Clinical Considerations for Managing RPGN: Pauci-immune Glomerulonephritis

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Objectives

▶ Explain the pathophysiology behind RPGN, including pauci-immune glomerulonephritis
▶ Differentiate between the various types of RPGN
▶ Recognize the hallmark presentation associated with pauci-immune glomerulonephritis
▶ Identify the measures used to diagnose pauci-immune glomerulonephritis
▶ Describe the modalities used for the treatment of pauci-immune glomerulonephritis
RPGN

- Rapidly Progressive Glomerulonephritis

- Clinical syndrome expressed by
  - Glomerular disease
  - Increase loss of renal function over short time

- Characterized morphologically by crescent formation
  - > 2 layers of proliferating cells in Bowman’s space

Pathogenesis of Crescent Formation

- Non-specific response to major injury to glomerular capillary wall
- Rents are induced in glomerular capillary wall, GBM, & Bowman’s capsule
- Influx of plasma products, macrophages, & T cells into Bowman’s space
- Subsequent fibrin formation & release of pro-inflammatory cytokines

Pathogenesis of Crescent Formation

- **a** Endothelial Cell
- **b** Parietal Epithelial Cell
- **c** Bowman Capsule
- **d** Bowman Space
- GBM
- **b** Plasma Proteins
- Fibrin
- Inflammatory Cells
- Gaps or Holes in GBM Caused by Glomerular Disease
- **c** Interstitial Fibroblast
- Infiltrating Macrophage
- **d** Fibrocellular Crescent
- Proliferating Parietal Epithelial Cells

http://what-when-how.com/acp-medicine/glomerular-diseases-part-3/
RPGN

**Mild – Moderate Disease**
- Crescent formation in < 50% of glomeruli
- Non-circumferential
- Indolent course
- Remission likely

**Advanced Disease**
- Crescent formation in > 80% of glomeruli
- Circumferential
- May not respond to tx
- Poor outcome likely

Anti-GBM Antibody GN

- AKA Goodpasture’s disease
- Anti-GBM antibodies attack collagen
  - Lungs = alveolar basement membrane
  - Kidneys = glomerular basement membrane
- Results in pulmonary hemorrhage & glomerulonephritis
- Eight times more common in males
- Presents in early adulthood

Immune Complex GN

- Immune deposits in glomeruli as result of:
  - Mesangial IgA deposits in IgA nephropathy
  - Anti-streptococcal antibodies & subepithelial humps in post-infectious GN
  - Mesangial + subendothelial deposits in lupus nephritis
  - Circulating cryoglobulins & intraluminal thrombi in cryoglobulinemia

- Others

Idiopathic GN

- An immune complex disease that does not fall in other categories
- Includes pauci-immune disease that is ANCA- negative
- Accounts for < 5% of cases of crescentic GN

Pauci-immune GN

- Necrotizing GN with little to no immune deposits
- Most cases of renal-limited vasculitis are ANCA- positive
- **Antineutrophil Cytoplasmic Antibody**
  - Attack inside of neutrophils
  - WBC’s attack walls of small vessels of various organs
- For kidney: causes hematuria/proteinuria with renal failure
- 75-80% are MPO-ANCA positive
  - Systemic symptoms
- Drug-induced: PTU, hydralazine, allopurinol, penicillamine, minocycline

Clinical Presentation

Common Sx
- Fatigue & edema with insidious onset
- Renal insufficiency (SCr >3 mg/dl)*
- Systemic manifestations
  - Pulmonary, musculoskeletal, skin, nervous system
  - Granulomatosis with polyangitis or MPA
- U/A reveals proteinuria, hematuria with dysmorphic RBCs & casts

Less Common Sx
- Acute onset of gross hematuria & ↓ U/O
- Nephrotic syndrome

If pt presents with clinical symptoms suggestive of RPGN
- URGENT appropriate serologic tests needed
  - ANCA
  - Anti-GBM antibodies
  - Complement component assays
  - Antinuclear antibodies
- Renal biopsy (if needed)
Treatment

- Induction of remission (3 – 6 mo.)
- Cyclophosphamide IV 0.75 g/m² Q 3-4 weeks
  - Less leucopenia & fewer infections
- Cyclophosphamide PO 1.5-2 mg/kg/d
  - Less risk of remission or need for RRT
- Methylprednisolone IV 500 mg daily x 3 days
- Prednisone PO 1 mg/kg/d x 4 weeks (max dose: 60 mg)
- Rituximab 375 mg/m² weekly x 4
- Plasmapheresis 60 ml/kg volume replacement
  - Diffuse alveolar hemorrhage or SCr > 5.66 mg/dl
- IVIG 2 g/kg x 1 for resistant cases

Treatment

- Prevention of relapse aka maintenance tx (6-18 mo.)

- Risk factors for relapse:
  - Persistence of PR3-ANCA, h/o of URT dx or LRT dx

- Azathioprine PO 1-2 mg/kg/d first line

- MMF PO up to 1 GM BID second line

- Methotrexate PO initially 0.3 mg/kg/wk (max: 25mg/wk) third line

- Bactrim as adjunctive tx for pts with URT dx

Treatment

- **Severe relapses from remission:**
  - Same tx as initial therapy for induction
  - Rituximab > cyclophosphamide
    - Cumulative dosage of cyclophosphamide approaching 36 GM

- **Other relapses from remission:**
  - Restart IMS
  - Corticosteroids > cyclophosphamide

Rituximab is recommended first line for induction tx for severe cases

Cyclophosphamide no longer used after 3 mo. induction tx in HD pts with no extra-renal sx

No maintenance tx for HD pts with no extra-renal sx

Plasmapheresis for ANCA-vasculitis + anti-GBM antibody dx

Avoid using ANCA titer alone to change IMS tx
Take Home Points

- RPGN is a serious disease that can lead to irreversible renal damage

- Current therapies are potentially lengthy & associated with significant risks

- Treatments are often individualized pending pt preference & tolerance

- Pharmacists can play an integral role in helping pts choose appropriate therapy
  - Decrease adverse effects
  - Increase compliance
  - Save health care costs
JM is a 54 YO male admitted to Hixson Campus with CC of left sided paresthesia

PMH significant for: HA, blindness in L eye, deafness in L ear, COPD, chronic back pain s/p spine fx, depression/anxiety, wt loss of 40 lbs, anemia, Hepatitis C, & substance abuse

Within 10 days of admission, SCr increases from 0.9 – 2.0

Lab work reveals MPO-ANCA +

Pt sent to Glenwood for renal biopsy & possible HD
Patient Case

- JM receives Solu-medrol 1000 mg daily x 3 days initially while awaiting biopsy results
  - Was this appropriate?
- Biopsy confirms pauci-immune GN with ATN
- JM receives Cytoxan 2 GM IV x 1 with plasmapheresis, & PO steroids
  - Was this appropriate? (Hint: his BSA: 1.74)
  - Should pt have received Mesna?
- Despite all these therapies, JM must go on chronic HD
  - If JM does not have extra-renal manifestations, how long do we continue Cytoxan tx while he’s on HD?
Patient Case- Answers

- According to guidelines: NO. 500 mg IV daily is recommended as 1000 mg doses have not shown to be superior & are associated with more AE's.

- According to KDOQI guidelines-no. Cytoxan is dosed 0.75 g/m\(^2\) \(1.74\) = 1.3 GM. Pt received significantly higher dosage. However, in practice it can be given as high as 1 g/m\(^2\) \(1.74\) = 1.74 GM, so pt still got higher dosage than typically used.

- NO. Mesna is really reserved for pts receiving high doses of Cytoxan (such as 1.5 – 2 g/m\(^2\)).

- After 3 months, it is recommended to D/C Cytoxan for pts on HD with no extra-renal manifestations due to lack of any clear benefit in this pt population.