A PRACTICAL APPROACH TO RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

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OVERVIEW

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* PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS
* REFERENCE
Glomerulonephritis

Non-Proliferative

- Minimal Change Glomerulonephritis
  - Abnormal Podocytes
  - Seen on Electron Microscopy
  - Treat with Supportive care + Prednisolone
  - Most respond well

- Focal Segmental Glomerulosclerosis
  - Segments of Glomeruli Develop Sclerosis
  - Presents with Nephrotic Syndrome
  - Genetic causes identified
  - Steroids often ineffective
  - 50% Progress to Renal Failure

Proliferative

- Membranous Glomerulonephritis (MGN)
  - Thickened Glomerular Basement Membrane
  - Usually idiopathic
  - 1/3 have chronic MGN
  - 1/3 go into remission
  - 1/3 progress to renal failure

- IgA Nephropathy
  - Most common type of GN in adults
  - Macroscopic haematuria
  - Appears 24-48hrs post URTI/GI infection
  - IgA deposits seen in the matrix

- Membranoproliferative Glomerulonephritis
  - Primary (immune mediated)
  - Secondary (SLE, Hep)
  - Usually progresses to End Stage Renal Failure

- Rapidly Progressive Glomerulonephritis (Crescentic)

- Vasculitic Disorders
  - Wegener's Granulomatosis
    - Vasculitis
    - Lungs, Kidney & other organs
    - c-ANCA +ve
    - Treat with Steroids + Cyclophosphamide
  - Microscopic Polyangitis
    - Small vessel vasculitis
    - p-ANCA +ve
    - Treat with long term steroids +/− cytotoxic agents

- Goodpastures Syndrome
  - Autoimmune
  - anti-GBM antibody
  - Glomerulus & Lung affected
  - Haematuria & Haemoptysis
  - Treat with steroids +/− steroid sparing agents

- Post Infectious Glomerulonephritis
  - Occurs weeks after URTI
  - Usually Strep Pyogenes
  - Supportive treatment
  - Resolves over 2-4 weeks
Normal Glomerulus

Light micrograph of a normal glomerulus. There are only 1 or 2 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 cells and mesangial matrix are located in the central or stalk regions of the tuft (arrows).
* **DEFI-** The term *Rapidly progressive glomerulonephritis* (RPGN) refers to a clinical syndrome characterized by a rapid loss of kidney function (GFR > 50%) from a **few days to weeks**, often accompanied by oliguria or anuria, and by features of glomerulonephritis, including D*ysmorphic erythrocyturias*, E*rythrocyte cylindruria*, and G*glomerular proteinuria*.

* The clinical term *rapidly progressive glomerulonephritis* is used interchangeably with the **Pathologic term** *crescentic glomerulonephritis*.

* It is the result of focal rupture of glomerular capillary walls that allows inflammatory mediators and leukocytes to enter Bowman's space, where they induce epithelial cell proliferation and macrophage influx and maturation that together produce cellular crescents.
ETIOLOGY

* Infectious diseases
  * Post-streptococcal GN
  * Infectious endocarditis
  * Visceral sepsis
  * Hepatitis B or C infection with vasculitis and/or cryoimmunoglobulinemia

* Idiopathic
  * Type I: Antiglomerular basement membrane antibody disease
  * Type II: immune complex-mediated disease
  * Type III: pauci-immune (ANCA-associated) disease
  * Type IV: mixed and anti-GBM and ANCA associated disease

* Multisystemic diseases
  * Systemic lupus erythematosus
  * Goodpasture’s disease
  * Henoch-Schonlein purpura
  * Necrotizing vasculitis (including Wegener’s granulomatosis)
  * Neoplasia
  * Relapsing polychondritis
  * Behcet’s disease

* Superimposed on primary glomerular disease
  * Membranoproliferative GN (type I, II)
  * Membranous GN
  * IgA nephropathy

* Drugs and toxic agents
  * Allopurinol
  * D-Penicillamine
  * Hydralazine
  * Rifampicin
Classification of RPGN

* Type I - Anti glomerular basement membrane disease
* Type 2 – Immune complex disease
* Type 3 – Pauci immune disease ANCA positive
* Type 4 – Pauci immune disease ANCA negative
* Type 5 – Anti GBM + ANCA positive
Crescent glomerulonephritis (Histological classification)

* **Type I:** Anti-glomerular basement membrane (anti-GBM) antibody-associated RPGN (95% crescents)
  * Goodpasture’s syndrome
  * Renal limited

* **Type II:** Immune complex RPGN (20~50% crescents)
  * Systemic lupus erythematosus
  * IgA nephropathy (including Henoch-Schönlein purpura)
  * Cryoglobulinemic vasculitis

* **Type III:** Pauci immune-associated glomerulonephritis
  * Idiopathic crescentic GN
  * Wegener’s granulomatosis GN
  * Microscopic polyangiitis GN
RPGN
Clinical/serology/Bx

- Linear IF, IgG
  - Anti GBM +ve
  - Lung Hmrhge
    - YES: Goodpasture syndrome
    - NO: Anti GBM GN
- Granular IF, immune complex
  - Anti dsDNA, ANA/ Low C3-C4/ IgA/ ASLO, etc +ve
- No IF, ANCA +ve
RPGN
Clinical/serology/Bx

Granular IF, immune complex
Anti dsDNA, ANA/
Low C3-C4/LgA/
ASLO, etc +ve

No IF, ANCA +ve

IgA

No Vasc.
IgA

Acute Staph/strep infection

Systemic Vasculitis HSP

PSGN

MPGN

Mesangio Cap.

MPGN I

MPGN II

DD

Others

Sub Epithelial

Others

MN

SLE, etc

MN-Membranous nephropathy
DD-Dense deposit disease
ANTI–GLOMERULAR BASEMENT MEMBRANE GLOMERULONEPHRITIS

EPIDEMIOLOGY

* Anti-GBM disease accounts for about 10% to 20% of crescentic glomerulonephritides.
* This disease is characterized by circulating antibodies to the GBM (anti-GBM) and deposition of IgG or, rarely, IgA along the GBM.
* The incidence of anti-GBM disease has two peaks (Bimodal) with respect to age.
  * The first peak is in the 2nd and 3rd of life, more common in MEN and anti-GBM disease in this age group shows a higher frequency of pulmonary hemorrhage (Goodpasture’s syndrome).
  * The second peak is in the 6th and 7th, and this later-onset disease is more common in WOMEN, who more often have renal limited disease.
* Genetic susceptibility to anti-GBM disease is associated with HLA-DR2
PATHOLOGY

1. Light Microscopy

* At the time of biopsy, 97% of patients with anti-GBM disease have some degree of crescent formation.

* Glomeruli with crescents typically have fibrinoid necrosis in adjacent glomerular segments.

* **Special stains** that outline basement membranes, such as Jones’ methenamine silver stain or periodic acid–Schiff stain, demonstrate focal breaks in GBMs in areas of necrosis and also show focal breaks in Bowman’s capsule.
* The acute necrotizing glomerular lesions and the cellular crescents evolve into glomerular sclerosis and fibrotic crescents, respectively.

* The most severely injured glomeruli have global glomerular necrosis, circumferential cellular crescents, and extensive disruption of Bowman’s capsule.
2. Immunofluorescence Microscopy

* The pathologic finding of **linear staining of the GBMs** for immunoglobulin is indicative of anti-GBM glomerulonephritis.

* The immunoglobulin is predominantly IgG; rarely IgA dominant anti-GBM glomerulonephritis have also been reported.

* Linear staining for both κ- and λ-light chains typically accompanies the staining for γ-heavy chains. Linear staining for γ-heavy chains alone indicates γ-heavy chain deposition disease.
3. **Electron Microscopy**

* In acute disease, there is focal glomerular necrosis with disruption of capillary walls. Bowman’s capsule also have focal gaps. Leukocytes, including neutrophils and monocytes, often are present at sites of necrosis.

* **Fibrin tactoids** including sites of capillary thrombosis, fibrinoid necrosis, and fibrin formation in Bowman’s space.

* An important negative observation is the absence of immune complex–type electron-dense deposits.

* In chronic lesions, amorphous and banded collagen deposition distorts or replaces the normal architecture.
PATHOGENESIS

* The antigen to which anti-GBM antibodies react was found to be in the part of type IV collagen

* Noncollagenous domain (NC1 domain)(α3α4α5 chains)

* The antigenic epitopes found in the NC1 domain are in a cryptic form, as evidenced by the fact that little reactivity is found against the native hexameric structure of the NC1 domain.

* About 90% of antibodies are directed against the α3-chain.
A small percentage of patients with anti-GBM disease may also have limited reactivity with the NC1 domains of the \( \alpha_1 \)- or \( \alpha_4 \)-chains. These additional reactivities seem to be more frequent in patients with anti-GBM–mediated glomerulonephritis alone.

The majority of patients with anti-GBM disease express antibodies to two major conformational epitopes (EA and EB) located within the C-terminal noncollagenous (NC1) domain of the \( \alpha_3 \)-chain.

About one third of patients with anti-GBM/Goodpasture’s syndrome also have circulating ANCA, the majority being to MPO (MPO-ANCA).
Anti-GBM Glomerulo-Nephritis

Patient produces antibodies against his own BM in glomerular and alveolar capillaries (Goodpasture’s syndrome)

Bowman’s space

Disruptions

Basement membrane (BM)

Mesangial cells proliferate

Extreme proliferation

Fig. 25-20
CLINICAL FEATURES

* The onset of renal anti-GBM disease is typically characterized by an abrupt, acute glomerulonephritis with severe oliguria or anuria. There is a high risk of progression to ESKD.

* The onset of disease may be associated with arthralgias, fever, myalgias, and abdominal pain.

* Goodpasture’s syndrome is characterized by the presence of pulmonary hemorrhage concurrent with glomerulonephritis and associated with haemoptysis, unexplained anemia.
* Seen in smokers and exposures to hydrocarbons or upper respiratory tract infections, petroleum-based mineral oils

* The diagnosis made by increased diffusing capacity of carbon monoxide and by findings on CT of the chest. The diagnostic evaluation of alveolar hemorrhage usually includes bronchoscopic examination and bronchoalveolar lavage (hemosiderin laden macrophages)
LABORATORY FINDINGS

* Kidney involvement causes an acute nephritic syndrome with hematuria that includes dysmorphic erythrocytes and red blood cell casts.

* The diagnostic investing is in detection of circulating antibodies to GBM, and specifically to the α3-chain of type IV collagen.

* These antibodies are detected in approximately 95% of patients by immunoassays, with the latter being seen more often in females than in males.
TREATMENT

* The standard treatment for anti-GBM disease is combination of below
  1. Intensive plasmapheresis
  2. Corticosteroids
  3. Cyclophosphamide.

* Plasmapheresis consists of removal of 2 to 4 L of plasma and its replacement with a 5% albumin solution continued on a daily basis until circulating antibody levels become undetectable.

* In those patients with pulmonary hemorrhage, clotting factors should be replaced by administering fresh-frozen plasma at the end of each treatment.
* Prednisone should be administered starting at a dose of 1 mg/kg of body weight for at least the first month and then tapered to alternate-day therapy during the second and third months of treatment.

* Cyclophosphamide is administered orally (at a dosage of 2 mg/kg/day, adjusted with consideration for the degree of impairment of kidney function and the white blood cell count) for 8 to 12 weeks.

* When the regimen of aggressive plasmapheresis with corticosteroids and cyclophosphamide is used, patient survival is approximately 85% with 40% progression to ESKD.

* Patients who have both circulating anti-GBM antibodies and ANCAAs, may have a better chance of recovery of kidney function. In these patients, immunosuppressive therapy should not be withheld, even with serum creatinine levels higher than 7 mg/dL,
IMMUNE COMPLEX–MEDIATED CRESCENTIC GLOMERULONEPHRITIS

EPIDEMIOLOGY

1. Primary glomerulonephritis.
   * IgA nephropathy
   * Post-infectious glomerulonephritis
   * MPGN

2. Secondary glomerulonephritis (systemic).
   * SLE,
   * Cryoglobulinemia
   * IgA vasculitis (HSP).

Immune complex–mediated CGN accounts for the majority in children but for only a minority in older adults.
PATHOLOGY

1. Light Microscopy

*In their most aggressive expressions, MPGN, acute postinfectious glomerulonephritis, or proliferative glomerulonephritis, including IgA nephropathy, can all have crescent formation.

*This underlying phenotype of immune complex glomerulonephritis is recognized best in the intact glomeruli or glomerular segments.
* Immune complex–mediated glomerulonephritis and C3 glomerulopathy usually have varying combinations of capillary wall thickening and endocapillary hypercellularity in the intact glomeruli.

* In glomerular segments adjacent to crescents in immune complex glomerulonephritis, there usually is some degree of necrosis with karyorrhexis, there is less destruction of Bowman’s capsule.
2. Immunofluorescence Microscopy

* Crescentic glomerulonephritis with predominantly mesangial IgA-dominant deposits is indicative of crescentic IgA nephropathy.

* C3-dominant deposits with peripheral bandlike configurations suggest crescentic MPGN.

* Coarsely granular capillary wall deposits raise the possibility of crescentic postinfectious glomerulonephritis.

* Finely granular IgG dominant capillary wall deposits suggest crescentic MN.
Granular staining on if in PSGN
3. **Electron Microscopy**

* The hallmark is deposits can be mesangial, subendothelial, intramembranous, subepithelial, or any combination of these.

* Ultrastructural findings suggest that the disease is secondary.

* Endothelial tubuloreticular inclusions suggest lupus nephritis.

* Microtubular configurations in immune deposits suggest cryoglobulinemia
PATHOGENESIS

* Immune complex localization in glomerular capillary walls and mesangium, by either deposition or in situ formation or both, activates multiple inflammatory mediator systems.

* This includes humoral mediator systems, such as the coagulation system, kinin system, and complement system, as well as phlogogenic cells, such as neutrophils, monocytes/macrophages, lymphocytes, platelets, endothelial cells, and mesangial cells.

* The activated cells also release soluble mediators, such as cytokines and chemokines.
* If the resultant inflammation is contained internal to the GBM, a proliferative or membranoproliferative phenotype of injury ensues with only **endocapillary hypercellularity**.

* If the inflammation breaks through capillary walls into Bowman’s space, **extracapillary hypercellularity** (crescent formation) results.

* Complement activation has often been considered a major mediator of injury in immune complex glomerulonephritis.

* Experimental data also indicate the importance of Fc receptors in immune complex–mediated injury.
PATHOGENESIS

- Infection of streptococci
- Immune complexes, antigens
- Activation of complements recruitment of leukocytes
- Hematuria, Proteinuria, RBC casts
- GBM damage, blood ingredients leakage
- Oliguria, sodium and water retention, hypervolemia
- Blockage of renal capillaries and decreased GFR
- Edema, hypertension, heart failure, encephalopathy, renal failure
- Inflammation mediates, cytokines, proliferative factors
- Proliferation of MC and EC
**TREATMENT**

* The therapy for immune complex–mediated crescentic glomerulonephritis is influenced by the nature of the **underlying category** of immune complex glomerulonephritis.

* The most common treatment is immunosuppressive therapy with **pulse methylprednisolone**, followed by prednisone at a dosage of 1 mg/kg daily tapered over the second to third month to an alternate-day regimen until completely discontinued.

* In patients with a rapid decline in kidney function, cytotoxic agents with or without plasma exchange in addition to corticosteroids may be considered.
Epidemiology

* The characteristic feature of the glomerular lesion is focal necrotizing and crescentic glomerulonephritis with little or no glomerular staining for immunoglobulins by immunofluorescence microscopy.

* Pauci-immune crescentic glomerulonephritis usually is a component of a systemic small vessel vasculitis; is the most common category of RPGN in adults, especially older adults. The disease has a predilection for whites compared with blacks.

* However, some patients have renal-limited (primary) pauci-immune crescentic glomerulonephritis.
PATHOLOGY

1. Light Microscopy

* The light microscopic appearance of ANCA-associated Pauci immune crescentic glomerulonephritis is **indistinguishable** from that of anti-GBM crescentic glomerulonephritis.

* Renal-limited (primary) pauci-immune crescentic glomerulonephritis also **is indistinguishable** from pauci-immune crescentic glomerulonephritis that occurs as a component of a systemic small vessel vasculitis, such as GPA, MPA, or EGPA.
Figure 32.38  Light micrograph showing segmental fibrinoid necrosis in a glomerulus from a patient with antineutrophil cytoplasmic autoantibody–associated pauci-immune crescentic glomerulonephritis. (Periodic acid–Schiff stain, ×300.)
Immunofluorescence Microscopy

* The distinguishing pathologic difference between pauci-immune crescentic glomerulonephritis and anti-GBM and immune complex–mediated crescentic glomerulonephritis is the absence or paucity of glomerular staining for immunoglobulins.

* There is irregular staining for fibrin at sites of intraglomerular fibrinoid necrosis and capillary thrombosis and in the interstices of crescents.

* If the patient is likely to be ANCA positive, which increases the likelihood of certain systemic small vessel vasculitides.
* At the time of biopsy, approximately 90% of kidney biopsy specimens with ANCA-associated pauci-immune glomerulonephritis have some degree of crescent formation, and approximately half of the specimens have crescents involving 50% or more of glomeruli. Over 90% of specimens have **focal segmental to global fibrinoid necrosis**.

* The presence of **arteritis** in a biopsy specimen that has pauci-immune crescentic glomerulonephritis indicates that the glomerulonephritis is a component of a more widespread vasculitis, such as MPA, GPA, or EGPA.
Scanty Background staining of puaci immune
Electron Microscopy

* The findings by electron microscopy are indistinguishable from those described earlier for anti-GBM glomerulonephritis.

* Specimens with pure pauci-immune crescentic glomerulonephritis have no or only a few immune complex–type electron-dense deposits.

* Foci of glomerular necrosis have leukocyte influx, breaks in GBMs, and fibrin tactoids in capillary thrombi and sites of fibrinoid necrosis.
PATHOGENESIS

* ANCA IgG is a major pathogenic factor.
* The substantial accumulation of polymorphonuclear leukocytes at sites of vascular necrosis has lead to neutrophil activation in this disease.
* Anti-MPO autoantibodies, anti-PR3 autoantibodies, or autoantibodies to other neutrophil antigens contained within the azurophilic granules to interact with their corresponding antigens, either the antibodies must penetrate the cell or, alternatively, those antigens must translocate to the cell surface.
* Small amounts of cytokine (e.g., TNF-α and IL-1) at concentrations too low to cause full neutrophil activation are capable of inducing such a translocation of ANCA antigens to the cell surface.
* When the antigen is expressed on the surface of the cell as a consequence of cytokine stimulation or gene expression, in the presence of circulating ANCA,

* The interaction of the autoantibody with its externalized antigen results in full activation of the neutrophil, which leads to the respiratory burst and degranulation of primary and secondary granule constituents.

* ANCA induce a premature degranulation and activation of neutrophils at the time of their margination and diapedesis, which leads to the release of lytic enzymes and toxic oxygen metabolites at the site of the vessel wall, thereby producing a necrotizing inflammatory injury.
**CLINICAL FEATURES AND NATURAL HISTORY**

* The majority of patients with have glomerular disease as part of a systemic small vessel vasculitis. The disease is clinically **limited to the kidney** in about one third of patients.

* Renal -rapid loss of kidney function associated with hematuria, proteinuria, and hypertension. latter group of patients, episodes of focal necrosis and hematuria resolve with focal glomerular scarring.

* Patients have pulmonary-renal, dermal-renal, or a multisystem disease.
* Frequent sites of involvement are the eyes, ears, sinuses, upper airways, lungs, gastrointestinal tract, skin, peripheral nerves, joints, and central nervous system.

* Extra renal manifestations of active vasculitis, systemic symptoms consisting of fever, fatigue, myalgias, and arthralgias are common.
LABORATORY FINDINGS

* Approximately 80% to 90% of patients with have circulating ANCA.

* On indirect immunofluorescence microscopy of alcohol-fixed neutrophils, ANCA causes two patterns of staining: perinuclear (P-ANCA) and cytoplasmic (C-ANCA). The two major antigen specificities for ANCA are MPO and PR3.

* About two thirds of patients with pauci-immune necrotizing crescentic glomerulonephritis without clinical evidence of systemic vasculitis will have MPO-ANCA or P-ANCA, and approximately 30% have PR3-ANCA or C-ANCA.
C-ANCA pattern  Demonstration of *cytoplasmic* antineutrophil cytoplasmic antibodies (C-ANCA) by indirect immunofluorescence with normal neutrophils. There is heavy staining in the cytoplasm while the multilobulated nuclei (clear zones) are nonreactive. These antibodies are usually directed against proteinase 3 and most patients have Wegener’s granulomatosis. Courtesy of Helmut Rennke, MD.
**P-ANCA pattern** Demonstration of *perinuclear* antineutrophil cytoplasmic antibodies (P-ANCA) by indirect immunofluorescence with normal neutrophils. Staining is limited to the perinuclear region and the cytoplasm is nonreactive. Among patients with vasculitis, the antibodies are usually directed against myeloperoxidase. However, a P-ANCA pattern can also be seen with autoantibodies against a number of other antigens including lactoferrin and elastase. Non-MPO P-ANCA can be seen in a variety of nonvasculitic disorders. Courtesy of Helmut Rennke, MD.
* In patients with hematuria and proteinuria, the positive predictive value (PPV) of a positive ANCA result is 84% if the serum creatinine is greater than 3 mg/dL,

* 60% if the serum creatinine is 1.5 to 3.0 mg/dL.

* 29% if the serum creatinine is less than 1 mg/dL.

* Urinalysis findings include hematuria with dysmorphic red blood cells, with or without red cell casts, and proteinuria. The proteinuria ranges from 1 g of protein per 24 hours to as much as 16 g of protein per 24 hours.
CONTII

* Serum creatinine concentration, Erythrocyte sedimentation rate and C-reactive protein level are elevated during active disease.

* Serum complement component levels are typically within normal limits

* Whether a kidney biopsy is essential for the management.
TREATMENT

* Induction therapy should be instituted using

* Pulse methylprednisolone at a dose of 7 mg/kg/day for three consecutive days in an attempt to halt the aggressive, destructive, inflammatory process. This is followed by the institution of daily oral prednisone,

* Prednisone is usually started at a dosage of 1 mg/kg/day for the first month, then tapered to an alternate-day regimen, and then discontinued by the end of the fourth to fifth month.
* Cyclophosphamide, either orally or intravenously.

* Regimen of monthly intravenous doses of cyclophosphamide is used, the starting dose should be about 0.5 g/m2 and should be adjusted upward to 1 g/m2 based on the 2-week leukocyte count.

* Regimen based on daily oral cyclophosphamide should begin at a dose of 2 mg/kg/day and should be adjusted downward as needed to keep a nadir leukocyte count above 3000 cells/mm3 as well as appropriate dose adjustment based on degree of reduction in GFR.
NOTE

* The use of plasmapheresis in addition to immunosuppressive therapy appears to be beneficial in the subset of patients who require dialysis at the time of presentation.

* The risk/benefit ratio does not support the routine use of maintenance immunosuppression therapy in patients with ANCA small vessel vasculitis who are on long-term dialysis.

* Trimethoprim-sulfamethoxazole has been suggested to be of benefit in the treatment of patients with GPA. (Granulomatosis with polyangiitis)

* Whether the use of cyclophosphamide can be reduced or voided completely by the use of rituximab has been the subject of two randomized controlled trials. In the RITUXVAS trial,