INFLAMMATORY BOWEL DISEASES OF INFANCY AND CHILDHOOD
Basel Seminars in Paediatric Pathology and Genetics

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INFLAMMATORY BOWEL DISEASES OF INFANCY AND CHILDHOOD - OUTLINE

- Iatrogenic disorders
- Ischemic and vascular diseases
- Eosinophilic (allergic) gastroenteritis
- Immunodeficiency syndromes
- Inflammatory Bowel Disease in children
  - Very early onset (VEO) colitis
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## Histologic Patterns of drug-induced colitis

### Epithelial apoptosis
- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Mycophenolate Mofetil
- Chemotherapeutic agents
- Colchicine
- Laxatives (anthranoids)

### Non-specific acute colitis
- NSAIDS
- Antimicrobials
- Laxatives
- Saline enemas

### Erosions and ulcers
- NSAIDS

### Eosinophilic colitis
- Clozapine
- Carbamazepine
- NSAIDS
- Tacrolimus

### Lymphocytic colitis
- NSAIDS
- Proton pump inhibitors

### Inflammatory bowel disease-like pattern
- NSAIDS
- Mycophenolate mofetil (MMF)
- Diclofenac

### Fibrosing colonopathy
- Pancreatic enzyme supplements
Iatrogenic disorders: Changes induced by bowel preparation

- Surface epithelial mucin depletion
- Mild superficial inflammation and hemorrhage

Phosphosoda-induced changes
Drug-induced colitis

NSAIDS
- Non-specific colitis
- Increased basal apoptosis
- Collagenous and eosinophilic colitis
Drug-induced colitis

Mycophenolate Mofetil (MMF)
degenerating crypts
basal apoptosis
may mimic GVHD

15 yo carried a dx of IBD
persistent symptoms
biopsy to assess activity
and response to Rx
Graft vs Host Disease (GVHD)
Diversion colitis

2 yr old female with mucus fistula following imperforate anus repair
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Ischemic disease – Henoch-Schonlein Purpura

Most common vasculitis in children
Median age 4 yrs
Rash, arthritis, abdominal pain, nephritis
Ulcers
Acute cryptitis to ischemic necrosis
Vasculitis of small vessels and arterioles
Behcet’s disease

- Usual onset 20’s – 30’s
- Turkey, SE Asia
- HLA B51
- Vasculitis unknown etiology
- Oral, genital ulcers, ocular inflammation, arthritis
- GI involvement 5% - 25%
- Terminal ileum, right colon
- Neutrophilic/lymphocytic infiltrate of small vessels
- Inflammation mimicking IBD
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Eosinophilic Gastroenteropathies
The New Epidemic

Spectrum of disease or unique diseases

Colón

Allergic proctocolitis  Eosinophilic gastroenteritis

Eosinophilic esophagitis
### Eosinophilic Gastroenteritis

- Usually occurs from infancy through adolescence  
  (most frequent in 3rd – 4th decade)
- Variable symptomatology: FTT, emesis, diarrhea, occult blood in stool, perforation
- Variable involvement of stomach, small bowel and colon
- > 90% of cases have involvement of gastric antrum
- Approximately, 50% are atopic; 50% have peripheral blood eosinophilia
- Most common foods: cow's milk, egg, soy, cereals, fish
- Treatment includes dietary withdrawal, steroids
- Typically prolonged; natural history not well understood

### Eosinophilic Proctocolitis

- Reported to occur in 2-6% of children in developed countries
- Patients are typically <1 year of age
- Well-appearing baby with blood-streaked stools
- No involvement of upper GI tract
- Cow's milk protein
- Soy milk
  - 30-50% crossover with cow's milk
- 50-60% exclusively breast fed
- Clinical symptoms improve by 72 hours
- Re-introduce foods
  - 80% by 1 year
  - > 95% by 3 years
Eosinophilic Gastroenteritis

Mucosa, 95%

Muscle wall, 5%
Eosinophilic (allergic) proctocolitis

Eosinophilic infiltrate with few neutrophils
No significant crypt architectural changes
Some patients may present with constipation, leading to suction rectal biopsies to rule out Hirschsprung disease
“Normal” Number of Eosinophils

Lowichik and Weinberg  *Mod Pathol* 1995;9:110-4

Associated histopathologic features that favor eosinophilic gastrointestinal disease

Crypt/surface infiltration
Reactive epithelial changes
Consider *infection* if numerous neutrophils
Caution: large numbers of eosinophils may also be seen in IBD and immunodeficiencies. Consider IBD if there are significant crypt architectural changes.
Eosinophilia in the GI Tract

- Allergy ≠ Eosinophilia
- Eosinophilia ≠ Allergy
Eosinophilic Gastroenteritis – Differential Diagnosis

- Infections, particularly parasitic
  - Stool ova and parasite study may be diagnostic
- Drug reactions
  - Check drug history – Azathioprine, NSAIDS, tacrolimus
- Crohn’s disease
  - May primarily show eosinophilic abscesses
  - Typically more of a focal lesion
- Some primary immunodeficiencies
- Inflammatory fibroid polyps
  - Check configuration of lesion on endoscopy
- Hypereosinophilic syndrome.
  - Are tumorous lesions present, particularly in soft tissue?
- Post-transplant eosinophilic gastroenteritis
  - Check transplant history, immunomodulatory drugs
Post-Liver Transplant Eosinophilic Gastroenteritis

2yr-old girl 18 months post-OLT with weight loss, food refusal, peripheral eosinophilia
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Manifestations of Immunodeficiency in the GI tract:

– Over 50% present with chronic diarrhea
– Increased susceptibility to infections (2nd most common site after respiratory tract)
  • Giardia, Cryptosporidium, Salmonella, CMV, Ebstein-Barr, Candida
– Increased association with chronic inflammatory conditions
– Increased risk of malignancy (lymphoma, gastric and colorectal adenocarcinoma)
# Inflammatory GI lesions in Primary Immunodeficiencies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Manifestations</th>
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<tbody>
<tr>
<td>IgA deficiency</td>
<td>Celiac disease, food allergies, Crohn’s-like enteritis</td>
</tr>
<tr>
<td>Common Variable Immunodeficiency</td>
<td>Atrophic gastritis, villous atrophy, Crohn’s-like enteritis</td>
</tr>
<tr>
<td>X-linked agammaglobulinemia</td>
<td>Giardia, absence of plasma cells, Crohn’s-like enteritis</td>
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<tr>
<td>Severe Combined Immunodeficiency</td>
<td>Graft-versus-host disease-like lesions</td>
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<tr>
<td>Chronic mucocutaneous candidiasis</td>
<td>Atrophic gastritis</td>
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<tr>
<td>Chronic granulomatous disease</td>
<td>Crohn’s –like enteritis</td>
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IgA deficiency

- Most common primary immunodeficiency; prevalence ~1:300
- Overstimulation of the immune system and hyperplasia of lymphoid structures
- *Giardia* infection
- Increased risk for autoimmune diseases such as diabetes, food allergies, Crohn’s-like enteritis and nodular lymphoid hyperplasia

Celiac disease occurs in 5% - 15% of pts with IgA deficiency, vs ~ 1% of the general population

Negative IgA-EMA and tTG

Absence of IgA-staining plasma cells
IgA deficiency - 6 yr-old boy with chronic diarrhea and FTT

- Duodenum – celiac-like
- Colon – focal marked lymphoid hyperplasia
- Colon – focal crypt architectural distortion
Common Variable Immunodeficiency (CVID)

- 2\textsuperscript{nd} most common PID
- Most likely to present to gastroenterologist without a primary diagnosis
- May present from infancy to adult
- Frequently delayed diagnosis
- Recurrent respiratory infections most common clinical feature
- Hypogammaglobulinemia involving multiple Ab classes
- 40\% have associated T cell dysfunction

- GI complications
  - Enteric infections (Giardia, cryptosporidium)
  - Nodular lymphoid hyperplasia
  - Crohn’s-like enteritis including granulomas
  - Malabsorption
  - Atrophic gastritis
  - Chronic hepatitis
  - Increased incidence of non-Hodgkin lymphoma
15 yr old male, suspected celiac, continued weight loss despite diet

- Atrophic gastritis, rare in younger patients
- Celiac-like disease
  - Relative paucity/absence of plasma cells
  - Few IEL’s
  - Loss of goblet and Paneth cells
  - Negative EMA and tTG
CVID - a great histologic mimic!

Crohn’s-like enteritis, especially in younger age (< 5 yrs); relatively sparse inflammatory infiltrate
CVID- a great histologic mimic!

Increased basal crypt apoptotic activity, or extensive loss of goblet and Paneth cells
GVHD-like or IPEX-like histology
Common variable immunodeficiency

CD3

CD79

CVID

normal
Severe Combined Immunodeficiency

- Most severe PID
- Genetically heterogeneous; AR or X-linked
- Multiple defects
- Severe chronic diarrhea, FTT, infections
- Neonatal GVHD from maternal lymphocytes, blood products

“Empty” lamina propria, absence of plasma cells
Chronic Granulomatous Disease

- Mutation in gene for component of NADPH oxidase
- Disorder of phagocyte function with inability to produce hydrogen peroxide
- Stomatitis, oral ulcers, esophageal gastric strictures and intestinal involvement
- Infections most often due to organisms which generate catalase, such as Aspergillus, Candida albicans, Mycobacterium tuberculosis and Pseudomonas cepacia
<table>
<thead>
<tr>
<th>Feature</th>
<th>XLA</th>
<th>CVID</th>
<th>IgA deficiency</th>
<th>SCID</th>
<th>CGD</th>
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<tr>
<td>Paucity of plasma cells in LP</td>
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<tr>
<td>Nodular lymphoid hyperplasia</td>
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<tr>
<td>Giardia infections</td>
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<tr>
<td><strong>Crohn’s disease-like lesion</strong></td>
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<tr>
<td>Celiac-like changes</td>
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<td>Crypt apoptosis</td>
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<td><strong>Granulomas</strong></td>
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<td><strong>Foamy macrophages in LP</strong></td>
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Genome-wide association studies (GWAS) in IBD

163 IBD loci identified
110 associated with both diseases
30 CD-specific
23 UC-specific
66 loci associated with other autoimmune disorders
Marked enrichment of genes associated with primary immunodeficiencies and susceptibility to mycobacterial infections

From Goyette et al, Nature 2012;491:119
Pediatric IBD – Incidence and age at presentation

- 30% of all IBD patients have an established diagnosis < 20 yrs of age
- Swedish studies suggest an increase in pediatric IBD (mainly CD)
- North Am. Pediatric IBD consortium
  - 37% diagnosed 13 – 17 yrs of age
  - 48% diagnosed 6 – 12 yrs of age
  - 15% diagnosed < 6 yrs of age, 1% diagnosed during 1st year
- Early (or very early) onset IBD: 0 – 5 yrs of age
- Later onset IBD: 6 – 18 yrs of age
Contrasting features between IBD in children vs adults

- Genetic factors important in pediatric IBD
  - Family history of IBD present in 40% of children
- CD:
  - children more often present as colitis
  - children have more inflammatory disease than adults as per Vienna classification (stricturing/ fistulizing/ inflammatory)
  - growth failure is major presenting feature
  - ileal disease less frequent in younger children (increases with age)
- UC:
  - pancolitis more frequent at presentation in children than adults
  - more frequent progression to extensive disease in children with initially limited disease
Pitfalls in biopsy diagnosis: Acute Self-Limited Colitis (ASLC) vs IBD

- Pediatric cases more frequently manifest with early IBD
- There may be significant overlap with infectious diarrheas
- Infections may trigger or exacerbate IBD
- Endoscopic findings frequently similar in ASLC and IBD
- Histologic diagnosis of IBD requires presence of chronic changes: **crypt architectural distorsion**

Salmonella enteritis in a 3 year-old

Active chronic colitis
IBD in children – early biopsies

- Subtle or absent features of chronicity or atypical features (rectal sparing) do not exclude a diagnosis of IBD
- Multiple biopsies at endoscopy are advised to increase likelihood of diagnosis
- Appropriate follow-up and re-biopsy may be necessary
- Always consider possibility of other diagnoses, such as autimmune enteropathy and immunodeficiencies, esp in younger (< 5 yrs) pts
Very Early Onset IBD (VEO-IBD)

• Very early onset IBD (VEO-IBD)
  – 15% of pediatric IBD diagnosed < 6 yrs of age
  – 6% diagnosed < 3 yrs of age
  – 1% diagnosed in first year of life

• VEO-IBD is characterized by an aggressive disease phenotype with poor response to conventional IBD therapy
# Features of very early – onset (VEO) and older-onset inflammatory bowel disease

## VEO-IBD
- **Disease Distribution**
  - Predominately colonic
  - Ileal involvement <20%
  - Extensive disease at presentation
- **Disease classification**
  - CD: 30-35%
  - UC: 35-59%
  - IC: 11-22%
- **Positive Family History**: 40-50%
- **Genetic Contribution**
  - Increased prevalence monogenic disorders <2 yrs
- **Therapeutic Response to Conventional therapy**: decreased
- **Surgical intervention**: ~71%
- **Consanguinity**

## Older-Onset IBD
- **Disease Distribution**
  - Ileocolonic
  - Less extensive disease at presentation
- **Disease Classification**
  - CD: 55-60%
  - UC: 40-45%
  - IC: 4-10%
- **Positive Family History**: 10-20%
- **Genetic Contribution**
  - Polygenic inheritance
- **Surgical intervention**: ~55%
VEO-IBD

• A spectrum of rare monogenic disorders confers increased susceptibility to IBD-like disease
• Most have onset of colitis in early childhood (VEO colitis)
• There are few common genes between those that cluster within the 163 known IBD loci and monogenic disorders with IBD phenotype
9 yo female with severe failure to thrive and chronic diarrhea for many years

Diagnosis unknown until GWAS demonstrated mutation in **DOCK 8** (dedicator of cytokinesis 8 protein)
Combined T and B cell immunodeficiency
Severe chronic colitis
Cured by BMT
Colectomy for colonic strictures
Male, onset of disease 3-4 months
Numerous GI biopsies
Total colectomy at age 10
Segmental ileal resection age 14

**X-linked inhibitor of apoptosis (XIAP) deficiency**
X-linked lymphoproliferative disease type 2, Severe Crohn’s-like disease
VEO-IBD Pathways

Epithelial Barrier
- ADAM17, IKBKG, COL7A1, FEMT1, TTC7A, GUEY2

Phagocyte Defects
- NADPH Complex
- IL10, IL10RA, IL10RB, FOXP3, CTLA

Immuno-regulation
- RAG1/2, IL7R, PTEN, WASP

T & B Cell Defects

Hyper-inflammatory
- XIAP, STXBP2, LYST, RAGB27a

Courtesy of Judith Kelsen, CHOP
Monogenic disorders associated with IBD-like pathology

• Epithelial barrier defects
  – Dystrophic EB
  – Kindler syndrome
  – X-linked ectodermal dysplasia
  – ADAM-17 deficiency
  – Familial diarrhea

• Neutropenia and phagocyte defects
  – CGD
  – GSD type I
  – Congenital Neutropenia
  – Leukocyte adhesion deficiency

• Hyper- and autoinflammatory disorders
  – Mevalonate kinase deficiency
  – Phospholipase C2 defects
  – Familial Mediterranean fever
  – Familial macrophage activation syndrome
  – X-linked lymphoproliferative syndromes
  – Hermansky-Pudlak syndrome

• Complex defects in T- and B-cell function (WAS, CVID, SCID)
• Defects in regulatory T-cells and IL-10 signaling
2-month-old female with diarrhea required PICU admission
All standard infectious/immune work-up negative
No response to standard therapy (incl. infliximab and > 20 X standard steroid dose)
WES **activating mutation** of NLRC4 gene
The product of NLRC4 is an **inflammasome**
NLRC4 belongs to a group of proteins called Inflammasomes

- Multimeric protein complexes that orchestrate host defense against pathogens and are typically composed of:
  - Sensor protein (Pattern recognition receptor, PRR)
  - Adaptor protein apoptosis-associated speck-like protein (ASC)
  - Caspase-1
- Found in cells of the innate immune system (macrophages, neutrophils), adaptive immune system (T-cells) and epithelial cells
- Triggered by infection or cellular stress
- Result in activation of caspase-1, production of pro-inflammatory cytokines (IL-1, IL-18) and inflammatory cell death (pyroptosis) to blunt intracellular pathogen replication
Inflammasomes

- A component of inflammasomes are PRR’s act as scaffolds to activate caspase and release inflammatory cytokines
- The best known are the Nucleotide oligomerization domain (NOD)-like receptors (NLRs) which include
  - NOD1, NOD2, NLRP3, **NLRC4**, NLRP6
  - Mutations in the Leucine-rich domain of NOD2 confer increased risk of Crohn’s disease

*From Man and Kanneganti, Immunol Rev 2015;265:6-21*
Clinical Course

- Severely ill initially in PICU
- Required 20X therapeutic dose steroids, *vedolizumab*, *infliximab* and cyclosporine without clinical improvement
- Treated with IL-18BP (*tadekinig alfa*, clinical trial for Still’s disease and approved for compassionate use) with immediate improvement
- Discharged home 4 days after onset of therapy
Conclusions. Inflammatory Bowel Disease of infancy and childhood

- Medications may mimic IBD clinically and histologically
- Eosinophilic GI inflammatory disorders are relatively frequent disorders in childhood for which the main diagnostic modality is the GI biopsy
- Colitis similar to IBD is a feature of many primary immunodeficiencies
- 30% of IBD cases are diagnosed in the pediatric age group; early biopsies may have subtle features and need to be differentiated from infectious causes (acute self-limited colitis)
- Approximately 15% of pediatric IBD manifest in children < 5 years of age
- These correspond to an increasing number of rare monogenic variants who have severe clinical disease and whose therapy differs from conventional IBD
- Identifying and understanding these disorders provides targeted treatment options for these patients (personalized medicine) but also add to our understanding of the immune response and pathogenesis of IBD