Objectives

• Detail the entities that can mimic celiac disease

• Identify the clinical and/or histologic differences to be able to distinguish between the differing disorders

• Outline an approach to the patient with a serologically-negative enteropathy
Diagnosis of Celiac Disease

1. Clinical feature(s) compatible
2. Serologies supportive
3. Small bowel biopsies characteristic
4. Clinical response to gluten-free diet

We need to be as sure as we can!!!
Celiac Disease

- Flattened villi (partial/total)
  - Crypt hyperplasia
- Increased intraepithelial lymphocytes (IELs)
  - Chronic inflammatory cell infiltrate in lamina propria
## Histologic Classification for Celiac Disease

<table>
<thead>
<tr>
<th>Marsh Modified (Oberhuber)</th>
<th>Corazza</th>
<th>IELs*</th>
<th>Crypts</th>
<th>Villous blunting</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Grade A</td>
<td>Increased</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Increased</td>
<td>Hyperplastic</td>
<td>None</td>
</tr>
<tr>
<td>3a</td>
<td>Grade B1</td>
<td>Increased</td>
<td>Hyperplastic</td>
<td>Partial</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>Increased</td>
<td>Hyperplastic</td>
<td>Subtotal</td>
</tr>
<tr>
<td>3c</td>
<td>Grade B2</td>
<td>Increased</td>
<td>Hyperplastic</td>
<td>Total</td>
</tr>
</tbody>
</table>

*IELs = intraepithelial lymphocytes

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### The Challenge

- Celiac-like symptoms
- Celiac
- Celiac-like histology

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Early Histologic Mimickers
IELs, no atrophy

Intraepithelial Lymphocytes (IELs): What is “Abnormal”?

• 1975 → 2005 > 40 IELs/100 epithelial cells
• 2005 → current ≥ 25 IELs/100 epithelial cells

• Early criteria of > 40 IELs based on jejunal biopsies

• Some may base counts on anti-CD-3 staining, which would require a higher benchmark
  ▪ Not recommended in practice
  ▪ May lead to over-diagnosis
Isolated IELs on Duodenal Biopsies

- All duodenal bxs from 2000-2010 with normal villous architecture and isolated IELs, adults > 18 years
- 15,839 total duodenal bxs → 1105 (7.0%) with IELs alone
  - 3.0% (2000) → 10.9% (2010)

Increased IELs, No Villous Atrophy: Is it all CD?

- Excluding known CD, only 6.8% with increased IELs had CD
- Other smaller studies have found 9-20% with CD
### Conditions a/w Increased IELs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Kakar (N=43)</th>
<th>Mahadeva (N=14)</th>
<th>Shmidt (N=1105)</th>
<th>Hammer (N=100)</th>
<th>Aziz (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac*</td>
<td>9%</td>
<td>21%</td>
<td>20%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>Tropical</td>
<td>1%</td>
<td>-----</td>
<td>-----</td>
<td>1%</td>
<td>-----</td>
</tr>
<tr>
<td>H. pylori</td>
<td>-----</td>
<td>-----</td>
<td>3%</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>SIBO</td>
<td>5%</td>
<td>-----</td>
<td>9%</td>
<td>3%</td>
<td>-----</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>14%</td>
<td>-----</td>
<td>14%</td>
<td>8%</td>
<td>21%</td>
</tr>
<tr>
<td>IBD*</td>
<td>12%</td>
<td>-----</td>
<td>8%</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>14%</td>
<td>-----</td>
<td>-----</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Unexplained</td>
<td>7%</td>
<td>21%</td>
<td>33%</td>
<td>26%</td>
<td>34%</td>
</tr>
<tr>
<td>IBS</td>
<td>9%</td>
<td>14%</td>
<td>-----</td>
<td>20%</td>
<td>-----</td>
</tr>
<tr>
<td>Other</td>
<td>28%</td>
<td>43%</td>
<td>13%</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>

* = New and known cases

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### Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean Age at IEL Finding (yrs)</th>
<th>Mean IEL Count</th>
<th>IEL Distribution (even/sides/tip)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• UC (n=13)</td>
<td>40</td>
<td>45</td>
<td>11-1-1</td>
</tr>
<tr>
<td>• Crohn’s (n=54)</td>
<td>39</td>
<td>44</td>
<td>49-3-2</td>
</tr>
<tr>
<td>• Indeterminate (n=3)</td>
<td>25</td>
<td>35</td>
<td>2-1-0</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Crohn’s (n=4)</td>
<td>4</td>
<td>55</td>
<td>4/0/0</td>
</tr>
</tbody>
</table>

➢ Of the 74 with IBD and increased IELs with no villous atrophy, only 3 had a tip-predominant infiltrate of IELs ➟ All 3 negative for celiac disease
Late Histologic Mimickers

Villous atrophy
Partial/total

Villous Atrophy and Negative Celiac Serology

• 10-year period (2001-2011)
• Adults with: - Villous atrophy in duodenum AND
  - Negative celiac serology
    ➢ TTG, DGP, EMA

• Testing done:
  • HLA haplotyping
  • Anti-enterocyte antibodies
  • Giardia stool antigen
  • HIV testing
  • Immunoglobulin levels
  • Breath testing for SIBO
  • T-cell gene rearrangement
  • Medication review

How Seronegative CD Defined

- Negative TTG, DGP, EMA
- Positive for HLA DQ2 or DQ8
- Histology c/w celiac disease
- Response to gluten-free diet
  - Clinically and/or histologically
- Tested negative for other entities


Etiologies Seronegative Villous Atrophy

N = 72 patients

SN CD = seronegative CD; MRVA = medication-related VA; US = unclassified sprue; AIE = autoimmune enteropathy; CD4L = CD4+ T-cell lymphoma; TS = tropical sprue; CS = collagenous sprue; GM = gastric metaplasia
Medications: Olmesartan

- Angiotensin 2 receptor blocker (ARB)
- Approved 2002 USA (2003 Europe)
  - Indication: hypertension
- Report in 2012 from Mayo (22 pts)
  - Serologically negative
  - Referred as “refractory celiac disease”
  - All on olmesartan for hypertension

5-3-2013

Olmesartan-Induced Enteropathy

<table>
<thead>
<tr>
<th></th>
<th>Mayo 1</th>
<th>French 2</th>
<th>Spain 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (#)</td>
<td>22</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>69.5</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Median dose (mg)</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Mean time on drug (years)</td>
<td>3.1</td>
<td>2.3</td>
<td>36 (median)</td>
</tr>
<tr>
<td>HLA DQ2 or 8 positivity</td>
<td>81% of tested</td>
<td>61% of tested</td>
<td>100%</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>100%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>50%</td>
<td>75%</td>
<td>45%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>18 kg</td>
<td>18% wt loss</td>
<td>73% lost wt</td>
</tr>
<tr>
<td>Villous atrophy (#)</td>
<td>22</td>
<td>32</td>
<td>?</td>
</tr>
<tr>
<td>Collagenous deposition (#)</td>
<td>7</td>
<td>2</td>
<td>?</td>
</tr>
<tr>
<td>Acute inflammation (#)</td>
<td>15</td>
<td>?</td>
<td>?</td>
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</tbody>
</table>

Etiologies Seronegative Villous Atrophy

N = 72 patients

- 16/19 = olmesartan
- 2/19 = MMF
- 1/19 = MTX
- 11/16 = collagenous
- 1/2 = collagenous

SN CD = seronegative CD; MRVA = medication-related VA; US = unclassified sprue; AIE = autoimmune enteropathy; CD4L = CD4+ T-cell lymphoma; TS = tropical sprue; CS = collagenous sprue; GM = gastric metaplasia

### Other Medication Mimics

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ipilimumab (anti-CTLA4)</strong></td>
<td>- Humanized monoclonal antibody&lt;br&gt;- Unresectable metastatic melanoma or prostate cancer&lt;br&gt;- Can mimic celiac disease or autoimmune enteropathy&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Mycophenylate mofetil (MMF)</strong></td>
<td>- Marked villous/crypt changes; inflammation in the LP&lt;br&gt;- Epithelial cell apoptosis (like GVHD)</td>
</tr>
<tr>
<td><strong>Colchicine</strong></td>
<td>- Causes mitotic arrest&lt;br&gt;- Low dose → minimal mucosal changes&lt;br&gt;- High dose → severe flattening</td>
</tr>
<tr>
<td><strong>Methotrexate (MTX)</strong></td>
<td>- Prevents crypt mitotic activity&lt;br&gt;- Maximal effect ~ 21 hours after dose</td>
</tr>
<tr>
<td><strong>Azathioprine</strong></td>
<td>- Reports of enteropathy that reversed with cessation&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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### Collagenous Sprue

- Histologic features of CD + thickened layer type 1 collagen
- May have surface epithelial damage and detachment
- Management:
  - Review medications
  - Often initiate a gluten-free diet
  - Frequent immunosuppression
  - Histology may persist
Immunodeficiency

- Common variable immunodeficiency (CVID)
- Can cause increased IELs; villous atrophy

**CVID Criteria:**
- IgG 2 SD below normal AND
- One other low Ig level AND
- Failure to mount vaccine reaction

- Any age (most < 30), M:F equal
- Respiratory and GI infections

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CVID

- Reduced/absent plasma cells
  - 30% w/ normal numbers*

- May have neutrophils, lymphoid aggregates, glandular apoptosis
- Secondary infections

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Small Intestinal Bacterial Overgrowth

• 52 subjects with no risk for SIBO
• Duodenal aspirates and biopsies taken
• 26/52 (50%) had SIBO

• No difference in those with vs w/o SIBO
  • Villous height, crypt depth, ratios, lamina propria cell count
• Was a difference in:
  • IEL counts with colonic type bacteria (higher in SIBO)
  • Yet within normal range

Another Study: SIBO and Small Bowel Histology

• 67 pts with SIBO; 55 control
  • SIBO pts older (60 vs 52, p 0.02)
  • SIBO pts more likely to have risk factor (66 vs 36%, p 0.002)

<table>
<thead>
<tr>
<th>Finding</th>
<th>SIBO (n=67)</th>
<th>Controls (n=55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villous:crypt &lt;3:1</td>
<td>16 (24)</td>
<td>4 (7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Increased IELs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villi</td>
<td>15 (22)</td>
<td>8 (15)</td>
<td>0.35</td>
</tr>
<tr>
<td>Crypts</td>
<td>3 (4)</td>
<td>1 (2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>5 (7)</td>
<td>2 (4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Crypt apoptosis</td>
<td>3 (4)</td>
<td>2 (4)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>ANY abnormality</td>
<td>32 (48)</td>
<td>20 (36)</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Tropical Sprue

• Areas of risk:
  • Asia, India, Caribbean, Central/South America
• Symptoms: Identical to CD
• Tests:
  • None specific
  • Negative CD serologies
• Treatment: folate, B12, tetracycline

• TRAVEL HISTORY IMPORTANT!!!
Autoimmune Enteropathy

- Increased adult recognition
  - Equal M:F, age 55 yrs

- May be associated with IPEX or APECED
  - FOXP3 mutation that controls regulatory T cells*

- Refractory diarrhea and nutritional issues


Criteria for Diagnosis: Autoimmune Enteropathy

1. Chronic diarrhea (> 6 weeks)
2. Malabsorption
3. Partial/total villous blunting, deep crypt lymphocytosis, increased apoptotic bodies, minimal IELs (< 40/100 cells)
   - May be absence of goblet and Paneth cells
4. Exclusion of other causes of villous atrophy
5. Anti-enterocyte or anti-goblet cell antibodies supportive
   - Sensitivity 85-87%; non-specific

**Autoimmune Enteropathy vs Others**

**Autoimmune**
- No goblet cells; no Paneth cells
- Surface IELs less prominent
- Lymphoplasmacytic infiltrate

**Other (Tropical Sprue)**
- Goblet and Paneth cells present
- Surface IELs more prominent

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**T-cell Receptor Testing for Lymphoproliferative Disease**

- Two stains are most important:
  - CD3 (all T cells)
  - CD8 (T suppressor cells)
- Should be equal in the surface epithelium
- Loss of CD8 → abnormal clone
T-cell Lymphoma

USUAL
- Villous atrophy
  - Partial, total
- Crypt hyperplasia
- Intraepithelial lymphocytes
  - Tip-predominant
- Lymphocyte and plasma cell infiltrate in lamina propria
- Normal CD3+/CD8+ infiltrate

UNUSUAL
- Mucosal erosions/ulcers
- Neutrophilic infiltrates
- Non-tip predominant intraepithelial lymphocytes
- Loss of goblet cells
- Loss of plasma cells
- Crypt abscesses
- Loss of CD8 expression

Celiac Disease
Proposed Algorithm

Seronegative enteropathy

Adequate small bowel histology?

Medication review

Anti-enterocyte antibody

Travel history

Giardia antigen

HLA haplotyping

HIV testing

Immunoglobulins

Breath testing for SIBO

Adequate small bowel histology?

T-cell receptor staining

Adequate small bowel histology?

Proposed Algorithm

Seronegative enteropathy

Testing negative for etiology

HLA DQ 2/8 positive

Gluten-free trial

HLA DQ 2/8 negative

Immunosuppression
Take-Away Points

• The most important things in evaluating a patient with serologically-negative enteropathy are 1) a careful history, and 2) a good pathologist

• Isolated duodenal IELs is being seen with increased frequency; NSAIDs are common, and up to a third of cases with unknown cause

• Medications (over-the-counter/prescription) can mimic CD and should be considered in all patients with a serologically-negative enteropathy

• Many mimickers of celiac disease have clues to the diagnosis and a targeted therapy; patients will prefer a correct diagnosis over a lifetime of an unnecessary gluten-free diet

<table>
<thead>
<tr>
<th>Histology</th>
<th>Important to Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropical Sprue</td>
<td>Identical to CD</td>
</tr>
<tr>
<td>Collagenous Sprue</td>
<td>CD-like with thickened collagen band &gt; 5 microns, detached surface</td>
</tr>
<tr>
<td>Medication Effect</td>
<td>May ranges from IELs only to total villous atrophy, +/- collagen</td>
</tr>
<tr>
<td>H. pylori Infection</td>
<td>May have increased IELs, but also neutrophils, metaplasia</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease</td>
<td>May have increased IELs as a sole duodenal feature IELs more on sides or evenly distributed</td>
</tr>
<tr>
<td>Bacterial Overgrowth</td>
<td>May not have any change other than mildly &lt; V:C ratio Look for other causes of enteropathy</td>
</tr>
<tr>
<td>Autoimmune Enteropathy</td>
<td>Loss of goblet cells and Paneth cells, more neutrophils, apoptosis Can check anti-enterocyte antibody</td>
</tr>
<tr>
<td>Combined Variable Immunodeficiency</td>
<td>Loss of plasma cells; LP appears somewhat empty Up to 30% with normal plasma cells; check IgGs</td>
</tr>
<tr>
<td>Whipple’s Disease</td>
<td>Broad rather than flat villi, filled macrophages, lipid deposits Staining (AFB, PAS) and PCR testing</td>
</tr>
</tbody>
</table>