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TUMS

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

RPGN IS CHARACTERIZED BY:

- Rapid loss of renal function over a very short period (days to weeks)
- Nephritic urine analysis—micro- or macroscopic hematuria, dysmorphic RBCs, RBC casts, and proteinuria.
- Characteristic histopathological findings on renal biopsy—cellular crescent formation in the glomeruli, a proliferative cellular response of parietal epithelial cells within the Bowman space. So this condition is also known as crescentic glomerulonephritis

RPGN CLASSIFICATION BASED ON HISTOPATHOLOGY AND IMMUNE COMPLEX DEPOSITION

- Type I: Anti-glomerular basement membrane (GBM) linear antibody deposition disease.
- Type II: Granular immune complex deposition disorders.
- Type III: Pauci-immune disease (absence of deposition, generally ANCA positive vasculitis).
- Type IV: Double antibody positive for both ANCA and anti-GBM

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

- Circulating IgG antibodies are directed against an antigen normally present in the GBM and alveolar basement membrane, specifically the non-collagenous domain of the α-3 chain of type IV collagen.

- About 40% to 60% of these cases are associated with alveolar hemorrhage, a condition known as Goodpasture syndrome.

GRANULAR IMMUNE COMPLEX GLOMERULONEPHRITIS

- Immune complex RPGN is frequently encountered in children.
- Most common causes include IgA nephropathy, lupus nephritis, cryoglobulinemia, IgA vasculitis, and postinfectious glomerulonephritis. Immune complex glomerulonephritis.
- In adults, it can be idiopathic or secondary to the following:

Postinfectious glomerulonephritis, especially *Streptococcus* infection/ Collagen vascular disease/Lupus nephritis/IgA vasculitis, Henoch-Schönlein purpura/IgA nephropathy, Berger disease/Mixed cryoglobulinemia/MPGN/Membranous nephropathy/Fibrillary glomerulonephritis/glomerulonephritis associated with hepatitis B&C

PAUCI-IMMUNE GLOMERULONEPHRITIS OR ANCA-ASSOCIATED VASCULITIS

Typically fall into 3 main types as follows:

- Granulomatosis with polyangiitis, formerly known as Wegener granulomatosis, with renal involvement observed in about 80% of cases.
- Microscopic polyangiitis, with renal involvement observed in about 90% of cases.
- Eosinophilic granulomatosis with polyangiitis, also referred to as Churg-Strauss syndrome, with renal involvement observed in about 45% of total cases. It is associated with ANCA positivity in about 40% to 60% of patients, typically anti-MPO

DRUGS LINKED TO ANCA–ASSOCIATED CRESCENTIC GLOMERULONEPHRITIS

- Treatment is the same as that of other ANCA-associated RPGN cases, but possibly with shorter induction.

The most common offending medications include:

- Hydralazine/Propylthiouracil and methimazole/Allopurinol/Sulfasalazine/Minocycline/ Penicillamine/Rifampicin/Aminoguanidine/Sofosbuvir/

Anti-tumor necrosis factor-alpha (TNF-α) therapy for rheumatoid arthritis and ankylosing spondylitis.

DOUBLE-POSITIVE ANTIBODY DISEASE

- This type of crescentic glomerulonephritis is associated with a positive ANCA and anti-GBM antibody
- Renal manifestations follow an anti-GBM pattern, whereas systemic symptoms are similar to those of ANCA vasculitis

TREATMENT / MANAGEMENT

- Initiating treatment as soon as possible is crucial to preserve renal function. **Immunosuppression therapy** is similar for all 3 disease etiologies
- **Glucocorticoids** are the longest-used and most-studied drugs. Glucocorticoid receptor inhibition helps reduce cellular crescent formation and proliferation and the migration of parietal epithelial cells into the Bowman space. Initial treatment with corticosteroids along with **immunosuppression** results in greater effectiveness and lower rates of relapse. when immunosuppression is contraindicated, **plasmapheresis** is an alternative. The **coadministration of IV corticosteroids and cyclophosphamide** has been the most commonly used regimen

TREATMENT / MANAGEMENT

- Other medications include **azathioprine, methotrexate, cyclosporine, and mycophenolate mofetil.**
- Although immunosuppression along with corticosteroids is the preferred treatment, it may be contraindicated in situations of active infection, leukopenia, or liver dysfunction. Dose adjustments should also be made based on age and renal function. **Cyclophosphamide** can be given orally at a dose of 25 to 100 mg daily or as monthly pulses at a dose of 250 to 750 mg/m^2 intravenously.

PULSED CYCLOPHOSPHAMIDE REDUCTIONS FOR RENAL FUNCTION AND AGE

Age (years)	Creatinine, 1.7–3.4 mg/dL	Creatinine, 3.4–5.7 mg/dL
<60	15 mg/kg/pulse	12.5 mg/kg/pulse
60-70	12.5 mg/kg/pulse	10 mg/kg/pulse
>70	10 mg/kg/pulse	7.5 mg/kg/pulse

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE

- Immunosuppression with **cyclophosphamide plus corticosteroids and plasma exchange ,Rituximab** can be substituted for cyclophosphamide in cases of adverse effects of cyclophosphamide or concerns for fertility in younger patients.
- **Plasmapheresis** is 4 L of an exchange over 2 to 4 weeks. 5% albumin is the replacement fluid, FFP (0.3-2 L) in cases of invasive procedures or pulmonary hemorrhage. Plasmapheresis continues until antibody levels are suppressed or for 14 days.
- **Anti-lymphocytic agent alemtuzumab** halt the progression of anti-GBM disease. **Imlifidase**, an IgG protease approved for severe anti-GBM disease.

IMMUNE COMPLEX CRESCENTIC GLOMERULONEPHRITIS

- Treatment depends on the underlying cause.
  Immunosuppressive treatment is recommended for all causes except infectious agents, which are the most common etiology.

- **Poststreptococcal glomerulonephritis** typically recovers **spontaneously, but glucocorticoids** are used in cases of severely crescentic RPGN.

ANCA–POSITIVE PAUCI-IMMUNE CRESCENTIC GLOMERULONEPHRITIS

Treatment involves the following:

- **Methylprednisolone** IV followed by oral prednisone
- IV or oral **Cyclophosphamide or Rituximab**
- **Plasmapheresis**, if Serum creatinine levels greater than **4 mg/dL**, the requirement for dialysis, pulmonary hemorrhage,coexisting anti-GBM antibodies
- The duration of the therapy is 3 to 4 months, Maintenance therapy is mandatory.

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- ***ANCA levels*** should be monitored **at least every 1 to 3 months** to assess for any signs of relapse.
- B-cell modulators, such as **Rituximab**, may effectively inhibit ANCA-producing plasma cells and decrease antigen presentation.
- **Rituximab** is as effective as cyclophosphamide for disease remission and may be more effective compared to cyclophosphamide in preventing relapse.

DRUGS ASSOCIATED WITH ANCA VASCULITIS

- **After discontinuing** the medication or drug, the RPGN typically resolves.
- If renal function does not improve, **treatment** may be necessary for pauci-immune glomerulonephritis.

DOUBLE-POSITIVE ANTIBODY CRESCENTIC GLOMERULONEPHRITIS

- Treatment for double-positive antibody crescentic glomerulonephritis **the same approach as for pauci-immune glomerulonephritis**, but **plasmapheresis** should be included.
- **Prolonged immunosuppression** and long-term monitoring are crucial, as relapses can occur.

DIFFERENTIAL DIAGNOSIS

- Prerenal acute kidney injury
- Acute kidney injury due to acute tubular necrosis
- Obstructive uropathy
- Nephrotic syndrome caused by focal segmental glomerulonephritis, minimal change disease, or membranous nephropathies
- Hematuria due to a urologic etiology
- Antiphospholipid antibody syndrome
- Thrombotic microangiopathy

PROGNOSIS

- **Age and gender** do not significantly affect prognosis, children typically do better after treatment. **Persistent proteinuria**, despite treatment, indicates poor long-term outcomes. **Renal function** at the time of presentation reflects the severity of the disease, **higher serum creatinine** at presentation, **anuria**, or **dialysis requirement** is associated with a poor outcome.
- The **extent of crescentic** involvement in microscopic findings, **more than 50% normal glomeruli has a more favorable prognosis with 90% renal recovery at a 5-year follow-up. When more than 50% of glomeruli are globally sclerosed, the renal recovery is less than 25% at a 5-year follow-up period.**
- The higher the anti-GBM antibody levels, the **worse** renal outcome. **ANCA levels** that **do not** decrease with treatment or increase post-treatment suggest a more severe disease form. **Relapse in anti-GBM disease is reported less than 3%.**

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- Mortality rate of pauci-immune RPGN Without treatment is **80%**. aggressive immunosuppression increases survival rates to 75% at 5 years. **25% of patients progress to end-stage kidney disease, and worse outcomes are found in older patients, those who require dialysis, and pulmonary hemorrhage. 40% of patients have a disease relapse; therefore, close monitoring is crucial.**

- Mortality in patients with ANCA-associated disease is related to pulmonary involvement, especially in younger individuals. **With immunosuppressive treatment, infection is the most common cause of mortality.**

- Crescentic glomerulonephritis is a known complication of **IgA nephropathy**. If crescents are present **in more than 25% of glomeruli**, the prognosis is **worse**.

COMPLICATIONS

- **Disease-Related Complications**
- **Pulmonary hemorrhage** in cases of **anti-GBM** disease.
- In **lupus-related RPGN**, various immune complex deposits causing the renal **RPGN**,

  These patterns present with **extrarenal manifestations**, serositis, cerebritis, skin lesions.
- **Treatment-Related Complications**
- Complications associated with immunosuppressive therapy **are various opportunistic infections**. **Cyclophosphamide causes cystitis and hematuria**. Older patients are particularly prone to infections and complications arising from cyclophosphamide use. **Plasmapheresis** is associated with removing clotting factors, **increasing susceptibility to bleeding**.

THANKS FOR YOUR ATTENTION