Evolution of Atypical Hemolytic Uremic Syndrome

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Learning Objectives
1. Review TTP-HUS classification
2. Consider atypical HUS (aHUS) in the setting of persistent progressive STEC HUS
3. Recognize indications for Eculizumab

Case Description
A 25 year old woman with PMH of HTN, hyperthyroidism, fibromyalgia required hemodialysis -HUS classification
- ADAMTS 13 mildly decreased suggestive of non-STEC HUS
- 6 days later was found to have anuric renal failure (Scr 10.1, BUN 104), anemia (Hct 26.1 from 33.9) and thrombocytopenia (128 from 270), was then transferred to OHU and started on hemodialysis
- Was discharged on day 21, Hct and Platelets had been stable at that time, though still anuric and required hemodialysis 3 times a week
- Treatment consisted of conservative measures including hemodialysis and transfusions. No antibiotics or phlebotomy was provided

Past Medical History
- HTN, hyperthyroidism, fibromyalgia

Medication
- Clonidine
- Hydrocortisone-isonalmonphen
- Lorazepam
- Metoprolol succinate
- Nifedipine
- Ondansetron
- Thyroid tablet

Social History
- Nonsmoker, no alcohol or illicit drug use

Physical Exam
- BP 165/92, RR 16, SpO2 91%
- T 36.7 °C (98.1 °F), RR 16, SpO2 91%
- Gen: pleasant pale female sitting up in bed with moderate respiratory distress - unable to speak full continuous sentences without taking a breath.
- HEENT: prominent periocular sclera, mmm, minimal conjunctival pallor
- CV: systolic LS, mmm, normal jugular excursion
- Lungs: CTA B/L
- Abd: soft, NT, ND
- Ext: skin: pale but good cap refill, no rashes

Labs
- Hct/Hb 19.5/8.2 (from 29.8/9.7 prior to discharge)
- PL 76 (from 163), retic count 2.2
- LDH 315 (from 406), haptoglobin <30
- C3 123 (WNL), CD46 (MCP) present (NL)

Figure 1 - Classification of Timas
- TMA are diagnosed by thrombocytopenia, hemolysis, and schistocytes on peripheral smear
- HUS is characterized by the triad of MAHA, thrombocytopenia and AKI

Figure 2 - The alternative pathway (AP)
- The AP begins with activation of C3 and leads to assembly of the membrane attack complex (MAC) as a mechanism for prevention from infectious agents
- In aHUS continuous formation of MAC causes renal endothelium damage leading to activation of the coagulations cascade and thrombotic microangiopathy

Background of aHUS

Pathophysiology
- The pathophysiology of aHUS is explained by uncontrolled complement activation on endothelial cell surface

Epidemiology
- aHUS affects both children and adults, increased ratio of female patients in adult years
- The permeability of genetic mutation of the disease is only 50%

Clinical Features
- Triad of MAHA, thrombocytopenia, and renal impairment
- Other symptoms include CNS involvement, GI symptoms, MI

Diagnosis of atypical HUS
- About 60% of patients with aHUS carry mutations in genes encoding regulatory proteins of the alternative pathway of complement
- Complement factor H (CFH) mutations are the most common and account for 25-37% of mutations, less common mutations include MCP, CFI, C3, CFB, and thrombomodulin mutations

Absence of shiga-toxin
- There is no specific acute marker to differentiate aHUS from the other, so treatment strategy for HUS will depend on the clinical presentation and presumed diagnosis

Treatment
- Plasmapheresis
- Eculizumab
- Liver transplantation, which will provide a source of normal protein

Prognosis
- About 50% of cases progress to ESRD
- Up to 25% may die during the acute phase

Discussion
This case illustrates a primary case of STEC HUS which was found out one month later to have persistent progressive MAHA and thrombocytopenia. It is known that hematocrit manifestations of STEC HUS usually resolve within 2 weeks of the acute episode, as patients produce neutralizing anti-STEC antibodies which protect from STEC HUS recurrences. Therefore, this severe clinical picture of HUS would be explained by a development of secondary atypical HUS that was triggered by conditions of complement activation and vascular endothelium damage in genetically susceptible people.

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References