Evaluation of the “Flat” Small-Intestinal Mucosal Biopsy

Contributions of Dr. Donald A. Antonioli to Small-Intestinal Mucosal Biopsy Analysis

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Case Presentation

- **Clinical history**
  - 66 year old male with hypothyroidism and pancreatic insufficiency
  - 8-10 episodes of watery diarrhea/day
  - Approximately 40 pound weight loss over 6 weeks

- **Radiology**
  - Small bowel follow through and CT imaging
    - Multi-focal ileal thickening without ulceration or fistulae

- **Laboratory studies**
  - Normal serum chromogranin, gastrin, serotonin, VIP
  - Polyclonal hypergammaglobulinemia
  - Mildly elevated celiac markers (IgA and IgG gliadin, tTG) with negative HLA DQ2 and HLA DQ8 haplotype
  - Abundant fecal fat
**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Chronic enteritis with villous shortening and crypt hyperplasia</th>
<th>Small-intestinal disease associated with extra-duodenal inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Inflammatory bowel disease</td>
<td>- Inflammatory bowel disease</td>
</tr>
<tr>
<td>- Celiac disease</td>
<td>- Celiac disease</td>
</tr>
<tr>
<td>- Autoimmune enteropathy</td>
<td>- Autoimmune enteropathy</td>
</tr>
<tr>
<td>- Common variable immunodeficiency</td>
<td>- Common variable immunodeficiency</td>
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<tr>
<td>- Refractory sprue</td>
<td>- Refractory sprue</td>
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<tr>
<td>- Infection</td>
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<tr>
<td>- Tropical sprue</td>
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<tr>
<td>- Bacterial overgrowth</td>
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<tr>
<td>- Microvillous inclusion disease</td>
<td></td>
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<tr>
<td>- Protein intolerance</td>
<td></td>
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<tr>
<td>- Nutritional deficiency</td>
<td></td>
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<tr>
<td>- Medications</td>
<td></td>
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</tbody>
</table>
Overlapping Features of Immune-Mediated Small-Intestinal Diseases

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Crohn’s Disease</th>
<th>Celiac Disease</th>
<th>Autoimmune Enteropathy</th>
<th>Common Variable Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric and adult patients</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>Malabsorption/diarrhea</td>
<td>+</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Weight loss/failure to thrive</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other autoimmune disorders</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Pathogenesis**

<table>
<thead>
<tr>
<th>Molecular predisposition</th>
<th>NOD2, TLR4</th>
<th>HLADQ2, HLADQ8</th>
<th>FOXP3 (IPEX syndrome)</th>
<th>TACI, BAFF, APRIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Defective immune response to environmental antigens</td>
<td>Dysregulation of T cells</td>
<td>Abnormal B cell maturation</td>
<td></td>
</tr>
</tbody>
</table>

**Serologic Markers**

| Anti-tissue transglutaminase      | <5%         | +              | 30%                   | unreliable        |
| Anti-endomysial IgA antibody      | +/-         | +              | +/-                   | unreliable        |
| Anti-gliadin IgG antibody         | +/-         | +              | +/-                   | unreliable        |
| Anti-Saccharomyces Cerevisiae     | 40-90%      | 30%            | +/-                   | unreliable        |
| Anti-enterocyte antibody          | 50-90%      |                | +/-                   | +/-               |
“Lymphocytic Gastritis” May Reflect Immune-Mediated Gastrointestinal Injury
Gastric Intraepithelial Lymphocytes in Pediatric Celiac Disease

- 33 pediatric biopsies evaluated for gastric intraepithelial lymphocytes (IELS)
  - 23 patients with celiac disease
  - 10 normal controls
  - Assessed for IELs/100 enterocytes

<table>
<thead>
<tr>
<th>Gluten Sensitivity</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IELs (range)</td>
<td>21 (4-50)</td>
<td>3 (1-8)</td>
</tr>
</tbody>
</table>

- 70% of celiac disease cases had >8 IELs/100 enterocytes
- Re-biopsy after gluten withdrawal showed decreased gastric lymphocytosis (mean: 20 versus 4, n=4)

- Lymphocytic gastritis present in
  - 4% of patients with *Helicobacter pylori* infection
  - 33% of patients with celiac disease

Immune-Mediated Disorders May Manifest as Lymphocytic Colitis
Ileal Lymphocytosis Occurs in “Microscopic” Colitis

<table>
<thead>
<tr>
<th></th>
<th>Lymphocytic Colitis</th>
<th>Collagenous Colitis</th>
<th>Controls</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>11.8±1.8</td>
<td>10.3±1.9</td>
<td>2.2±0.2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

## Manifestations of Immune-Mediated Diseases in the GI Tract

<table>
<thead>
<tr>
<th></th>
<th>Crohn's Disease</th>
<th>Celiac Disease</th>
<th>Autoimmune Enteropathy</th>
<th>Common Variable Immunodeficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stomach</strong></td>
<td></td>
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</tr>
<tr>
<td>Mild chronic gastritis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic active pangastritis</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocytic gastritis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td><strong>Colon</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-specific colitis</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lymphocytic colitis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chronic colitis</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Duodenum/jejunum</strong></td>
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<tr>
<td>Chronic enteritis with villous shortening</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

### Specific Interrelationships

- **Celiac disease**: 0.85%  
- **Crohn's disease**: 1.7%  
- **Common variable immunodeficiency**: 13%

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Evaluation of Small-Intestinal Mucosal Biopsies

- **Checklist**
  - Architecture
  - Distribution (diffuse or patchy)
  - Location of inflammation
    - Superficial or deep lamina propria
    - Surface, crypts or both
  - Nature of inflammation
    - Lymphocyte predominant
    - Neutrophilic cryptitis
  - Other abnormal features
    - Apoptosis
    - Infection (CMV)
  - Presence of normal elements
    - Plasma cells
    - Goblet, Paneth, endocrine cells
Crohn’s Disease of the Proximal Small Bowel


Crohn’s Disease of the Proximal Small Bowel
Histologic Features of Celiac Disease

Celiac Disease
Autoimmune Enteropathy
Autoimmune Enteropathy
Common Variable Immunodeficiency
Common Variable Immunodeficiency
Common Variable Immunodeficiency
Classification of Chronic Enteritis

Crohn’s disease
- Mixed inflammation
- Multifocal neutrophilic cryptitis
- Granulomas
- Gastric metaplasia

Celiac disease
- Surface and crypt lymphocytosis
- No neutrophilic cryptitis

Chronic enteritis with villous shortening and crypt hyperplasia
- Associated gastric and/or colonic injury

- Relative sparing of surface epithelium
- Crypt neutrophils
- Apoptosis
- Loss of goblet, endocrine, and Paneth cells

- Relative sparing of surface epithelium
- Lymphoid aggregates
- Decreased plasma cells
- Neutrophilic cryptitis
- Apoptosis
- Associated Giardia and/or CMV infection

Autoimmune enteropathy

Common variable immunodeficiency
Case
Diagnosis: Autoimmune Enteropathy
Summary and Conclusions

Contributions of Dr. Donald A. Antonioli

- The diagnostician
  - Methodic approach to mucosal biopsy analysis
    - Villous architecture
    - Distribution of disease
    - Location of inflammation
    - Nature of inflammation
    - Presence of other features
      - Apoptosis or infection
    - Presence of normal elements
      - Paneth, goblet, and plasma cells

- The educator
  - More than 100 lectures
  - 9 USCAP courses

- The academician
  - More than 100 original articles
  - More than 30 reviews and book chapters
Many thanks to our teacher, colleague and friend