A Practical Approach to Small Bowel Biopsies:
“All that flattens is not sprue”

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Challenges in Small Bowel Pathology

• Lack of pertinent clinical information
  – e.g., “r/o sprue”
• Lack of adequate biopsy and good tissue orientation
• Understanding spectrum of normal small bowel
• Extensive Ddx in nonspecific lesions
• Understanding clinical implications of diagnoses
What is normal duodenum?

• Normal villous/crypt ratio is 3-5:1
• Easily identifiable goblet cells and Paneth cells
• 1-2 mitotic figures per crypt

What is normal?

• Lamina propria:
  – Should have plenty of lymphocytes, plasma cells, macrophages
  – Scattered eosinophils and neutrophils okay

So “chronic inflammation” is not an appropriate diagnosis!

What is normal?

• Approximately 25 lymphocytes per 100 epithelial cells
• Concentrated along base and sides of villi, with sparing of tips
Caveats

- Crypts more crowded, more goblet cells in kids
- Brunner glands, lymphoid follicles cause false blunting
  - No marked increase in IELs
- Stripped-off muscularis mucosa causes false blunting
- People who live in the tropics have shorter villi
- Beware tangential sectioning

There is no shame in a diagnosis of normal!

Approach to Small Bowel Biopsy:

**General Classification**

1. Normal villous architecture
2. Variable/moderate villous lesion
3. Severe (totally flat) villous lesion

Are there any specific/diagnostic features, vs. nonspecific histologic changes?
### Celiac Disease (Gluten-Sensitive Enteropathy)

- Diagnosis is multifactorial:
  - Clinical symptoms (typical or atypical)
  - Characteristic but nonspecific biopsy findings
  - Positive serologies
    - Anti-gliadin, anti-endomysial, TTG
  - Genetic analysis
    - HLA-DQ2/DQ8
  - Unequivocal clinical response to gluten-free diet

### TTG

- Theoretically, most sensitive and specific lab test (ELISA assay) for celiac disease
- Original sensitivity 95%, specificity 94%
- More recent studies sensitivity 71%, specificity 65%
  - Lower in patients with mild to moderate lesion
  - Clinical testing (kits) in real-life labs less accurate than research lab setting
  - Many diseases cause false positive
    - IBD, PBC, heart disease, autoimmune disease
  - IgA deficient patients need special testing

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**Normal Villi Variable Defect Severe Defect**

<table>
<thead>
<tr>
<th></th>
<th>Normal Villi</th>
<th>Variable Defect</th>
<th>Severe Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased IELs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Immuno-deficiency*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Amyloid*</td>
<td>X</td>
<td></td>
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<tr>
<td>Mastocytosis*</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Infection*</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug Injury</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Autoimmune enteritis</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Peptic duodenitis</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemotx/radia-tion*</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic enteritis*</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Protein injury</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Stasis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*may have more specific or diagnostic histologic features
Moderate Villous Defect

Severe Villous Defect

Severe villous atrophy with marked intraepithelial lymphocytosis and crypt hyperplasia
“Increased villous lymphocytes”

- Normal architecture
- Only abnormality is increased villous lymphocytes, often extending over villous tips
  - More than 40/100 epithelial cells
  - Up to 2.5% of proximal SB biopsies

Increased IELs with Normal Villous Architecture

- Ddx:
  - Peptic ulcer disease
  - NSAIDs
  - Nongluten food hypersensitivity
  - Infection (particularly viral)
  - Autoimmune enteritis and other autoimmune dz
  - Some first degree relatives of celiac patients, DH
  - Autism (+/- lactose intolerance)
  - IBD, Microscopic colitides
  - Celiac disease*
*Controversy

- Increased IELs in the context of normal architecture can represent celiac disease in a minority of cases
  - Helpful histologic features
    - Some say no, never, wrong
- Is the patient symptomatic?
  - Anemia
  - Osteoporosis
- What do serologies show?
- Response to gluten-free diet?
  - Some non-celiac patients still respond to gluten-free diet

**Differential Diagnosis**

**Entities Causing Villous Defect and/or Increased IELs**

- Peptic duodenitis
- Infections
- Crohn’s disease
- Lymphoma
- Mastocytosis
- Protein malnutrition
- Stasis obstruction
- Lymphangiectasia
- Eosinophilic enteritis
- Drugs/Radiation
- Autoimmune enteritis
- Immunodeficiency
- Protein injury
- Tropical sprue
- Tropical enteropathy

**Ddx: Crohn’s Disease**

- May have increased IELs, villous blunting
  - Has been called “sprue-like” pattern of Crohn’s
- Other areas usually show more typical features of Crohn’s (dependent on liberal sampling)
  - Ulceration
  - Active enteritis
  - Granulomas/giant cells
  - Pyloric metaplasia

The “sprue-like” pattern of Crohn’s disease
Differential Diagnosis
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DDx: Peptic Duodenitis

- Villous blunting and intra-epithelial lymphocytosis may overlap with celiac disease histologically
  - Excess of neutrophils, pyloric metaplasia favor peptic duodenitis
Differential Diagnosis
Entities Causing Villous Defect and/or Increased IELs

- Peptic duodenitis
- Infections
- Crohn's disease
- Lymphoma
- Mastocytosis
- Protein malnutrition
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- Eosinophilic enteritis
  - Drugs/Radiation
  - Autoimmune enteritis
  - Immunodeficiency
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  - Tropical sprue
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Ddx: Idiopathic Eosinophilic Gastroenteritis

- Infiltration of one or more segments of GI tract by eosinophils, including pancreas and biliary tree
- Villous blunting, increased IELs overlap with celiac disease in mucosal-predominant IEG
  - Excess of eosinophils favors IEG
  - 75% of patients have peripheral eosinophilia
  - Negative TTG, no response to gluten free diet

Idiopathic Eosinophilic Enteritis

Marked villous blunting in eosinophilic enteritis
Differential Diagnosis

Entities Causing Villous Defect and/or Increased IELs

- Peptic duodenitis
- Infections
- Crohn’s disease
- Lymphoma
- Mastocytosis
- Protein malnutrition
- Stasis/obstruction
- Lymphangiectasia

- Eosinophilic enteritis
- Drugs/Radiation
- **Autoimmune enteritis**
- Immunodeficiency
- Protein injury
- Tropical sprue
- Tropical enteropathy

Ddx: Autoimmune Enteritis

- Well recognized in children; probably markedly under-recognized in adults
- Associated with thymomas, other autoimmune illnesses
- Profound diarrhea and weight loss
- No response to gluten-free diet; need immunosuppression
- Anti-enterocyte and/or anti-goblet cell antibodies

Ddx: Autoimmune Enteritis

- Villous atrophy, intraepithelial lymphs can mimic celiac disease
  - Often fewer intraepithelial lymphs
  - Lack of goblet cells and/or Paneth cells
  - Excess of lamina propria plasma cells
  - Cryptitis/crypt abscesses
  - Apoptotic enterocytes
  - Entire gut may be involved
Moderate to marked villous blunting and virtually no goblet cells!
Autoimmune Enterocolitis may involve entire gut

Ddx: Common Variable Immunodeficiency

- Malabsorption, chronic giardiasis are common
- Several patterns of small bowel injury; one resembles celiac disease
  - Lack of plasma cells, many apoptotic enterocytes, *Giardia* favor CVID
  - May involve entire gut

Differential Diagnosis
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Giardia are also common in CVID

**Differential Diagnosis**

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- **Drugs/Radiation**
  - Autoimmune enteritis
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  - Tropical enteropathy
Drugs That Can Cause Villous Blunting, Increased IELs

- NSAIDs-intraepithelial lymphocytosis
- Mycophenolate-villous blunting, changes mimicking GVHD
- Chemotherapy: Villous blunting, marked reactive epithelial changes, increased apoptotic epithelial cells

Differential Diagnosis

Entities Causing Villous Defect and/or Increased IELs

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- **Infections**
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- Lymphoma
- Mastocytosis
- Protein malnutrition
- Stasis/obstruction
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- Eosinophilic enteritis
- NSAIDs
- Autoimmune enteritis
- Immunodeficiency
- Protein injury
- Tropical sprue
- Tropical enteropathy
DDx: Infections Causing Villous Abnormalities and/or Increased IELs

- MAI
- Viral enteritis
- AIDS enteropathy
- Whipple’s disease
- Histoplasmosis
- Coccidians

Severe viral enteritis
IELs in HIV enteropathy
Courtesy Dr. Joe Misdraji

Whipple’s Disease
MAI

Histoplasmosis

Cryptosporidia

Courtesy Dr. Joel Greenson
Increased IELs in Microsporidia

Mild villous blunting in Cyclospora

Courtesy Dr. Rhonda Yantiss
Summary

- Try to ensure an adequate specimen, ideally with clinical and laboratory info
- Understand the spectrum of normal
- Be aware of the extensive differential diagnosis
- Be aware of clinical implications of diagnoses
### Feature Helpful test/finding

<table>
<thead>
<tr>
<th>Eosinophilic enteritis</th>
<th>Increased eos</th>
<th>Peripheral count H/o atopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune enteritis</td>
<td>Too many polys Absent goblet cells Apoptotic cells</td>
<td>Anti-enterocyte and anti-goblet cell abs; other autoimmune diseases</td>
</tr>
<tr>
<td>CVID</td>
<td>Absent plasma cells Apoptotic cells</td>
<td>Immune-deficiency w/u</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Too many polys; other features of CD</td>
<td>Small bowel f/t; colonoscopy</td>
</tr>
<tr>
<td>Peptic duodenitis</td>
<td>Too many polys Pyloric metaplasia</td>
<td>Look for <em>H. Pylori</em> infection</td>
</tr>
</tbody>
</table>

“An incorrect diagnosis [of celiac disease] is harmful because the rigid dietary demands of treatment interfere with the joy of eating and can be especially damaging to the social development of children.” – Cyrus Rubin M.D.