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

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Goals for this lecture:
Understand the differential diagnosis of villous blunting and/or increased intraepithelial lymphocytes
Illustrate with humbling personal real-life stories based on cases that I have experienced in my own practice

Challenges in Small Bowel Pathology
- No pertinent clinical information
  - Every requisition says “r/o sprue”
- Lack of adequate biopsy/optimal tissue orientation
- Need to understand spectrum of normal small bowel
- Lesions are nonspecific and Ddx is broad
- Clinical implications of diagnoses are significant
What is adequate?

We need help from our clinical colleagues

- Sample bulb as well as second part of duodenum or beyond
  - Patchy distribution
  - Brunner glands distort architecture
- “Single pass” biopsy preferred
- 3-4 oriented villi for evaluation

What is normal duodenum?

Normal villus/crypt height ratio is 3-5:1

Easily identifiable goblet cells and Paneth cells

1-2 mitotic figures per crypt

What is normal duodenum?

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 duodenum?

Approximately 25 lymphocytes per 100 epithelial cells
(or 1 lymph/5 enterocytes)

Concentrated along sides of villi, with sparing of tips
Normal jejunum

Normal ileum
There is no shame in a diagnosis of normal!
Caveats

- Crypts can appear more crowded, with more goblet cells in kids
- Stripped-off muscularis mucosae causes false blunting
- People who live in the tropics may have shorter villi
- Beware tangential sectioning

Separation from muscularis mucosae falsely blunts villi, gives appearance of gland loss

Approach to Small Bowel Biopsy:
General Classification

What does the architecture look like?
- Normal
- Variable/moderate blunting
- Severe blunting (totally flat)

Are there any specific/diagnostic features that help?
<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal Villi</th>
<th>Variable Defect</th>
<th>Severe Defect</th>
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</thead>
<tbody>
<tr>
<td>Immunodeficiency*</td>
<td>X</td>
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<tr>
<td>Amyloid</td>
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<td>Mastocytosis*</td>
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<tr>
<td>Celiac Disease</td>
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<td>Infection*</td>
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<td>Drug Injury</td>
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<td>GVHD</td>
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<tr>
<td>Autoimmune enteritis</td>
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<tr>
<td>Peptic Duodenitis</td>
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<td>Chemo/radiation*</td>
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<td>Eosinophilic enteritis*</td>
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<td>Protein injury</td>
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<td>X</td>
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<tr>
<td>Stasis</td>
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</tbody>
</table>

*May have more specific or diagnostic histologic features

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Celiac Disease-diagnosis

**Clinical**
- Symptoms
- Response to diet

**Histologic**

**Lab**
- Serologies
- Genotype [HLA DQ2/DQ8]
Celiac disease—clinical

Classic
- Malabsorption/diarrhea
- Steatorrhea
- Weight loss
- Nutrient deficiencies

Atypical
- Anemia
- Infertility
- Failure to thrive
- Arthritis
- Elevated transaminases
- Osteoporosis
- Tooth enamel defects
- IgA deficiency
- Dermatitis herpetiformis

Serologic diagnosis
- Best if patients on gluten at time of testing
- Caveats:
  - Lower titers with mild histology
  - Variation among commercial labs
  - False positives: IBD, PBC, autoimmune disease
  - IgA deficient patients need special kit

Flattened, atrophic mucosa in classic celiac disease

“Mosaic or "cracked mud" pattern seen on endoscopy

**Approach to Small Bowel Biopsy:**

General Classification

What does the architecture look like?
- Normal
- Variable/moderate blunting
- Severe blunting (totally flat)

Are there any specific/diagnostic features that help?
Celiac disease-severe villous defect

Celiac disease-moderate villous defect

Celiac disease-crypt hyperplasia
Severe villous atrophy
Marked intraepithelial lymphocytosis
Crypt hyperplasia
Increased, upwardly displaced mitoses are common

Normal architecture with increased lymphocytes

Up to 2.5% of otherwise normal duodenal biopsies
- Often extending over villous tips
- More than 30-40/100 epithelial cells
**Increased IELs with normal villous architecture**

**Ddx:**
- Peptic ulcer disease/H. pylori infection in stomach
- 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

**Increased IELs with normal villous architecture**

- Important to note that increased IELs in the context of normal architecture does represent celiac disease in some cases
  - Villous atrophy happens last
  - Broad differential
- 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

**“Bulb-Limited” Celiac Disease**

- Historically bulb avoided due to Brunner glands
- Some evidence to suggest that celiac disease may present solely in bulb, esp. in kids
  - Changes of celiac may be patchy, and appear to be limited to bulb in minority (6%)
  - Bulb should be biopsied as one of multiple biopsies

Unresponsive celiac disease

- Review dx biopsies and titers
- Consider HLA typing

Confirm diagnosis

- Normal TTG does not ensure compliance
- Meds, cosmetics, glue

Check compliance

- Microscopic colitis (50-70 higher in CD)
- Collagenous sprue

Associated diseases

- Persistent/recurrent disease despite diet compliance and excluding other diseases
- ? evolution to lymphoma

Refractory sprue

Lymphocytic colitis in patient with celiac disease

Lymphocytic gastritis is also associated with celiac disease
May or may not be associated with celiac disease
May need additional therapy

Collagenous Sprue
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
The “sprue-like” pattern of Crohn’s disease with villous blunting and increased IELs

16M, history of Crohn’s, persistent diarrhea

Other foci usually show more typical features of Crohn’s:
- Ulceration
- Active enteritis
- Granulomas/giant cells
- Pyloric metaplasia
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DDx: Peptic Duodenitis

- Spectrum of H. pylori infection
- H. pylori usually not seen in duodenum, however
- Villous blunting and intra-epithelial lymphocytosis may overlap with celiac disease histologically
  - Excess of neutrophils, pyloric metaplasia favor peptic duodenitis
Vilious blunting, increased IELs may overlap with CD

Neutrophils, pyloric metaplasia favor peptic disease
Differential Diagnosis
Entities Causing Villous Defect and/or Increased IELs

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Eosinophilic Gastroenteritis

Infiltration of one or more segments of GI tract, including pancreas and biliary tree

Historically, 3 types:

- **Mucosal predominant**
  - Most common
  - Diarrhea/bleeding/malabsorption

- **Mural**
  - Obstruction
  - Mucosa may be totally normal

- **Serosal**
  - Least common
  - Eosinophilic ascites

60F with “sprue”
Negative TTG, peripheral eosinophilia
### Differential Diagnosis

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

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- Drugs/Radiation
  - *Autoimmune enteritis*
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**Idiopathic Eosinophilic Enteritis**

- Excess of eosinophils, typically pure
- Peripheral eosinophilia (75%)
- No response to gluten removal
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

Moderate to marked villous blunting and virtually no goblet cells!

Excess of plasma cells
No goblet cells
Apoptotic enterocytes
Neutrophilic activity
No goblet cells

Numerous apoptotic enterocytes

Autoimmune Enterocolitis may involve entire gut
Celiac Disease vs. Autoimmune Enteropathy

**Celiac disease**
- Villous blunting
- Intraepithelial lymphocytes
  - Usually more than AIE
- Neutrophilic inflammation
- Numerous lamina propria plasma cells
- Crypt hyperplasia

**Autoimmune enteropathy**
- Villous blunting
- Intraepithelial lymphocytes
- Neutrophilic inflammation
  - Often more than celiac disease
- Numerous lamina propria plasma cells
- Apoptotic epithelial cells
- May affect entire gut
**Differential Diagnosis**

Entities Causing Villous Defect and/or Increased IELs

- Peptic duodenitis
- Infections
- Crohn’s disease
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**Common Variable Immunodeficiency**

- GI symptoms, chronic giardiasis are common
- Don’t respond to gluten-free diet, may need TPN
- Several patterns of small bowel injury-one resembles celiac disease
  - Lack of plasma cells, apoptotic enterocytes, Giardia favor CVID
  - May involve entire gut
  - No response to gluten-free diet

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25M with “Crohn’s disease”

TPN dependent
No plasma cells!

Increased IELs

Chronic giardiasis in CVID

Pictures courtesy of Dr. Rodger Haggitt
Differential Diagnosis
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Drugs That Can Cause Villous Blunting, Increased IELs

- NSAIDs-intraepithelial lymphocytosis
- Mycophenolate-villous blunting, mimics GVHD
- Olmesartan
- Chemotherapy: Villous blunting, reactive epithelial changes, increased apoptotic epithelial cells
- Radiation: Villous blunting, reactive epithelial changes

Olmesartan Toxicity

- Common angiotensin II receptor antagonist (antihypertensive)
- Severe chronic diarrhea and weight loss, often requiring hospitalization
- Morphologic changes may resemble celiac disease, collagenous sprue, and/or microscopic colitis
Differential Diagnosis
Entities Causing Villous Defect and/or Increased IELs

- Peptic duodenitis
- Infections
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- Lymphoma
- Mastocytosis
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- Stasis obstruction
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- Eosinophilic enteritis
- NSAIDs
- Autoimmune enteritis
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- Tropical sprue
- Tropical enteropathy
DDx: Infections Causing Villous Abnormalities and/or Increased IELs

- Mycobacterium avium-intracellulare (MAI)
- Viral enteritis
- AIDS enteropathy
- Whipple’s disease
- Histoplasmosis
- Coccidians

Severe viral enteritis
IELs in HIV enteropathy
 Courtesy Dr. J. Misrahi

Apoptotic epithelial cells and plasma cell infiltrate in lamina propria
Whipple’s Disease

Whipple’s Disease

Whipple’s Disease
Histoplasmosis

Increased IELs in Microsporidia
Increased IELs in Cystoisospora
Courtesy Dr. Joel Greenson
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

A brief word about reporting...
Duodenum, bx:
  - Intact villous architecture with increased intraepithelial lymphocytes; see comment
  - Ddx: Celiac, NSAID, infection
  - Recommend serologies if patient has signs/symptoms of malabsorption

A brief word about reporting...
Duodenum, bx:
  Marked villous blunting with numerous intraepithelial lymphocytes; see comment
  Suggestive of celiac, although appropriate to give differential as well
  Recommend serologies for confirmation
A brief word about reporting...

Duodenum, bx:

- Moderate/variable villous blunting with numerous intra-epithelial lymphocytes and/or; see comment
- Note any other pertinent features (eos, absence of plasma cells, etc.)
- Give differential
- Recommend other tests that might help

<table>
<thead>
<tr>
<th>Feature</th>
<th>Helpful test</th>
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<tbody>
<tr>
<td>Eosinophilic enteritis</td>
<td>Increased eos Peripheral count H/o atopy</td>
</tr>
<tr>
<td>Autoimmune enteritis</td>
<td>Too many polys Absent goblet cells Anti-enterocyte and anti-goblet cell abs</td>
</tr>
<tr>
<td>CVID</td>
<td>Absent plasma cells Immune-deficiency w/u</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>Too many polys other features of CD Imaging Evidence of Crohn's elsewhere</td>
</tr>
<tr>
<td>Peptic duodenitis</td>
<td>Too many polys Pyloric metaplasia r/o H. pylori infection</td>
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“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.