Small Bowel Malabsorptive Disorders: celiac disease and other entities

John Hart, M.D.
Chief of GI and Hepatic Pathology
University of Chicago Medical Center

Classic Old School Celiac Disease
Clinical Correlation is Mandatory

- **HLA testing:** absence of HLA DQ2 and DQ8 essentially excludes celiac disease
- **Serologic tests:**
  - Anti-tissue transglutaminase IgA (gold standard)
  - Anti-endomysium IgA antibody
  - Anti-deaminated gliadin peptide IgA
  - [Anti-gliadin IgA – no longer recommended]
- **IgA deficient individuals** (quant IgA level):
  - Anti-TTG IgG (gold standard)
  - Anti-DGP IgG


Complete Villous Flattening with Crypt Hyperplasia

- **CELIAC DISEASE**
  - Autoimmune enterocolitis
  - Viral enteritis (rare cases)
  - Tropical sprue (rare cases)
  - Common variable immunodeficiency (rare cases)
  - Medication (sartan) induced enteropathy
Clinical History

- 32 year old male with abdominal distress and diarrhea
- Endoscopic findings:
  - Esophagus & stomach normal
  - Flattening and decreased folds in the 2nd and 3rd parts of the duodenum
  - Scalloped folds in the 2nd part of the duodenum

Moderate villous blunting and crypt hyperplasia

Increased intra-epithelial lymphocytes
Increased lamina propria mononuclear cells

No Knowledge of Celiac Panel Results

Upper GI endoscopic biopsies, duodenum:
- Duodenal mucosa with moderate villous blunting and increased intraepithelial lymphocytes. See comment

Comment: Celiac disease is a diagnostic consideration. Correlation with serologic tests results is necessary.

Pathologist is Aware Celiac Panel is Positive

Upper GI endoscopic biopsies, duodenum:
- Duodenal mucosa with moderate villous blunting and increased intraepithelial lymphocytes, consistent with celiac disease.
Provided Clinical History:
Rule out celiac disease
Normal duodenal mucosa

Whether the celiac panel is:
- not known
- negative
- positive

Upper GI endoscopic biopsies, duodenum:
- Duodenal mucosa without diagnostic abnormality.
  See comment.

Comment: Sections of these large and well oriented biopsies reveal that the duodenal villi are long and slender and there is no increase in intraepithelial lymphocytes.

Malabsorptive Disorders
Morphologic Patterns

1. Complete villous blunting with crypt hyperplasia
2. Lesser degree of villous blunting with crypt hyperplasia (focal or diffuse)
3. Villous and crypt shortening (mucosal atrophy)
4. Normal mucosal architecture + / - “distinctive features”

Intraepithelial lymphocytosis
Marsh Classification
Type 0 – Normal architecture; no increase in IELs
Type 1 – Normal architecture; > 40 IELs
Type 2 – Crypt hyperplasia, normal villi; > 40 IELs
Type 3 – Crypt hyperplasia & villous blunting; > 40 IELs
Type 4 – Crypt & villous atrophy

Modified Marsh Classification
Type 0  Normal architecture; no increase in IELs
Type 1  Normal architecture; > 25 IELs
Type 2  Crypt hyperplasia, normal villi; > 25 IELs
Type 3  Crypt hyperplasia, villous blunting; > 25 IELs
   3a – mild villous blunting
   3b – subtotal villous blunting
   3c – total villous blunting
Type 4  Crypt & villous atrophy


Current Treatment of Celiac Disease
by Marsh/Oberhuber subtype
Type 0  - Gluten free diet for symptomatic patients?
Type 1  - Gluten free diet
Type 2  - Gluten free diet
Type 3 3a   - Gluten free diet
       3b   - Gluten free diet
       3c   - Gluten free diet
Type 4 - Gluten free diet (?) and immunosuppression

You don’t have to give a MARSH score
(unless it will make your clinician love you)
Celiac Disease Type 1 (celiac serology panel positive)


Asymptomatic normal volunteers
Cutoff of 20 IELs / 100 enterocytes
CD3 Immunostain
(don’t do this)

ROC-king onwards: intraepithelial lymphocyte counts, distribution & role in coeliac disease mucosal interpretation

Cutoff of 25 IELs/100 enterocytes

3 celiac disease pts below cutoff (false negative)
12 control patients above cutoff (false positive)
Diagnosing Mild Enteropathy Celiac Disease: A Randomized, Controlled Clinical Study

GASTROENTEROLOGY 2002;126:816–823

Kalle Korpila, M.D., Gabriele Celler, M.D., Mervi Viljakka, M.D., Heli Hamalä, M.D., M.Sc., Tuula Haukka, M.D., Ph.D., Kaisa Paasikivi, M.D., Ph.D., Kari A. Haudenshield, M.D., and Jari Hauru, M.D.

Suspicion of CD  n=145

- Biopsies and Marsh I–III  n=70

Duodenal biopsies

- Marsh I–II
  - Study group  n=23
  - CD group  n=27
  - Randomization
  - Gluten-containing diet  n=12
  - Gluten-free diet  n=12

- Marsh III
  - Gluten-free diet  n=13

Celiac Disease Type 1
Celiac Disease without Villous Atrophy in Children: A Prospective Study

Katie Karpin, MD, Noelia Asensio, MD, PhD, Saul Pimentel, MD, PhD, Leila L., E. Kassinen, PhD, Paal Samuelsen, PhD, Eelko J. Kootstra, MD, PhD, and Kari Kaukinen, MD, PhD

(J Pediatr 2010;157:373-80)

<table>
<thead>
<tr>
<th>Table 11: Baseline and follow-up data on the 17 children who were endomyocardial biopsy positive with normal small bowel mucosal villus morphology at baseline</th>
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<tbody>
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Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate?

A. D. Hopper, S. S. Cross, D. S. Sanders

Endoscopy 2007; 39: 219 – 224
One biopsy of duodenal bulb and four of the distal duodenum

<table>
<thead>
<tr>
<th>Patients (no.)</th>
<th>Group 1A (16)</th>
<th>Group 1B (20)</th>
<th>Group 1C (629)</th>
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<tbody>
<tr>
<td>Type 1 (%)</td>
<td>1 (6.25)</td>
<td>1 (5)</td>
<td>23 (3.67)</td>
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<td>Type 2 (%)</td>
<td>1 (6.25)</td>
<td>0</td>
<td>19 (3.02)</td>
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<td>Type 3a (%)</td>
<td>1 (6.25)</td>
<td>1 (5)</td>
<td>76 (12.08)</td>
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<tr>
<td>Type 3b (%)</td>
<td>4 (25)</td>
<td>5 (25)</td>
<td>240 (38.15)</td>
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<tr>
<td>Type 3c (%)</td>
<td>9 (56.25)</td>
<td>13 (65)</td>
<td>271 (43.08)</td>
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CD = celiac disease; group 1A: only bulbar lesions; group 1B: lesions patchily distributed; group 1C: diffuse lesions.
Intraepithelial Lymphocytosis with Normal Villous Architecture

- Tropical sprue
- Autoimmune enterocolitis
- Viral enteritis
- Giardiasis
- Cryptosporidiosis
- Microsporidiosis
- Bacterial overgrowth
- Food allergies
- Crohn’s disease
- Common variable immunodeficiency
- Systemic autoimmune diseases
- NSAIDs (and other drugs)
- H. pylori infection
Anti-endomysial antibody test negative in all Crohn's patients

HLA testing is also very useful – absence of HLA DQ2 and DQ8 excludes celiac disease

28 year old female with Crohn's disease
Increased IELs in a patient with known Crohn's disease

Refractory Sprue
Clinical Features
- Redevelop diarrhea while on a GFD
- Usually elderly and with weight loss
- There should be a well established Dx of CD

Refractory Sprue
Causes
- Inadvertent gluten ingestion
- Lymphocytic or collagenous colitis
- Ulcerative jejuno-ileitis (lymphoma)
- Enteropathy associated T-cell lymphoma
- Collagenous sprue
- Pancreatic insufficiency
- Food allergy
- Nutrient deficiency (zinc, folic acid)
**Refractory Sprue**

**Pathologic Features**

- Persistent abnormal histology while on a GFD:
  - Usually there is severe villous blunting
  - Usually there is a marked increase in IELs

- **Type 1:**
  - IELs normally express CD3 with CD4 or CD8
  - Polyclonal by T-cell receptor gene rearrangement studies

- **Type 2:**
  - IELs CD3+ but CD8- and CD4- (and TCR-beta -)
  - Clonal T-cell receptor gene population

65 y.o. F with severe chronic diarrhea and 25 lb weight loss
Negative serologic tests for celiac disease
Diagnosed with “refractory celiac disease” based on duodenal biopsies
No response to gluten free diet
Severe Spruelike Enteropathy Associated With Olmesartan


<table>
<thead>
<tr>
<th>Case Number</th>
<th>Case Description</th>
<th>Histology Findings</th>
</tr>
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<tbody>
<tr>
<td>72 y.o. M with severe chronic diarrhea and weight loss</td>
<td>Serologic tests for celiac disease are all negative</td>
<td>Duodenal biopsy C11-27821</td>
</tr>
</tbody>
</table>

Case Courtesy of Dr James Taylor, Regional Medical Labs, Tulsa
Olmesartan Induced Enteropathy

- Angiotensin II receptor antagonist
- Commonly used to treat hypertension
- Clinical presentation:
  - Diarrhea begins 2-10 years after drug is started
  - Chronic watery diarrhea and weight loss
  - Celiac-like histology (+/- collagen thickening)
  - +/- coexistent lymphocytic or collagenous gastritis
  - +/- coexistent lymphocytic or collagenous colitis
  - Negative serologic tests for celiac disease
  - Diagnosis of "refractory sprue"
  - No response to a gluten free diet
  - Responds slowly to withdrawal of medication

Enteropathy Associated T-cell Lymphoma (EATL)
Ulcerative Jejuno-ileitis
Clinical History

- 31 y.o. M with a long history of non-bloody diarrhea
- 25 lb weight loss over the past two years (118 lbs.)
- Diagnosed with diabetes, but no weight gain with oral hypoglycemic agents
- Upper endoscopy:
  - Scalloped duodenal folds
  - Biopsies reveal features consistent with celiac disease
- Celiac HLA and serology panel:
  - DQ2 positive
  - IgA deficient (IgA less than 5)
  - Anti-gliadin IgG positive
- Placed on GFD – continued diarrhea; no weight gain
- Repeat upper endoscopy with duodenal biopsies
**Additional Laboratory Evaluation**

- DGP IgG negative
- Iron, vitamin D, zinc & folate deficient
- Quantitative immunoglobulin levels:
  - IgA = < 5 \( (110-490 \text{ mg/dL}) \)
  - IgG = 410 \( (800-1700 \text{ mg/dL}) \)
  - IgM = 6 \( (50-320 \text{ mg/dL}) \)

Dx: Common variable immunodeficiency with Giardia infection

**Histologic Features distinct to CVID**

- Absent or greatly decreased plasma cells
- Crypt cell apoptosis
- Significant neutrophilic infiltrates
- Mucosal lymphoid follicles
- Giardia lamblia infection
Colon biopsy

Colon biopsy – no plasma cells!

The Enteropathy Associated With Common Variable Immunodeficiency: The Delineated Frontiers With Celiac Disease

50 patients with CVID and duodenal biopsies
- Mean age at diagnosis of CVID was 36.8 +/- 15.6 yrs
- Mean onset of GI symptoms was 34.5 +/- 14.3 yrs
- Anemia in 56% and malabsorption in 54%
- DQ2 or DQ8 in 77% of tested patients
- 31 of 50 (62%) with increased duodenal IELs
- 21 of 31 (67%) with inc. IELs had villous atrophy
- 3 of 38 patients tested positive celiac serologic tests
- No response to gluten free diet in 10 treated patients
Clinical History

- 23-month-old M with failure to thrive and a 1 mo Hx of severe watery diarrhea.
- Diarrhea persisted despite discontinuation of oral feeding and administration of TPN.
- Serologic tests for celiac disease were all negative.
- HIV antibody test negative
- Duodenal biopsies obtained
Colonic Biopsy
**Autoimmune Enterocolitis**
- Presentation in first year of life, or as adult
- Severe diarrhea, even when NPO on TPN
- Do not respond to gluten free diet
- Serologic tests for celiac disease negative
- Anti-enterocyte/goblet cell antibodies (non-specific)
- **Usually affects both small and large bowel**
- Duodenal morphology similar to celiac disease in some cases
- Treated with immunosuppressive drugs

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**Other Rare Neonatal Enteropathies**
- Congenital transport protein defects:
  - Chloride-bicarbonate exchanger
  - Sodium-hydrogen exchanger
  - Ileal bile acid receptor
- Enterokinase deficiency
- Tufting enteropathy
- Microvillus inclusion disease
- IPEX syndrome

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**Crypt and Villous Atrophy Pattern**
- Collagenous sprue
- Microvillus inclusion disease
- Drug toxicity:
  - cis-platinum
  - Vincristine
- Cow’s milk protein intolerance
Clinical History

- 4-week-old F with poor weight gain and watery diarrhea and severe metabolic acidosis
- Diarrhea continued despite TPN and discontinuation of oral feedings
- Family history significant for a parental consanguineous marriage of cousins
- Older sibling died at 4 weeks of age of uncontrollable diarrhea

Microvillous Inclusion Disease

[Image of Microvillous Inclusion Disease]

Microvillous Inclusion Disease

[Image of Microvillous Inclusion Disease]
poorly developed brush border

PAS stain
Tufting enteropathy
8 y.o. F treated with procarbazine, CCNU, and vincristine for recurrent medulloblastoma

5-week-old F with failure to thrive and a 3-week history of watery diarrhea
Cow’s Milk Protein Intolerance

- Immune reaction to a variety of peptides within cow’s milk
- Metabolic acidosis and blood in stool in severe cases
- Peripheral blood eosinophilia uncommon
- Tissue eosinophilia uncommon
- Can effect small or large bowel or both
- No specific test – RAST testing often performed
- Re-challenge necessary for definite diagnosis

Variable Villous Blunting with Crypt Hyperplasia

- Viral enteritis
- Tropical sprue
- Bacterial overgrowth
- Zollinger-Ellison syndrome
- Whipple disease
- Mycobacterium avium intracellulare
- CMV infection
- Cryptosporidium
- Isospora
- Microsporidium
23 y.o. Male with AIDS

Fite Stain

Mycobacteria Avium Intracellulare
Normal Mucosal Architecture

- Celiac disease
- Cryptosporidium
- Giardia
- Eosinophilic gastroenteritis
- Lymphangectasia
- Abetalipoproteinemia
- Systemic mastocytosis
- Amyloidosis

Terminal ileal biopsy in a patient with diarrhea
Clinical History

- 40 y.o. F with sudden onset of abdominal pain
- She also reports mild intermittent diarrhea
- Similar episodes in the past but extensive work-up has been negative
- Colonoscopy and upper endoscopy with biopsies two years ago were reported normal
- No medications except for Tylenol during the painful episodes
Ascitic Fluid Cytospin

Incidental lymphangiectasia
Lymphangiectasia due to pancreatic cancer infiltrating the root of the mesentery

Clinical History

- 8-month-old F with diarrhea and failure to thrive
- Physical exam: listless & generalized mild hypotonia
- 72-hour stool collection reveals severe steatorrhea
- Liver chemistry tests mildly elevated
Normal physiologic change due to not being NPO before endoscopy

Summary
- As much clinical history as possible
- As many biopsies as possible
- Some conditions have distinctive features, but many do not
- Many conditions produce an increase in IELs
- Cooperation between endoscopist and surgical pathologist is essential