Refractory Diarrhea: When Rotavirus Goes Rogue

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Disclosures

We have no relevant financial relationships with the manufacturer of any commercial product and/or provider of commercial services discussed in this CME activity.
History of Present Illness

• 6 week old healthy baby boy presented with 36 hours of profuse, watery diarrhea, 20+ episodes per day
• Non bloody, yellow colored, watery stools
• Afebrile, eating well. Breast fed with some formula supplementation.
• No vomiting. No sick contacts. No travel. No animal exposure.
• Born full term via primary C-section, serology/GBS negative, no complications

Physical Exam

• **General:** No acute distress, social smile.
• **Eye:** Pupils are equal, round and reactive to light, Normal conjunctiva.
• **HENT:** Normocephalic, Oral mucosa is moist. Anterior fontanel depressed
• **Neck:** Supple.
• **Respiratory:** Lungs are clear to auscultation, Respirations are non-labored, Breath sounds are equal.
• **Cardiovascular:** Normal rate, Regular rhythm, No murmur.
• **Gastrointestinal:** Soft, Non-tender, Non-distended.
• **Genitourinary:** Normal genitalia for age and sex, No scrotal tenderness, circumcised.
• **Lymphatics:** No lymphadenopathy neck, axilla, groin.
• **Musculoskeletal:** Normal range of motion. Normal strength.
• **Integumentary:** Warm, Dry, Pink, Intact.
• **Neurologic:** Alert, Moves all extremities appropriately.
Initial Labs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca++</td>
<td>9.7</td>
</tr>
<tr>
<td>AST</td>
<td>48</td>
</tr>
<tr>
<td>ALT</td>
<td>33</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>387</td>
</tr>
<tr>
<td>T.Bili</td>
<td>1</td>
</tr>
<tr>
<td>Alb</td>
<td>3.2</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>38</td>
</tr>
<tr>
<td>Bands</td>
<td>6</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>43</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>1</td>
</tr>
</tbody>
</table>

Ova and parasite: Negative
Stool culture: Moderate normal intestinal flora, no Salmonella, Shigella, or Campylobacter isolated.

Rotavirus Antigen: Positive

Hospital Course

Admitted for severe dehydration with rotavirus positive gastroenteritis
- HD 2: transition from similac to soy based formula (concern for temporary lactase deficiency 2/2 rotavirus)
- HD 4: developed severe hypovolemia with metabolic acidosis, hyperkalemia and hyperchloremia; transferred to PICU.

Subsequent prolonged hospitalization for fluid management and TPN for nutritional support while work-up progressed. Hospital course complicated by persistent diarrhea, failure to thrive, hepatitis, hypoalbuminemia, anemia, recurrent infections.
- HD 10: normal IgG
- HD 15: normal lymphocyte subset panel, elevated IgA, IgE
- HD 22: dermatology consulted for rash consistent with miliaria
- HD 25: low-normal mitogen response panel
- HD 26: initial endoscopy with diffuse villous atrophy and inflammatory changes
- HD 25-39: development of diffuse xerosis, lichenification and scaling with progressive eosinophilia
# Immune Workup

- Newborn screens normal
- Immunoglobulins:

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Interpreted Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin G and M</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin E</td>
<td>High (2128 ku/L)</td>
<td>&lt;=13</td>
</tr>
<tr>
<td>Immunoglobulin A</td>
<td>High (63 mg/dL)</td>
<td>3-47</td>
</tr>
</tbody>
</table>

## Immune Workup, continued

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Interpreted Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute and % CD2, CD3, CD4, CD8, CD19, CD45RA, CD45RO, HLA-DR</td>
<td>Normal</td>
</tr>
<tr>
<td>Absolute and % Natural Killer cells</td>
<td>Normal</td>
</tr>
<tr>
<td>Lymphocyte Ag and Mitogen Panel</td>
<td>Absent lymphocyte responses to Candida, Low lymphocyte responses to Tetanus, Low-normal lymphocyte responses to PHA, Normal lymphocyte responses to ConA, Normal lymphocyte responses to Pokeweed Mitogen</td>
</tr>
<tr>
<td>% CD4+CD25+CD127LowCD45RO+ (N Tregs)</td>
<td>Low (1.6 % of CD4+) [reference interval 2.4-8.7]</td>
</tr>
</tbody>
</table>
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image

- Will insert image from pathology
Duodenal Mucosal Biopsy

- Diffuse epithelial injury and patchy necrosis
- Poor preservation of ultrastructural detail
- Marked reduction of microvilli on enterocytes
- Small to moderate sized vacuoles suggestive of lipid vacuoles in a few enterocytes
- No microvillous inclusions or diagnostic viral inclusions seen

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Regulatory T-Cell Panel

Further Work-Up

- Anti-enterocyte antibodies: negative
- SCID panel: negative
- Very Early Onset IBD panel—takes 12 weeks to obtain results—returned after results of whole exome sequencing available—pathogenic variant detected
Whole Exome Sequencing

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic Change</th>
<th>Zygosity</th>
<th>Coding Change</th>
<th>Protein Change</th>
<th>Classification</th>
<th>Inherited From</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOXP3</td>
<td>chrX:491119_58delCTT</td>
<td>Hemizygous</td>
<td>NM_014000.3:c.748_750delAA</td>
<td>p.Lys250del</td>
<td>Pathogenic</td>
<td>De novo</td>
</tr>
</tbody>
</table>

- De novo hemizygous variant in the FOXP3 gene
- Hemizygous c.748_750delAAG (p.Lys250del) variant in FOXP3 not previously observed in general population
- Has been reported as disease causing for IPEX syndrome in one symptomatic individual.

Nutritional Course

- Admitted with EBM and Similac supplementation
- HD 2: transition to soy based formula (concern for temporary lactase deficiency secondary to rotavirus)
- HD 4: NPO or TPN
- HD 11: small trials of EBM
- HD 13: Flecks of blood in stool so EBM transitioned to Nutramigen
- HD 16: Retrial EBM, blood returned, Neocate initiated
- HD 25: EBM resumes (goal to increase PO given poor taste for Neocate)
- HD 30: Neocate resumed, via NGT given poor PO (concern for disaccharidase deficiency given diffuse enteral inflammation)
- HD 35: Trial of carbohydrate free formula, not tolerated due to emesis
- HD 38: Neocate resumed
- HD 38-40: NPO with bacteremia, blood in stool, no signs of pneumonias on serial KUBs
- *ongoing profuse diarrhea as enteral feeds advanced. Large component of secondary osmotic diarrhea given diffuse villous atrophy from inflammatory changes
- HD 41: enteral feeds resume with Mead-Johnson 3232A (trickle feeds with 1-5ml/hr and very slowly advanced)
- No improvement, ultimately transitioned back to Neocate diluted to 10kcal/oz, never surpassing 5ml/hr without subsequent increase in output
- HD 75: DIAGNOSIS
- HD 79: Steroids and immunosuppression initiated
- HD 133: Solid foods (age 5.9 months)
- HD 140-145: TPN discontinued, IVF discontinued, central line removed
- HD 147: Discharged home on continuous Neocate feeds 20kcal/oz
Immune Dysregulation
Polyendocrinopathy Enteropathy
X-linked Syndrome
(IPEX Syndrome)

IPEX Syndrome

- Extremely rare monogenic primary immunodeficiency
- Caused by mutations in gene for T regulatory (Treg) cells-FOXP3
- Hallmark of disease is multi-organ autoimmunity due to malfunctioning T regulatory cells
IPEX Syndrome

• Classic triad
  – Severe enteropathy
  – Endocrinopathy such as Type I DM
  – Dermatitis

• Published case reports are limited
  – Incidence and prevalence difficult to establish

• Poor prognosis

IPEX presentation and course

• Birth typically unremarkable

• Symptom onset in 1st months of life
  – Chronic intractable diarrhea is common presentation
  – Type I DM and eczematous dermatitis can also be presenting symptoms

• Course characterized by disease flares/fluctuations
  – Variety of potential triggers
  – New symptoms can present over time
Presentation and course

- Varied phenotypes
  - Autoimmune disease
  - Allergic inflammation

- Other clinical manifestations
  - Failure to thrive
  - Severe food allergy
  - Thyroiditis
  - Immune mediated cytopenias
  - Increased infections
    - Enterococcal and staphylococcal species, cytomegalovirus (CMV), and Candida
    - Nephritis

Differential Diagnosis

- Diagnosis is challenging if patients present with single symptom
  - Vast differentials for infantile enteropathies and erythroderma
  - DDx for enteropathy includes infection, food allergy, celiac disease, inflammatory bowel disease, eosinophilic enteropathy
  - Multiple genetic syndromes associated with neonatal diabetes
- IPEX-like syndromes
- Other rare syndromes
  - NOMID/CINCA, ALPS, APS I or APECED
- Immune deficiency
  - SCID, Omenn syndrome, Netherton Syndrome
Evaluation and Diagnosis

- Extensive preliminary evaluation
  - CBC
  - Glucose, anti-islet cell antibodies
  - TFTs and thyroid antibodies
  - Antienterocyte antibodies
  - Immunoglobulins
  - Food hypersensitivity testing
  - Lymphocyte subsets and proliferation assays

- Advanced investigation
  - Endoscopy with biopsies
  - Skin biopsy
  - Regulatory T cell immunophenotyping and functional studies
  - Genetic sequencing of FOXP3 gene required for definitive diagnosis

Management

- Immune suppression is hallmark of treating acute flares
  - Presence of invasive infections can pose a dilemma
- Enteropathy flares managed with gut rest and TPN
- Long term management
  - Glucocorticoids, calcineurin inhibitors or sirolimus
  - Hematopoietic stem cell transplantation
    - Only curative therapy for patients with IPEX
    - High morbidity and mortality
    - Early HSCT provides better outcomes
    - Endocrinopathies may persist after successful transplantation
Pathogenic Autoantibodies Identified in Patients with IPEX

- Pancreas- GAD65, Insulin, Islet cell cytoplasmic antibodies (ICA), IA-2A
- Thyroid-Thyroglobulin, Thyroid peroxidase, TSH Receptor
- Liver= Liver/Kidney Microsomal (LKM), Smooth Muscle (SM), Mitochondrial

Pathogenic Autoantibodies Identified in Patients with IPEX

- GI- Anti-enterocyte, Anti-goblet cell
- Hematologic- Direct and Indirect Coombs
- Hypercoagulability-Anti-phospholipid antibody panel (Anti-β2 glycoprotein 1), Anti-cardiolipin, Lupus anticoagulant (Dilute Russel Viper Venom Time, DRVVT)
### Lab test results

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<tr>
<th>Lab test</th>
<th>Interpreted Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Thyroglobulin</td>
<td>&lt;3.0</td>
<td>3.0-20.0</td>
</tr>
<tr>
<td>Thyroid Peroxidase-G</td>
<td>0.3</td>
<td>0-9</td>
</tr>
<tr>
<td>Anti-Islet Cell Ab</td>
<td>&lt;1:4 (Normal low)</td>
<td></td>
</tr>
<tr>
<td>Glutamic Acid Decarboxylase Antibody (GAD)</td>
<td>&lt; 5 IU/mL</td>
<td>0.0-5.0</td>
</tr>
<tr>
<td>IA-2 Antibody</td>
<td>&lt;0.8 U/mL</td>
<td>0.0-0.8</td>
</tr>
<tr>
<td>Insulin Antibody</td>
<td>&lt; 0.4 U/mL</td>
<td>0.0-0.4</td>
</tr>
<tr>
<td>F-Actin (Smooth Muscle) Ab, IgG by ELISA</td>
<td>21 units (weak positive) *</td>
<td>0-19</td>
</tr>
<tr>
<td>Liver-Kidney Microsome-1 Ab, IgG by ELISA</td>
<td>1.6 units</td>
<td>0 – 24.9</td>
</tr>
<tr>
<td>Mitochondrial (M2) Antibody, IgG</td>
<td>5.3 units</td>
<td>0-20</td>
</tr>
<tr>
<td>Smooth Muscle Ab, IgG titer</td>
<td>1:20 (weak positive) *</td>
<td>&lt; 1:20</td>
</tr>
<tr>
<td>Direct Coombs (DAT IgG)</td>
<td>Positive *</td>
<td></td>
</tr>
<tr>
<td>Anti Enterocyte antibody</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

### Current patient status

- Our patient was diagnosed on hospital day 75 and initiated on immunosuppression on hospital day 79
- He demonstrated steady improvement in stool output and feeds were very slowly advanced and fortified
- On hospital day 133 he was able to initiate solid foods (purees) at age 5.9 months of age
- On hospital days 140-145 labs were closely followed while TPN was discontinued, IVF were discontinued and his central line was removed
- He was discharged home 147 days after his initial presentation on tacrolimus and continuous Neocate feeds at 20kcal/oz with an HLA matched donor identified and plans for relocation to a specialty stem cell transplant center for HSCT
Questions?

References


