Case 2

Diarrhoea Negative HUS : Unusual presentation on renal biopsy

Nanda Kachare,
Annie Jojo, Seethalekshmy NV.,
Susan Uthup*, Satish B.*
Department of Pathology, Amrita Institute of Medical Sciences,Kochi,
Department of Nephrology* SAT and KIMS, Trivandrum ,* Kerala.
INTRODUCTION

Haemolytic uremic syndrome (HUS)

• clinical syndrome -
  Microangiopathic hemolytic anemia,
  Thrombocytopenia,
  Acute renal failure.

• Typical HUS- diarrhoeal illness (d+ HUS),
  precipitating organism the toxin-producing *Escherichia coli* serotype 0157

• Atypical HUS (aHUS)
  Non-Shiga like toxin producing HUS
  D–HUS (diarrhea-negative HUS).
Atypical HUS -
5%-10% of total HUS

- genetic, acquired, or idiopathic
- **Genetic** -
  - multiplex familial; two or more affected family members
  - simplex - a single occurrence in a family.
- **Acquired** - underlying environmental factor such as drugs, systemic disease, viral agents, or bacterial agents other than Shiga-like exotoxins (Stx)
- **Idiopathic** - unknown cause
Case

- 9 yr old female child
- Oliguria, hematuria - 1 wk
- Fever, vomiting - 1 wk
- No H/O Diarrhoea

INVESTIGATIONS -
- Hb - 4.2 gm/dL
- TLC - 12,500/cmm
- Platelets - 65,000/cmm
Peripheral Smear - E/O hemolysis, **schistiocytes ++**

Urine RBCs - **Numerous**

24 hr proteins - **3.2 gm**
Serum urea - 177mg/dL
Serum creatinine - 2.5mg/dL

Serum LDH - 2960 U/L
Serum C3 levels - **markedly reduced**

ANA profile - Negative
USG Abdomen - CMD +, Increased echotexture
• Clinical Diagnosis - Atypical Hemolytic Uremic Syndrome

• Renal biopsy done
PAS
Jone’s silver
Granular capillary wall & mesangial C3
Salient Microscopic Features

- Enlarged glomeruli,
- Mesangial Hypercellularity,
- Lobular accentuation
- Thickened basement membranes
- Splitting, double contours,
- Mesangial interposition

**Immunofluorescence** - granular capillary wall and mesangial C3, IgM, IgG
• Diagnosis on Renal Biopsy

Membrano-proliferative Glomerulonephritis

(In a clinical set up of aHUS)
HUS Vs MPGN

Morphological distinction:

- Lack of mesangial hypercellularity
- Focal basement membrane splitting and double contours
- Negative Immunofluorescence for C3 and IgM
DISCUSSION

• Renal biopsy in D-HUS-

• Glomeruli - thrombosis, intracapillary foam cells, endocapillary swelling, endocapillary hypercellularity, mesangiolysis, doubled basement membranes.

• Arteries - intimal swelling with hypercellularity thrombosis.

• Arterioles - Thrombosis, fibrinoid necrosis.
Glomerular paralysis

Splitting BM

Thrombosis
• why some such patients develop HUS and others develop MPGN remains uncertain.

• In our patient condition evolved from clinical manifestations of HUS to a renal biopsy showing MPGN.

• Shared etiological mechanisms?
CFH deficiency -

• MPGN -
  Homozygous *CFH* mutations
  Severely reduced CFH levels.

• aHUS -
  Homozygous /heterozygous CFH mutation
Factor H & aHUS

- Factor H deficiency - 1981 - first described in 2 patients with familial aHUS, the relevance wasn’t appreciated until 1998.

- Poor prognosis
  - ~25% early mortality
  - ~50% progression to ESRD

- ~80% - risk of recurrence after renal transplantation
A Brief Review of the Complement Cascade:

- **Classical pathway** - C1 complexes- immune complexes
- **Lectin pathway** - binding of mannose-binding lection to bacteria
- **Alternative pathway** - interaction between C3b and pathogens / tumor cells
- **Final Common pathway** - cleavage of C3 subsequent formation of membrane-attack complex.

Factor H-

• Important regulator of the alternative pathway

• Acts by accelerating the breakdown of C3bBb, the alternative pathway C3 convertase - the rate-limiting enzyme

• Cofactor for Factor I - cleaves C3 to the inactive iC3b form.

• Factor H deficiency - HUS, CGN, MPGN

Collagen glomerulopathy
Factor H

- Synthesis - hepatocytes, macrophages, fibroblasts, endothelial cells, platelets.

- Plasma concentration ~ 500 µg/ml.

- ~ 20 complement control protein repeats CCPs

- On chromosome 1q32.
Factor H - Control Protein Repeats

Del124/132Stp He Case 9
Arg127Leu Ho Cases 3,4

C3b

RGD

Heparin

C3b

C3b

Heparin

Heparin

Gln400Lys He Case 16
Cys431Ser Ho Case 5

Cys673Tyr He Case 12
Cys673Ser Ho Case 6

+A2303/774Stp He Case 8

His893Arg He Case 11
His893Arg He Case 15
Tyr899Stp Ho Cases 1,2
Cys915Ser He Case 10
Gln924STP He Case 7

Phe1199Ser He Case 13
Trp1183Leu He Case 14
Factor I

- Synthesis - hepatocytes
- 12 mutations.
- Heterozygous FI mutations
- Chromosome 4q25.
- Poor prognosis
- recurs after renal transplantation
GRAY ZONES

- aHUS with homozygous mutations in $CFH$ and very low levels of circulating protein - blur the distinction between HUS and MPGN.

- Overlap in phenotypes - Evident in those few individuals who have a mixed diagnosis of aHUS and MPGN in the same biopsy or in biopsies taken at different points in time.
CONCLUSION

- Difficult to predict the outcome aHUS based on the clinical findings alone
- Renal biopsy examination helps in determining the long-term outcome.
- Factor H assay may be helpful in management of aHUS.
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