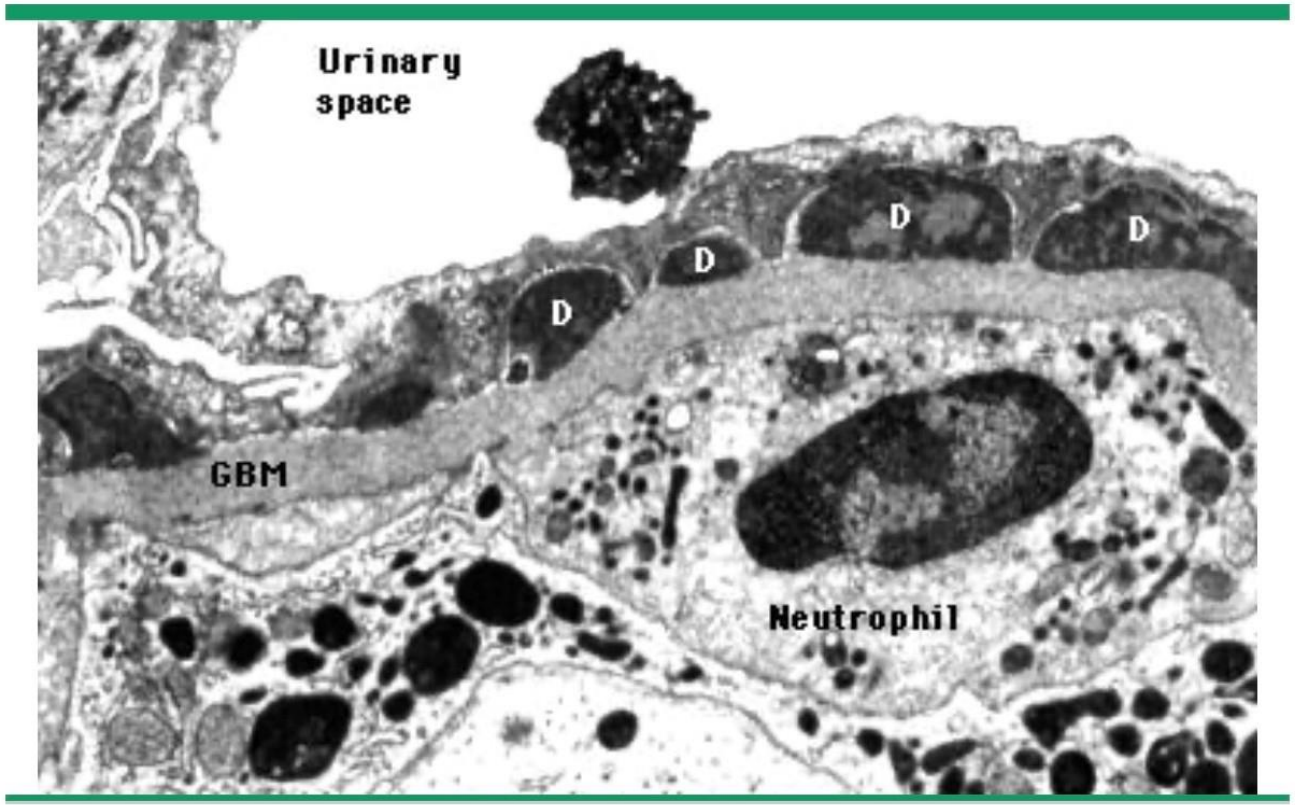
- In the first few weeks of the disease, fine granular deposits of C3 and usually IgG are found in the glomerular capillary walls as well as in mesangial areas, in what has been termed a "starry sky" pattern
- Later in the disease, with resorption of many of the capillary wall deposits, there is a predominantly mesangial pattern of staining with a predominance of C3. Coarse to confluent granular staining along the glomerular capillary walls in what is termed the "garland" pattern can also be seen

Electron Microscopy



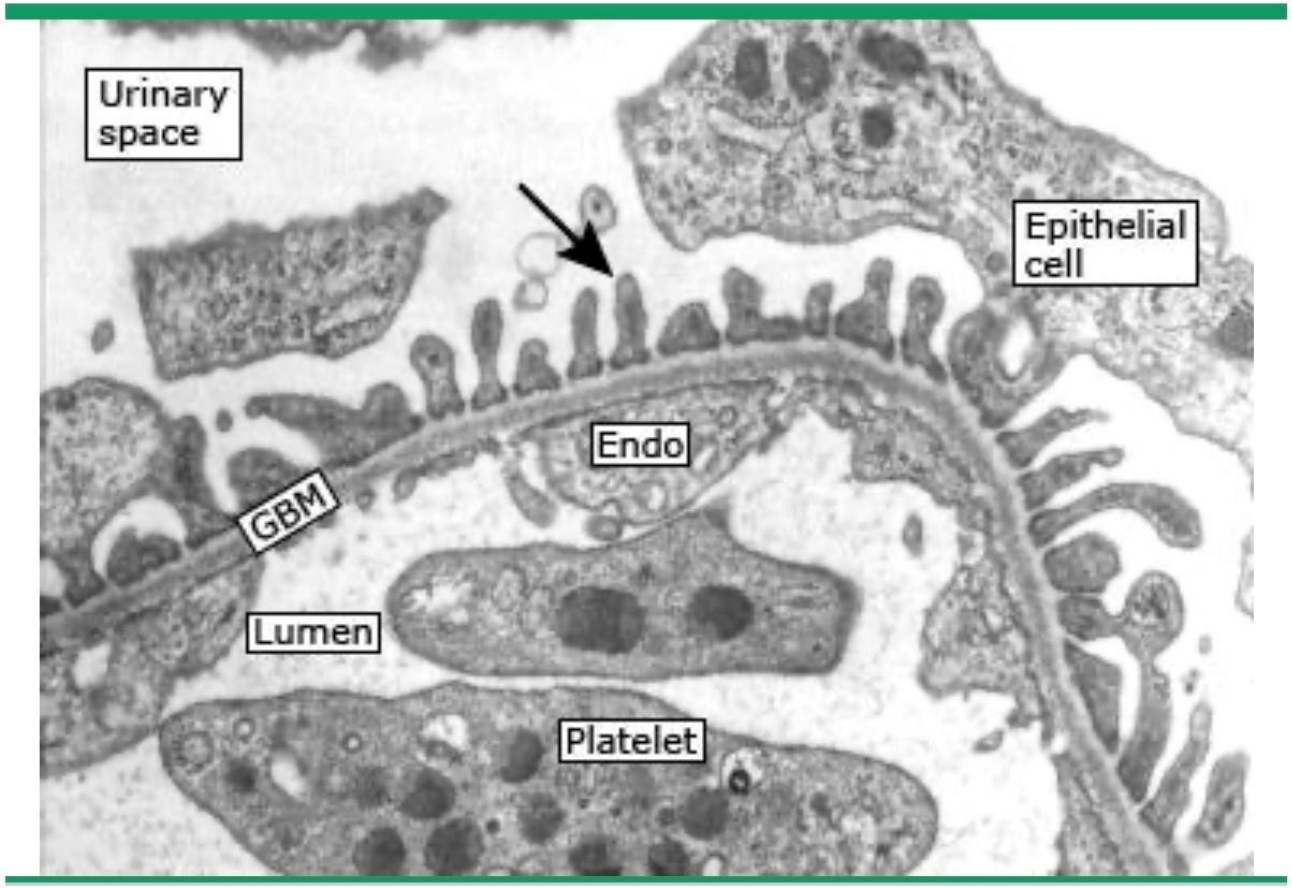
large subepithelial electron-dense deposits with a "humplike" appearance

Electron micrograph of postinfectious glomerulonephritis



- Electron micrograph shows subepithelial deposits (D) with a semilunar ,hump-shaped appearance in postinfectious glomerulonephritis.the humps sit on top of the glomerular basement membrane(GBM).A neutrophil is attached to the denuded GBM ,contributing to the glomerular inflammation.neutrophil attraction requires the initial presence of neutrophil attraction requires the initial presence of subepithelial immune deposits so that complement chemoattractants have access tho the systemic circulation.

Electron micrograph of a normal glomerulus



Diagnosis

- The typical clinical presentation is the sudden onset of dark urine with the development of swelling of the face and legs, oliguria, and hypertension.
- A history of a preceding upper respiratory or skin infection suggests a poststreptococcal etiology that may be confirmed by a positive streptococcal culture or rising anti-streptococcal antibody titers.
- Positive streptococcal cultures are frequent in epidemic conditions but are found in fewer than 25% of sporadic cases.
- Throat swabs for streptococcal culture should be done in the setting of symptomatic pharyngitis.

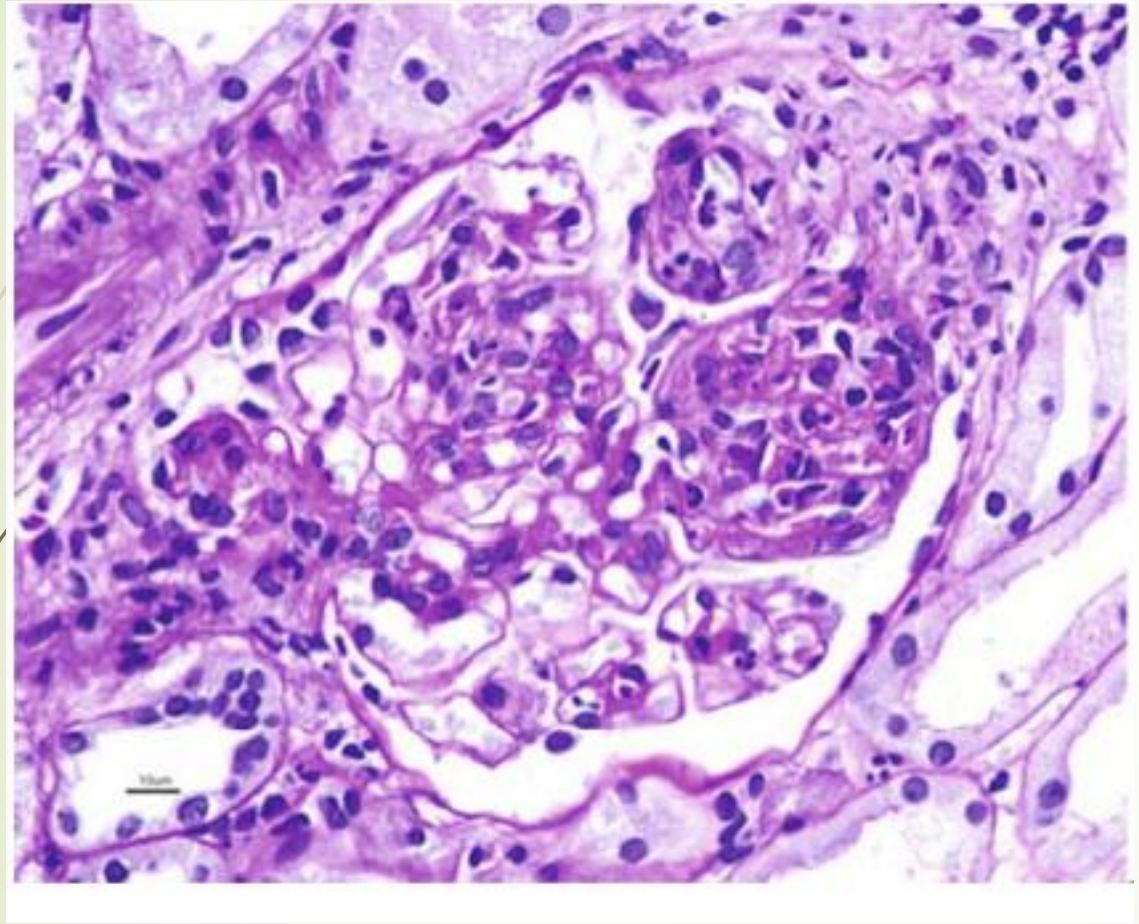
- Evidence of a previous streptococcal infection usually depends on the demonstration of an elevated titer of serum antistreptococcal antibodies.
- Anti-streptolysin O and anti-DNAse B titers are the most frequently elevated in upper respiratory infections and impetigo.
- The streptozyme test which includes four antigens (DNAse B, Streptolysin O, hyaluronidase, and streptokinase) is reported to be positive in more than 80% of the cases.
- It is important as part of the initial diagnostic approach to assess if the acute nephritic syndrome is associated with a systemic condition with other manifestations or if it results from a primary renal disease.
- In APSGN, serum complement levels return to normal quickly, often within a month and almost always within 3 months. Persistence of low complement levels should raise suspicion for a diagnosis different from APSGN and may prompt a kidney biopsy.

Infection-Related Glomerulonephritis

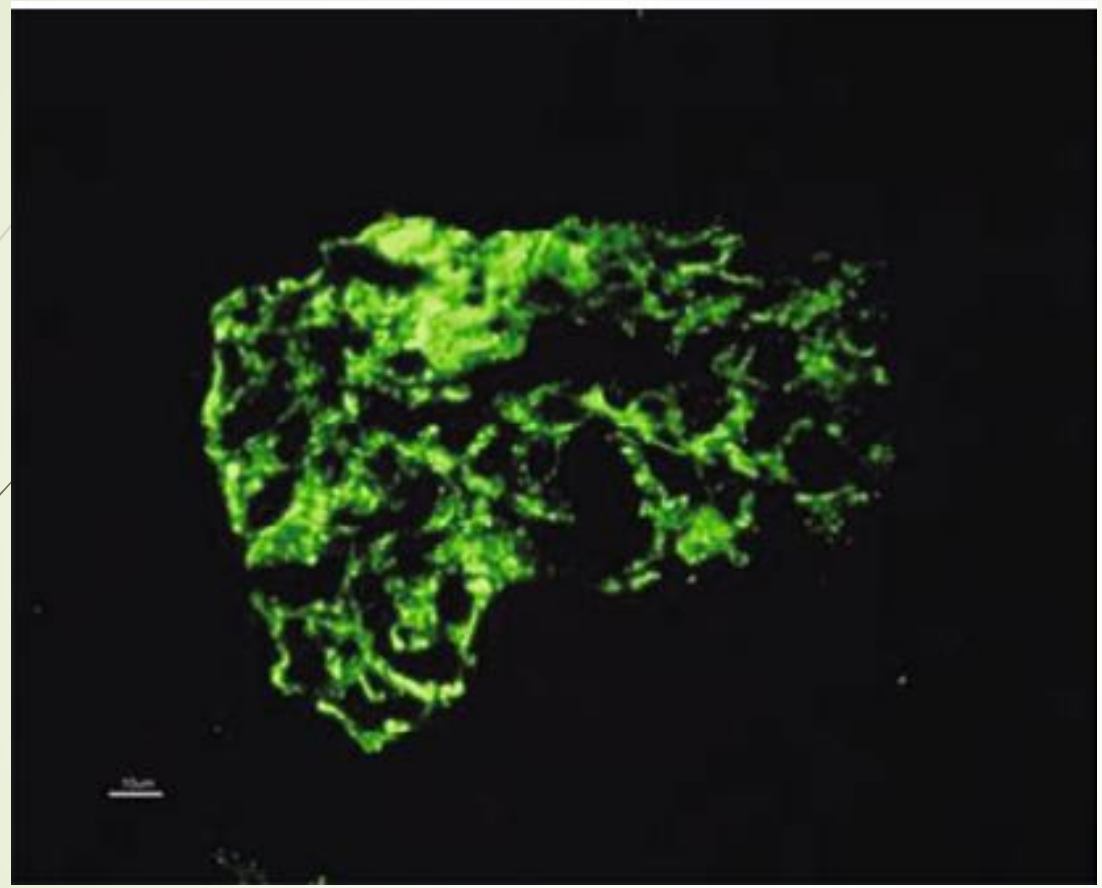
- Infection-related glomerulonephritis (IRGN):
  - syn-infectious)
  - post-infectious GN

Staphylococcus-infection-associated glomerulonephritis (SAGN)

- Non-streptococcal bacteria-associated glomerulonephritis mainly includes staphylococcal and other bacteria-related (intravascular and extravascular) glomerulonephritis.
- Staphylococcus-infection-associated glomerulonephritis (SAGN) is an entity that has emerged as one of the important causes for glomerulonephritis mainly in adults.
- While this specific entity is uncommon in children, staphylococcal endocarditis and shunt infection-related GN are not uncommon.
- In staphylococcal associated GN, nephritogenic antigens like the super antigens of Staphylococcus could trigger immune complex entrapment within the glomeruli or immune complexes formation in situ against planted glomerular antigens.
- Additionally, the alternate/lecithin pathway and activated plasmin and complement pathways act in concert to cause tissue injury.



Light microscopy shows global endocapillary proliferation with presence of neutrophils in the tufts. Cellular crescent is noted partially (PAS stain)



Immunofluorescence shows coarse granular deposits in the mesangial region and capillary walls with IgA (3+)

Table 2 Differences between PSGN and SAGN

Parameters	PSGN	SAGN
Age	Mainly children	Mainly adults, occasionally children
Infection source	Pharyngitis, pyoderma, otitis media, tonsillitis, infected scabies	Endocarditis, skin abscess, leg ulcers, osteomyelitis, septic arthritis, pneumonia
Infection free latent period	Present	Not present
Clinical features	Hematuria, hypertension, oliguria, mild proteinuria, occasionally renal dysfunction	AKI, microscopic hematuria, nephrotic range proteinuria, occasionally leukocytoclastic vasculitis rash
Laboratory features	Low C3, normal C4	Low C3 in 30–50%, normal C4
Renal histopathology	LM: Diffuse exudative proliferative GN	LM: Mesangial hypercellularity, endocapillary proliferation in some, segmental necrotizing lesions common, acute tubular necrosis frequent
	IF:C3 with or without IgG along capillary loops and mesangium EM: Predominantly subepithelial deposits	IF: IgA dominant or codominant with C3 or exclusive C3, pauci-immune in a few. EM: Predominantly mesangial deposits
Outcomes	Usually complete recovery	Unpredictable

Bacterial Endocarditis

- Renal manifestations in patients who underwent renal biopsies ranged from 18% to 25%.
- Common bacteria causing endocarditis are Staphylococcus, Streptococcus, and Bartonella henselae.
- Children at risk for endocarditis are those with valvular heart disease and congenital heart disease .
- Historical reports revealed microemboli from infected vegetations to cause renal lesions but ongoing evidence proposed immunologic mechanisms to be thpathogenic factor.
- The alternative mechanisms proposed are direct injury of endothelial cells by bacteria, trigger of antibodies against self-protein like proteinase 3 causing ANCA antibody-associated autoimmune renal injury, and abnormalities in complement regulatory protein.
- most common clinical syndromes of renal involvement were acute renal failure, acute nephritic syndrome, rapidly progressive glomerulonephritis, and nephrotic syndrome.
- Hematuria is seen in the majority with reduction in C3 levels seen in over 50% of patients. In a minority, low C4 and ANCA serology is positive.

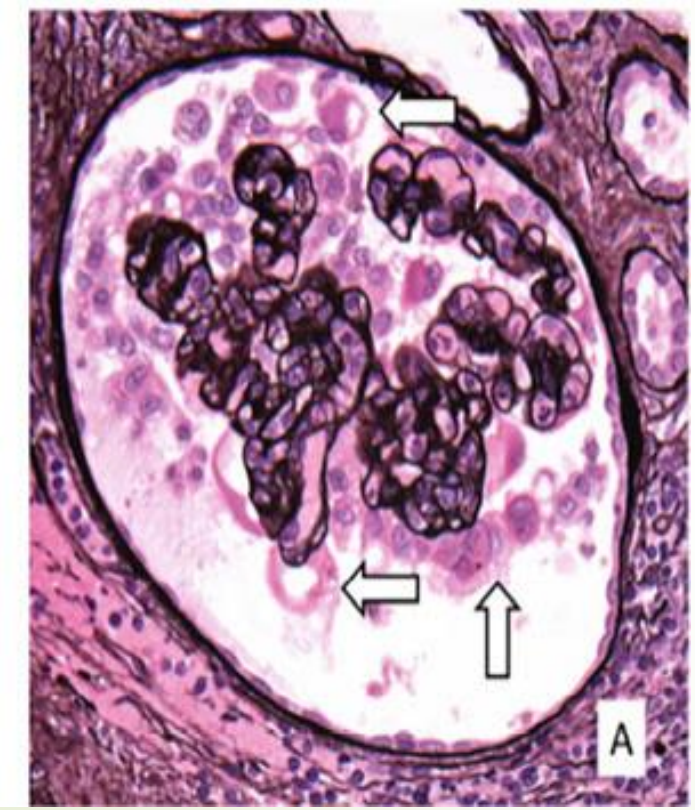
- The underlying histopathological lesions range from a spectrum of renal infarction due to septic emboli, acute interstitial nephritis, and cortical necrosis in the early reports to crescentic glomerulonephritis, diffuse proliferative glomerulonephritis, mesangial hypercellularity, and acute tubular injury with no micro-abscess or cortical necrosis among recent reports.
- IF : C3 deposits predominate followed by IgM and fewer IgG and IgA have been observed.
- Rarely, pauci-immune staining and full house under IF have been identified.
- there were no specific differences in the pathology features of streptococcal and staphylococcal endocarditis.
- Electron microscopy : typically reveals electron dense deposits in the mesangial area and subendothelial space.

Shunt Nephritis

- Shunt nephritis is an uncommon immune complex-mediated nephritic syndrome.
- The time to develop nephritis following shunt infection is widely variable ranging from weeks to years.
- Pathogenesis involves formation of immune complexes triggered by the bacterial antigen that get deposited in the glomeruli and activate the complement system.
- Patients present with fever, hematuria, hypertension, proteinuria, hepatosplenomegaly, skin rash, arthralgia, and anemia.
- Hypocomplementemia, elevated mixed cryoglobulins, and, rarely, positive ANCA have been reported.

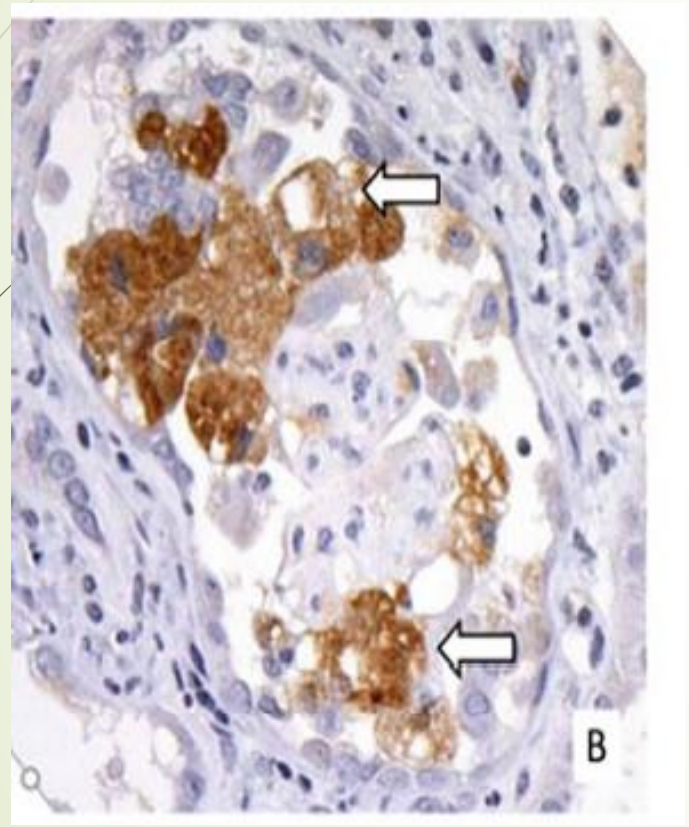
- Histopathology reveals : mesangial hypercellularity and features of membranoproliferative glomerulonephritis
- IF : with mesangial deposits of IgM and C3
- EM : Subendothelial deposits

Parvovirus B19 infection



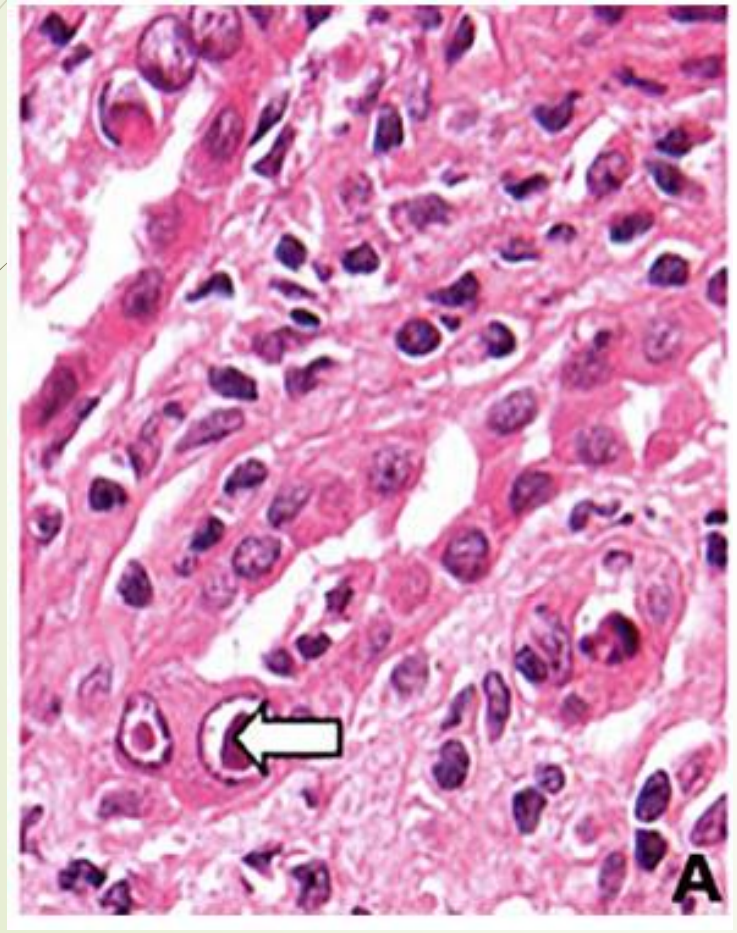
(A) Collapsing glomerulopathy with hypertrophic and hyperplastic epithelial cells (arrows) and capillary luminal obliteration due to collapse (Jones Silver stain x160 magnification)

Parvovirus B19 (PVB19)

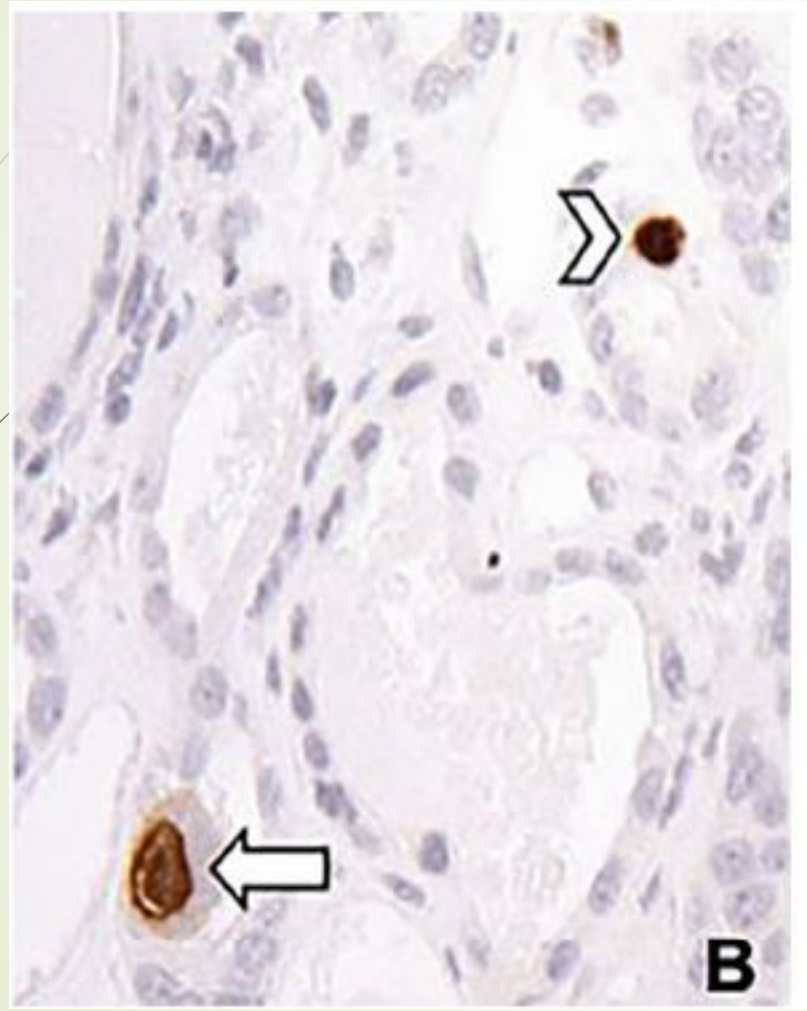


(B) Immunohistochemistry stain for parvovirus B19 showing infected hyperplastic and hypertrophic glomerular epithelial cells

Cytomegalovirus (CMV)

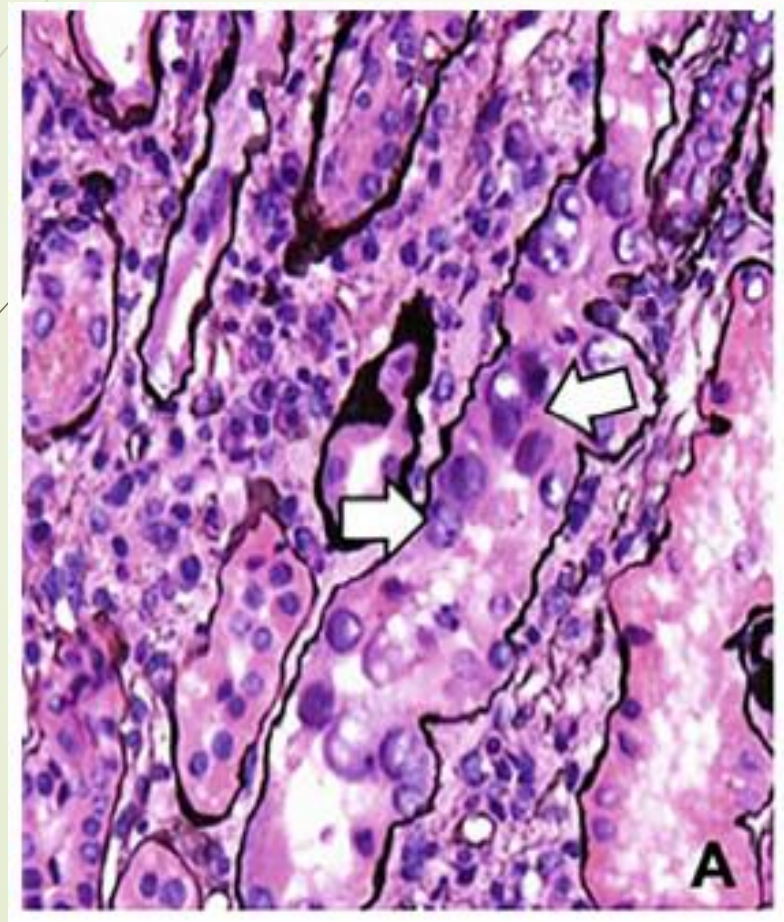


(A) Enlarged tubular cell nucleus with a large purple intranuclear inclusion (arrow) with a smaller inclusion in the cell to the left (cytopathic change). Note the sloughed degenerated cells in the tubular lumens (H&E x240 magnification).

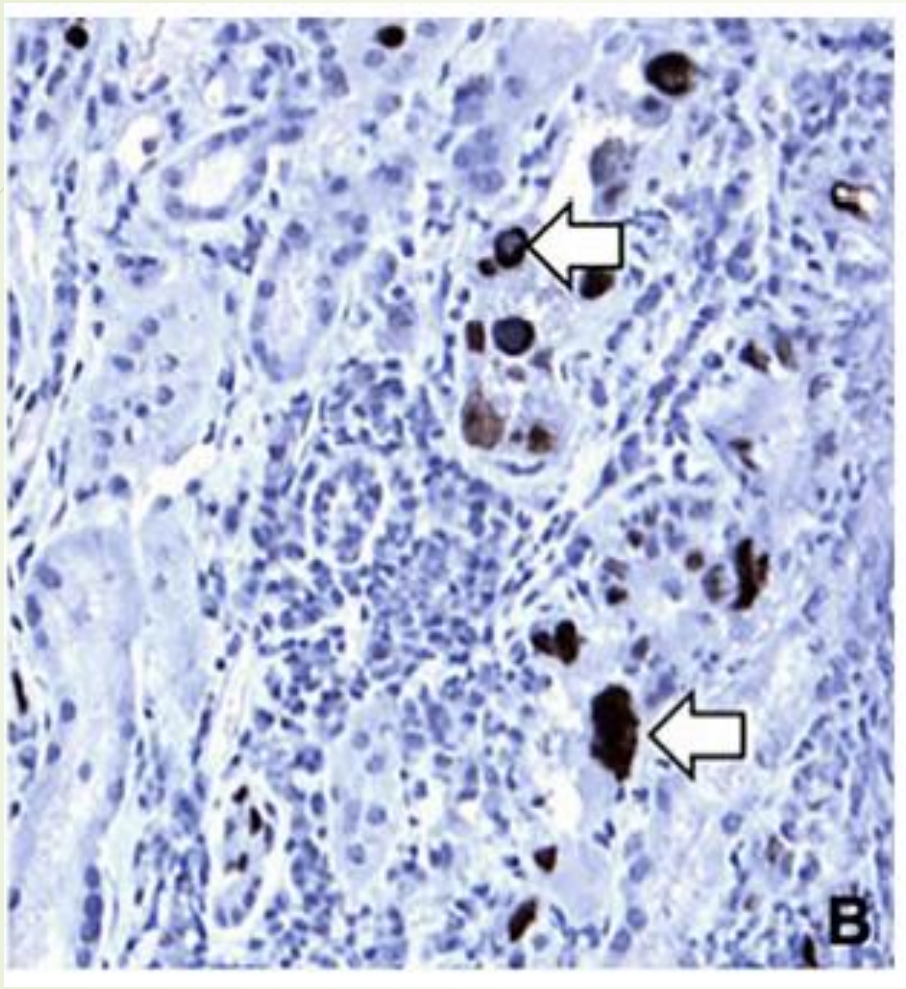


(B) Immunohistochemistry stain for CMV showing an infected tubular cell nucleus (arrow). An infected tubular cell that has sloughed into a tubular lumen is also present

BK-Virus (BKV)



Polyoma (BK) virus nephropathy. (A) Tubular cell nuclei (arrows) showing "cytopathic" change with enlarged nuclei containing viral inclusions and tubular cell degeneration with sloughing into the lumen (Jones silver x160 magnification)



(B) Immunohistochemistry for polyoma virus (SV40 antigen) showing positive staining within enlarged tubular cell nuclei (arrows)

Coronavirus (COVID-19)

- Coronaviruses are enveloped, single-stranded RNA viruses. Most coronaviruses cause mild respiratory infections without renal involvement .
- In the last 20 years, three potentially lethal coronaviruses had emerged that induce a severe acute respiratory syndrome (SARS) with multiorgan involvement and kidney complications; SARS-CoV, MERS-CoV , SARS-CoV2
- Virus-mediated injury to renal tubules, podocytes, and endothelial cells.
- Viral particles have been detected in renal tubular epithelial cells and podocytes by electron microscopy.
- SARS-CoV enters cells via angiotensin converting enzyme 2 (ACE2) which is expressed in several renal cell types.
- SARS-CoV-2 nuclear protein has been observed in proximal tubular cells by immunofluorescence.
- Acute tubular injury and collapsing glomerulopathy have been described in association with COVID-19.

- The renal damage observed in patients with COVID-19 appears to be the result of multiple mechanisms , including direct cytopathic effects, immune-mediated damage, rhabdomyolysis, impairment of renal microcirculation, and disseminated intravascular coagulation .
- Cases of COVID-19 associated AKI progressing chronic kidney disease (CKD) have been reported.
- Renal manifestations, if present, are usually seen in patients with severe COVID-19 infections.
- Proteinuria and hematuria are common signs of renal involvement among hospitalized patients.
- AKI can occur in seriously ill patients and appears to result from a complex process that includes traditional risk factors such as hypotension and hypoperfusion of the kidneys.

Management

- Management Children with SARS-CoV-2 infection with mild symptoms usually only require antipyretic therapy.
- In cases of dehydration, vomiting, or diarrhea, the use of ibuprofen should be avoided due to the risk of AKI.
- Some evidence suggests that intravenous corticosteroids and IVIG may be beneficial.
- No solid data supports that angiotensin converting enzyme inhibitors or angiotensin receptors blockers increase the susceptibility of people to a SARS-CoV-2 infection; thus, these drugs should not be discontinued in infected patients.
- Continuous renal replacement therapy can be used in critically ill children with AKI.
- Hypercoagulability leading to frequent filter clotting may occur in these children. Increased doses of unfractionated heparin are potential treatments for these issues.
- Acute peritoneal dialysis or intermittent hemodialysis can be used in patients who are hemodynamically stable.


با تشکر از توجه
شما عزیزان