The Histopathologic Spectrum of Bacterial Infection-related Glomerulonephritis

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Case 1

A 6 year-old male presents tea-colored urine. The patient also has hypertension, edema, and rash.

Lab evaluation reveals a creatinine of 1.1 mg/dl.

Urinalysis reveals hematuria and proteinuria.

Complements are low and ASO elevated (548).

He had a sore throat with fever approximately 3 weeks ago.
IgG and C3
Diagnosis

– Diffuse Proliferative and Exudative Glomerulonephritis, Consistent with Post-Infectious Glomerulonephritis.
Acute post-streptococcal glomerulonephritis

- Certain stains of nephritogenic *S pyogenes*

- Classic picture:
  - Peak age of 6-8 years (but up to 1/3 can be >40 years)
  - Sudden onset of hematuria (frequently gross), edema, and hypertension
  - Throat and skin cultures will be negative in 75% at presentation
  - Serologies for antistreptolyisin O (ASO) and anti-DNase-B
  - C3 decreased in 90%
Light microscopy

- Crescents may be present
- Interstitial inflammation often prominent
- Late biopsies: mesangial hypercellularity without proliferation
Immunofluorescence

- Primarily IgG and C3 with C3-predominance
- C3-only present in up to 30% of cases
- IgA and C1q typically absent in true post-strep
Clinical course

- Spontaneous resolution in children
- Complete recovery of renal function in days to weeks
- Microscopic hematuria can persist for years
‘Atypical’ post-infectious glomerulonephritis

- Mimics post-infectious glomerulonephritis on kidney biopsy, yet behaves differently

- Functional and genetic studies of the alternative pathway of complement identified autoantibodies or mutations in complement genes in 10 of 11 patients
  - 7 patients were positive for C3 Nephritic factor
  - 4 patients had mutations of complement genes including 3 with mutations in CFH and 1 with a mutation in CFHR5.
Case 2

60 year-old male with elevated serum Cr, proteinuria, and hematuria.

Serum Cr is 1.5 mg/dl (baseline 1.0).

11.3 grams of proteinuria per day.

Serum albumin low at 2.0 g/dl.

C3 and C4 are within normal limits.

ANA and ANCA are negative.
Diagnosis?

- Proliferative IgA Nephropathy?
Diagnosis

– Immune Complex-Mediated Proliferative Glomerulonephritis, See Comment.

Comment: The differential diagnosis would include proliferative IgA nephropathy versus infection-associated glomerulonephritis.
Diagnosis

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Follow-up

- Blood cultures positive for S. aureus
- Epidural abscess compressing spinal column discovered on imaging
- Treated with decompressive laminectomy and debridement of the infected tissues and antibiotics
IgA-predominant infection-associated glomerulonephritis

Adult patients – mean age 58.4 (range 21-89)

Presentation

– Acute kidney injury – 85%
– Hematuria – 97%
– Proteinuria – 96%
– Hypocomplementemia – 57%
IgA-predominant infection-associated glomerulonephritis

Cultures- 67% Staph aureus (49% MRSA)

25% of patients with Diabetes mellitus
Light Microscopy
Immunofluorescence Microscopy

- 95% C3
- 63% IgG
- 37% IgM
- 9% C1q
Electron microscopy

- 87% Mesangial
- 64% Subepithelial
- 30% Subendothelial
IgA-Dominant Infection-Associated Glomeruonephritis

Prognosis

- 55% Improved
- 12% Persistent renal dysfunction
- 20% Progressed to ESRD
- 14% Death
- Age >65 and diabetes mellitus were independent risk factors for ESRD or death.
Focus on Staph
Focus on Staph

- Generally, the IgA staining is mild to moderate compared with moderate to severe C3 staining
- 13% of cases were pauci-immune
- Capillary loop staining is more common in SA-associated GN (41%) compared with primary IgA (20%)
- Subepithelial humps were present in only 31%
- Glomerulonephritis with IgA and C3 along with purpuric rash
- 4/8 received steroid therapy for presumed HSP
- Poor renal outcome in 71%
Case 3

33 year-old male presented with a skin rash and fever.

Serum Cr -3.3 mg/dl (baseline 1.1 mg/dl)

Urinalysis positive for 3+ protein.
Active urine sediment with RBC casts.

pANCA positive.
ANA negative.
C3 decreased. C4 normal.

Medical history includes pulmonary valve atresia status post multiple cardiac surgeries with pulmonary and tricuspid valve replacement.
7/15 glomeruli with necrotizing cellular crescents
Findings

LM: Crescentic glomerulonephritis

IF and EM: 2+ IgM and C3 predominantly in the mesangium

Clinical: Nephritic with positive pANCA and slightly decreased C3
Diagnosis?

– Crescentic Glomerulonephritis consistent with pANCA-associated glomerulonephritis
Diagnosis

- Crescentic Glomerulonephritis, see Comment

Comment: The light microscopy findings in this biopsy are within the spectrum of ANCA-associated glomerulonephritis. However, the presence of glomerular immune complex deposition and hypocomplementemia are atypical for this disease. The differential diagnosis would include an infection-associated glomerulonephritis. Specifically, crescentic glomerulonephritis was the most common pattern of glomerulonephritis in a recent case series detailing the renal biopsy findings in endocarditis.
Follow-up

Transesophageal echocardiogram showed a large tricuspid valve vegetation.

Bartonella titers came back with markedly elevated IgM. He has had exposure to multiple cats and was scratched 3 months prior.
Histopathology of endocarditis-associated glomerulonephritis

53% 37% 10%

20% Focal 33% Diffuse 4% Focal 33% Diffuse
Crescentic endocarditis-associated glomerulonephritis staining pattern

8%  50%  42%
Crescentic endocarditis-associated glomerulonephritis

- 11/22 (42%) of crescentic cases were pauci-immune
- ANCA positive in 3/7 (43%) in which it was tested
- Complements normal ~50%
- Many of the patients did not have a known diagnosis of endocarditis at the time of biopsy
Acute proliferative endocarditis-associated glomerulonephritis staining pattern

0% 17% 88%
Acute proliferative endocarditis-associated glomerulonephritis

- 3% full house
- 33% C3 only
- 26% IgA-predominant or codominant

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<tr>
<th>IgG</th>
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<tr>
<td>IgA</td>
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<tr>
<td>IgM</td>
<td>17%</td>
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<tr>
<td>C3</td>
<td>100%</td>
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Endocarditis-associated glomerulonephritis

- Mesangial deposits- 84%
- Subendothelial deposits- 45%
- Subepithelial deposits- 35%
- Subepithelial ‘humps’- 14%
- No deposits- 10%

Endocarditis-associated glomerulonephritis

90% of cases with positive blood cultures

- Staphylococcus- 53%
- Streptococcus- 23%
- Bartonella henselae- 5%
- Coxiella burnetii- 4%
- Cardiobacterium hominis- 2%
- Gemella- 2%
Endocarditis-associated glomerulonephritis

Predisposing states/associated conditions

- IV drug abuse – 28%
- Prosthetic cardiac valve – 18%
- Hepatitis C – 20%
- Diabetes mellitus – 18%
When should the possibility of infection-associated glomerulonephritis enter the differential diagnosis?
Atypical features prompting consideration for infection

- Crescentic glomerulonephritis pattern
  - Clinical hypocomplementemia
  - Strong C3 staining in biopsy
  - Predisposing states for endocarditis such as IV drug abuse or prosthetic cardiac valve

- Glomerulonephritis with IgA predominance
  - Unusual pattern of deposition (not mesangial only)
  - C3>IgA
  - Hypocomplementemia
  - Predisposing state for infection such as diabetes mellitus
  - HSP in adults
Thank you!

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