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Case 3

- A seven month old white male presents with weight loss and protracted diarrhea since 3 weeks of age with heme positive stools and failure to thrive. He is on parenteral nutrition and Neokate. He has been tested for allergies and has a positive RAST test for cow’s milk and rice. There was no response initially to intravenous steroids, but has now been maintained on IVIG and steroids. A biopsy was done with the goal of assessing the disease and cause of the protracted diarrhea. An outside biopsy done at 2 months of age had shown villous alterations in the duodenum and prominent eosinophilia. A repeat upper endoscopy is performed and a representative biopsy of the duodenum is submitted. A subsequent lower GI biopsy was performed 2 years later and a representative image of the colon is provided.
Diagnosis

Autoimmune enteropathy associated with IPEX syndrome

Intractable diarrheas of infancy

- Definition: Noninfectious diarrhea lasting for more than 2 weeks, with onset before a few months of age, with consequent malabsorption and failure to thrive. (Avery et al. 1968)
- Includes a diverse group of conditions many of which have genetic and familial basis.
Causes of protracted diarrhea beginning during the first 6 months of life

- Normal villous-crypt architecture:
  - Transport defects:
    - Chloride-bicarbonate exchanger (chloride-losing diarrhea)
    - Sodium hydrogen exchanger (congenital sodium diarrhea)
    - Ileal bile acid receptor defect
    - Sodium-glucose cotransporter (glucose-galactose malabsorption)
  - Micronutrient deficiency
    - Acrodermatitis enteropathica (zinc deficiency)
  - Congenital short bowel

- Villous atrophy
  - Microvillous inclusion disease
  - Tufting enteropathy
  - Autoimmune enteropathy
  - IPEX syndrome
  - Infectious enteropathy
  - Allergic enteropathy
  - Idiopathic

AIE

- Term proposed by Unsworth et al.
- Protracted diarrhea with presence of autoantibodies against gut epithelium, with or without other system involvement
- Villus atrophy a feature e.g. IgA deficiency
- Most cases occur in infancy though some later in life
- Strong male predisposition, family history +, circulating antibodies
- Some cases of refractory sprue – AIE
- Anti-enterocyte antibody – detected by indirect immunofluorescence using patient’s serum on frozen sections of normal human bowel. Positive staining is a linear pattern along the apex and basolateral aspect of enterocyte
- Antibody is predominantly IgG but can be IgM and IgA.
- Antibody may wax and wane or disappear over time; or may be delayed so repeat testing needed if negative at diagnosis
- No HLA association like celiac

Pathology:
- Villous alterations and blunting and atrophy variable
- Crypt hyperplasia present
- Marked inflammatory destruction of crypts and epithelium (resembling IBD in cases)
- Hallmark is numerous crypt apoptoses (similar to GVHD or drug-induced injury)
- Ulceration may be seen in severe cases.
- Absence of Paneth cells, goblet cells and enterochromaffin cells.
- Atrophic gastritis pattern may also be seen
- Apoptosis evident throughout the GI tract from stomach to rectum

Case illustration

- An 8 month old girl presents with diarrhea with failure to thrive. She was status post repair of double outlet right ventricle early in her life. An endoscopy revealed a parched earth appearance of the duodenum, but the lower endoscopy was normal.
Duodenum with crypt showing multiple apoptosis and lymphocytic infiltrate

Crypts with apoptosis and neutrophilic infiltrate

Increased intraepithelial lymphocytes only rarely seen
Lymphocytic gastritis

Colon with lymphocytic colitis and apoptosis (arrow)
Another example

- A 14 month old male presented with severe failure to thrive, chronic secretory diarrhea and an endoscopy showed a cracked appearance of the duodenum with erosions in the rectosigmoid.
Initial diagnosis: Possible Autoimmune enteropathy

Case Contd.

- This patient went on to develop autoimmune thyroid disease, dyslipidemia, additional family members with autoimmune disease
- Reported to be anti-enterocyte antibody positive, anti-smooth muscle antibody positive and pANCA positive
- Steatotic liver but diabetes excluded.
- Low immunoglobulins
- A genetic test done

IPEX syndrome

- Immune dysregulation, polyendocrinopathy, enteropathy and X linkage
- Enteropathy cannot be differentiated from AIE.
- Mutation of the FOXP3 gene (scurfin) – results in the absence or dysfunction of regulatory T cells.

IPEX

- model of genetic autoimmunity
- primary immunodeficiency caused by mutations in the gene FOXP3
- tTreg cell dysfunction is the main pathogenic event
- FOXP3 is located in the centromeric region of the X chromosome (Xq11.3–q13.3).
IPEX

• similar clinical findings in males belonging to the maternal lineage, while females are usually healthy.
• May present at birth or in the first days of life
• High prevalence of miscarriages, often due to hydrops
• can be rapidly fatal if not diagnosed and treated.
• triad of clinical manifestations: intractable diarrhea, Type 1 Diabetes (T1D), and eczema
• Autoimmune enteropathy is a hallmark of IPEX syndrome.
• neonatal watery and sometimes mucoid or bloody diarrhea – results in malabsorption and failure to thrive – requiring TPN
• T1D related to inflammatory destruction of pancreas
• Dermatitis – eczematous, ichthyosiform, psoriasiform or any combination – superimposed infections.
• Other autoimmune manifestations: hypothyroidism, AIHA, autoimmune cytopenias; autoimmune hepatitis, membranous GN, arthritis

IPEX Pathology – GI tract

• Total or subtotal villous atrophy; mucosal lymphocytic or eosinophilic infiltration
• 3 patterns of involvement:
• GVHD pattern: with prominent crypt injury and apoptosis with Paneth cell loss; cryptitis and abscesses, LP mixed cellular infiltrate, gastritis and colitis
• Celiac pattern: subtotal villous atrophy, marked LP cellularity with L+PC+N+E. Increased intraepithelial lymphocytes.
• Enteropathy with intestinal goblet cell antibodies: subtotal villous atrophy, moderate LP cells L+PC; increased intraepithelial lymphocytes. Total goblet cell depletion, seen also in the stomach and decreased numbers in colon.

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AIE

Differential:
1. Celiac disease – similar villus changes but with increased IEL (not typically seen in AIE); rare crypt apoptoses only. Elevated TTG. Caveat is IgA deficiency
2. Cow’s milk protein allergy: can mimic AIE with villous changes and inflammation. No increase in IEL and no antibodies. Allergen testing or milk substitute – therapeutic trial
3. IBD: similar inflammatory changes but no significant villous alteration; age of presentation is different; cryptitis, crypt abscess and granulomas; rare apoptoses in IBD.
Milk protein allergy

- Important differential to keep in mind.
- Usually with eosinophils but these may appear late.
- Can present early
- Treatment with neocate formula helps
- No anti-enterocyte antibody.

Primary immunodeficiency disorders with prominent gastrointestinal manifestations

Antibody deficiencies:
- X-linked agammaglobulinemia
- IgA deficiency
- Immunodeficiency with elevated IgM
- Transient hyperimmunoglobulinemia of infancy
- IgG subclass deficiency

Combined immunodeficiencies:
- Severe combined immunodeficiency

T-cell disorders:
- Wiskott-Aldrich syndrome
- Ataxia telangiectasia
- DiGeorge syndrome

Disorders of phagocytic function:
- Chronic granulomatous disease
- CD11/CD18 leukocyte adhesion molecule deficiency
- Hermansky-Pudlak syndrome
- Glycogen storage type III

Others:
- Chronic mucocutaneous candidiasis
- Autoimmune polyendocrinopathy/candidiasis/ectodermal dystrophy (APECED) – AIRE gene
- JTC1 deficiency recently described
Onset Neonatal Neonatal 6-12 mo
Consanguinity or family history Frequent Frequent Rare
M:F 1:1 1:1 M>F
Extraintestinal disease Yes No Yes
Anti-enterocyte Ab No No Yes
Villous atrophy Moderate Moderate Moderate to severe
Surface epithelium N with no brush border Tufts Normal
Intraep lymph Normal Normal N or Increased
Crypts Normal Branching Apoptosis
LP cellularity N N Increased