How not to sprue-up a small bowel biopsy

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DISEASES OF MALABSORPTION

**Definitions**

**Malabsorption:**
- Used broadly to describe impaired uptake by the small intestine of one or more nutrients.

**Malabsorption Syndrome:**
- A group of clinical findings that typically includes diarrhea, steatorrhea, weight loss, malnutrition, etc.
Disorders of Malabsorption Classification

- Normal mucosal histology
- Non-specific inflammatory and architectural changes
- Demonstrable infectious agents
- Immunodeficiency present
- Misc. entities with characteristic findings
Celiac Disease

Also known as:
- Childhood Celiac Disease
- Adult Celiac Disease
- Sprue, Non-tropical Sprue, Celiac Sprue
- Gluten -Sensitive Enteropathy, Gluten -Induced Enteropathy
- Idiopathic Steatorrhea
Cause of Celiac Disease

Wheat Flour

Starch
Fat
Fiber
Protein

Water Insoluble Fraction
Gluten

Water Soluble Fraction

Alcohol Insoluble
Glutenin

Alcohol Soluble
Gliadin

Wheat Flour
Celiac Disease
Histopathology - prior to Tx

- Flat biopsy with surface damage
- Increased Intraepithelial lymphocytes
- Increased lamina propria inflammation
  - Plasma cells
- Increased crypt mitoses
Celiac Disease
Histopathology - Shortly after Tx

- Marked clinical improvement
- Surface epithelium restored
- Slight return of villi
- Other findings unchanged
Gluten Free Diet - 2 Weeks
Celiac Disease
Histopathology - Long term Tx

- Continued clinical improvement
- Further return of villi
- Mitotic rate subsides
- Chronic inflammation subsides
Celiac Disease
Gluten Challenge

Epithelial lymphocytes increase
Epithelial damage to upper villi
Full-blown lesion develops later
Genetic Aspects
- Familial Occurrence (11-22% first degree relative)
- Identical Twin Concordance (70%)
- HLA Associations (DR3, DQw2, B8)

Environmental Factors
- Dietary Gluten
- Twin non-concordance rate of 30%; separate onsets
- Viral exposure (Adenovirus type 12)
### Serologic Markers In Celiac Disease

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Anti-gliadin</td>
<td>31-100%</td>
<td>85-100%</td>
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<tr>
<td>Anti-reticulin</td>
<td>42-100%</td>
<td>95-100%</td>
</tr>
<tr>
<td>Anti-endomysium</td>
<td>60-100%</td>
<td>95-100%</td>
</tr>
<tr>
<td>Tissue Transglut</td>
<td>85-100%</td>
<td>92-97%</td>
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Celiac Disease
Variant and Overlap Forms

- **Latent Celiac Disease**
  - No symptoms, but histologic changes

- **Collagenous Sprue**
  - May also have Collagenous Colitis

- **Dermatitis Herpetiformis**
  - May have sprue-like small bowel biopsy without malabsorption
  - Histology often less severe
CD Iceberg

DQ2

CD
latent
normal

Diseased mucosa
Normal mucosa
Celiac Disease Complications

- **Refractory Celiac Disease**
  - Malabsorption that responds to gluten withdrawal initially, but is later unresponsive

- **Refractory Sprue**
  - Malabsorption that is unresponsive to gluten withdrawal from the start
Celiac Disease Complications

- Refractory Celiac Disease
- Ulcers of Small Bowel
- Malignancy
  - T cell Lymphoma of gut and regional nodes
  - Adenocarcinoma of small bowel
  - Squamous cell carcinoma of esophagus and oropharynx
Small Intestinal Ulcers In Celiac Disease
Malabsorption

Sprue-like Changes

Gluten Free Diet

Response
- Remain Well
- Benign Ulcer

No Response (Refractory Sprue)
- Deterioration
- Refractory Celiac Disease
- Lymphoma
Celiac Disease
Histologic Mimics

- **Celiac-related**
  - Dermatitis Herpetiformis
  - Lymphoma
  - Collagenous Sprue
- **Other Substance Sensitivities**
  - Soy protein
- **General**
  - Peptic duodenitis
  - Tropical Sprue, Bacterial overgrowth
  - Autoimmune enteropathy, Lymphocytic enterocolitis
  - Microvillus inclusion disease, Crohn’s disease
Normal Architecture
Increased IELs

- Gluten Sensitive Enteropathy
  - Early type 1 lesion or treated sprue
- Other food hypersensitivity
- H. Pylori (usually only in bulb)
- Autoimmune conditions (RA, SLE, MS, Graves, Hashimoto's, Diabetes)
- Post-infection
- Drugs (NSAIDs)
Celiacs do it gluten free
Tropical Sprue

- Chronic malabsorption after infectious diarrhea commonest in tropical regions
- Bacterial overgrowth with B-12 and Folate deficiencies - often responds to antibiotics and vitamin supplements
- Biopsy findings are variable
  - Sprue-like changes with less intense damage than full blown celiac disease
  - Both Jejunum and Ileum involved
In Lagos, Harare and Durban, evidence of postinfective malabsorption is limited to a few reports on small numbers of cases.
Stasis Syndrome
(Bacterial Overgrowth)

- Crohn’s Disease
- Diverticular Disease
- Scleroderma
- Pseudo-obstruction
- Post-Surgical
  - Blind loop or Pouch
  - Entero-enterostomy
  - Afferent loop
  - Fistulae
  - Adhesions/partial obstruction
Bacterial Overgrowth Biopsy Findings

- Irregular Villi
- Surface cell damage
- Plasmacytosis
- Neutrophils
- Crypt Hyperplasia
- “Doesn’t fit”
Pathophysiology of Stasis

Stasis
Small Intestine

Bacterial Overgrowth (Esp. Anaerobes)

Bile Salt Deconjugation
Malabsorption

Epithelial Injury
Malabsorption

B-12 Deficiency
Anemia
Disorders of Malabsorption Classification

- Normal mucosal histology
- Non-specific inflammatory and architectural changes
- Demonstrable infectious agents
- Immunodeficiency present
- Misc. entities with characteristic findings
Whipple’s Disease

- Described by George Whipple in 1907 as “intestinal lipodystrophy”
  - Whipple described rod shaped bacteria within lymphoid tissues and thought they might cause the disease
- Subsequently thought to be a lipid storage disorder until advent of EM in the early 1960’s
Whipple’s Disease

741 patients reported as of 1988, many multiple times

20,000 authors reported these patients

This works out to 27 authors per patient

- (a fairly high CV bulk ratio)
Whipple’s Disease

Clinical Presentation:
- Most patients are middle-aged white males
- T cell defect, Associated with HLA-B27
- Present with diarrhea, malabsorption, weight loss and abdominal pain
- Systemic and neurologic symptoms may overshadow GI complaints
- May present with only CNS symptoms
Whipple’s Disease
Histopathology

- Blunted and distorted villi
  - Contain macrophages, neutrophils, lipid droplets, and dilated lacteals
- Foamy macrophages fill the lamina propria
  - Granular PAS positive diastase resistant inclusions
  - May see PAS + rods in extracellular areas
  - AFB negative
Silver stains may help highlight intact bacteria
- May find bacteria in epithelium, endothelium, lymphocytes, even fibroblasts
EM shows phagosomes stuffed with bacteria in various phases of digestion
PAS+ macrophages remain for years, but intact bacteria should disappear soon after start of Tx
Lymph nodes, liver, heart, brain, eyes, and colon may all have foamy macrophages and granulomatous foci

- May or may not be PAS+
- Much harder to diagnose than Small bowel bx
- May mimic Sarcoidosis clinically and pathologically

Whipple’s Disease
Extra-intestinal Pathology
Whipple’s Disease
Diagnostic Pitfalls

**False Positives:**
- Mycobacteria avium/intracellularum
- Muciphages (rectal biopsy)
- Lymph nodes (other PAS+ substances)

**False Negatives:**
- Sampling error
- Submucosal form of disease
- May have no histologic involvement but be PCR+
AIDS IN A HAITIAN WOMAN WITH CARDIAC KAPOSI’S SARCOMA AND WHIPPLE’S DISEASE

Sir,—A 24-year-old Haitian woman was referred to us from Guadeloupe with giant chronic vulvar and perineal ulceration and a 2 year history of diarrhoea, weight loss, fever, and oesophageal candidiasis. She had received amphotericin B and cyclines for 8 months but her general condition had been getting worse, with a 25 kg weight loss.

She had a high grade fever, diarrhoea, a giant painful vulvoperineal herpetic ulceration, and a smaller perioral one without any other skin lesion. We noted a sinus tachycardia (150/min) with a gallop rhythm; liver enlargement but no peripheral or mediastinal lymphadenopathy; and, on chest X-ray, cardiomegaly with very slight interstitial lung involvement. Herpes simplex virus was detected in the giant ulcer, the gastrointestinal candidiasis was confirmed, and blood cultures indicated Staphylococcus aureus septicaemia.

The suspected diagnosis of a severe acquired immunodeficiency syndrome (AIDS) was confirmed by the profound lymphopenia (0.1 x 10^9/l) and cutaneous anergy and by an absolute defect of OKT4 lymphocyte subtype (with a helper/suppressor-cytotoxic T cell ratio of zero).
Muciphages

PAS

Alcian Blue
Whipple’s Disease
Diagnostic tests/Ancillary studies

- Small Bowel Biopsy
  - PAS stain
  - EM or Silver stain
- Blood Smear
- PCR
  - Tissue or blood
**Giardiasis**

- *Giardia lamblia* - first protozoa discovered in the human intestine
  - Described by Leeuwenhoek in 1681 (in his own stools)
- Most prevalent gut parasite in the U.S. (7.4%)
- May be endemic or epidemic
  - 23% of American travelers to Leningrad found to be infected over a 4 year period
  - Often spread by children via day care/school
Giardiasis
Epidemiology

- Fecal/oral spread
  - contaminated drinking water
  - intimate contact, “gay bowel disease”
- Children and patients with agammaglobulinemia, hypogammaglobulinemia, IgA deficiency, and/or achlorhydria are at increased risk
- Immunosuppressed patients more likely to have chronic infection
Giardiasis

Clinical Symptoms:

- Acute diarrhea with greasy foul smelling stools, no blood

- Abdominal distention, bloating, pain, and flatulence

- Weight loss and malabsorption
Trophozoites are identifiable on H&E stained sections

- Ventral view: pear shaped body with 2 nuclei
- Lateral view: Sickle shaped body
- “Smudgy blue-grey blobs” that mimic extravasated mucus
- Clumped together between villi or attached to epithelial surface, rare reports of invasion
**Giardiasis**

**Histopathology**

- Special stains may help bring out details of organism: trichrome, giemsa, PTAH or PAS
- Touch preps of biopsy may also help
- **Inflammatory response is quite variable:**
  - Some have normal biopsies, some have minor non-specific changes
  - Some get sprue-like changes, particularly hypogammaglobulinemic patients
Organisms are best found in distal duodenal or proximal jejunal biopsies.

Duodenal fluid aspirate or String test may have better yield.

Cysts may be identified in Stool exam (both cysts and trophs in stool if diarrhea is severe).

Stool antigen test available.
Cryptosporidium

C. parvum is the species
- Organism lives within brush border
- Common in animals, may be a zoonosis

Healthy persons
- Asymptomatic carrier state
- Endemic and epidemic infections
- Self-limited diarrheal illness

Immunodeficient persons
- Chronic diarrhea, malabsorption