Small Intestinal Non-neoplastic Pathology

Normal duodenal mucosa

Duodenal mucosa, PAS/AB stain

Duodenal mucosa with "lipid hang-up" in enterocytes

Cheater lesion

Disclosure Statement
Dr. Montgomery reports no relevant financial relationships with commercial interests.
"Artifact" Mistaken for Other Lesions

Crushed Brunner Glands may be mistaken for:
myxoid nerve sheath tumors.
Whipple’s disease
Crushed Brunner’s glands called Whipple’s disease – confirmed by PAS/AB (oops)

“Artifact” Mistaken for Other Lesions

Titanium from toothpaste and food products may be found in lymphoid aggregates in both the small intestine and colon

Ileum, note black material
"Peptic Duodenitis"

When esophagus and stomach are injured, intestinal metaplasia ensues. The duodenum undergoes gastric metaplasia. Helicobacter gastritis was originally strongly associated with duodenal ulceration. 

Old theory - H pylori infection upregulates gastric acid secretion by damaging D cells that secrete somatostatin (somatostatin normally reduces gastric secretion). Bulb (the area just beyond the pyloric sphincter) damaged. Gastric mucin cell metaplasia /Brunner gland hyperplasia.
Gastric mucin cell metaplasia, PAS/AB stain

Gastric mucin cell metaplasia can even support H. pylori.

Reactive or neoplastic? The mucin can be a clue.
Reactive or neoplastic? The gastric mucin can be a clue for reactive

Nodular gastric heterotopia

Occasionally an antral gastric hyperplastic polyp will “flop” down into the small bowel

Ampulla
Can be a source of diagnostic difficulty
In the ampulla of course it is entirely normal to encounter a mix of biliary type glands and smooth muscle

Ampulla with reactive changes
Atypical stromal cells that can be found in ulcer beds in any GI tract site are also found in the small bowel.
**Mycobacterium Avium Complex (MAI)**

Patients with CD4+ cell counts of less than 100/ul abdominal pain, fever, weight loss, chronic malabsorption, diarrhea etc. Clarithromycin or azithromycin are the preferred agents for MAI prophylaxis.

**Whipple’s disease**

Systemic bacterial infection caused by *Tropheryma whippelii* (an actinomycete). Male predominance of 8-10:1, with white males between the 4th-5th decade most commonly affected. diarrhea, low-grade fever, weight loss, malabsorption, abdominal pain, arthralgia, anemia, lymphadenopathy (50%), cardiac and central nervous system symptoms (10%). Most patients respond dramatically to antibiotics (trimethoprim and sulfamethoxazole).
Whipple’s Disease

First described by Dr. George Whipple at Johns Hopkins in 1907 as “intestinal lipodystrophy” due to the prominent accumulation of lipids in intestinal mucosa and lymph nodes. Bacterial etiology of this condition was confirmed by electron microscopy in 1961. An immunostain is now available.
Whipple’s disease, foamy macrophages, PAS/AB, stuffed with organisms, dilated lacteals

Whipple’s disease, electron micrograph

CNS Whipple Disease

Whipple immunohistochemistry

Whipple disease before and after treatment

Whipple Disease
**Whipple Disease – The Most Important thing – The Patient**

*Before*  
*After*

**Whipple v MAI - PAS**

Whipple has dilated lacteals  
On PAS, Whipple has much more “globular”, “chunky” staining than MAI.

---

**A Quick Hello To Parasites**

*Strongyloides stercoralis*  
Nematodal infection with a worldwide distribution affecting 30 to 100 million people.  
Endemic to Africa, Southeast Asia, South America, and parts of the US (e.g., Kentucky and Eastern Tennessee).

**Strongyloides stercoralis**

The life cycle:  
Female lays eggs without fertilization (parthenogenesis) in small intestinal crypts.  
Embryonated eggs hatch into rhabditiform larvae, which pass into the lumen and are expelled with feces.  
Rhabditiform larvae develop into filariform larvae (infective form), which penetrate human skin, then pass through blood vessels to the lungs and into the upper airways.  
When the patient coughs, the larvae are swallowed and ultimately reach the small intestine and mature into adult worms. The males are rapidly expelled after fertilizing the females.

**Strongyloides stercoralis**

Hyperinfection in the setting of immunosuppression can lead to the presence of *Strongyloides stercoralis* dissemination throughout the body with high mortality.
Anasakiasis (taken from CDC website)

“Anasakiasis is a parasitic disease caused by anisakid nematodes (worms) that can invade the stomach and/or intestine of humans. The transmission of this disease occurs when anisakid larvae are ingested from fish or squid that are sold undercooked or raw. In some cases, the infection is treated by removal of the larvae via endoscopy or surgery.”
Graft versus host disease

Secretory diarrhea, abdominal pain, and, at times, hemorrhage.
Syndrome of upper GI GVHD, presents clinically as anorexia, dyspepsia, food intolerance, nausea, and vomiting.
Original grading criteria were published by Snover
grade 1 = increased crypt apoptosis;
grade 2 = apoptosis with crypt abscess;
grade 3 = individual crypt necrosis
grade 4 = total denudation of areas of mucosa.
chronic graft versus host disease results in non-specific features of lamina propria fibrosis and mucosal atrophy.

Reporting GVHD

Attempt to grade the active component
Note the features of the chronic component.
Compare the biopsies to any prior ones.
GVHD-like response to CellCept® (Mycophenolate mofetil).
Widely used for maintenance immunosuppression in solid organ transplantation. Gastrointestinal toxicity, usually manifested as diarrhea, is its most common side effect.

Celiac Disease

Common (1%) systemic autoimmune disorder induced by gluten proteins found in wheat, barley, and rye.
Injury to the small intestine hallmark of disease, but manifestations are systemic.
Extra-intestinal sites include skin (classically with dermatitis herpetiformis), joints, and uterus such that clinical presentations can be subtle and not GI tract related.

Screening; anti-gliadin tests are no longer recommended as they produce too many false positives.
Patients with Crohn’s disease may have both false positive anti-gliadin tests as well as prominent intra-epithelial lymphocytes, a combination likely to result in misdiagnosis.
Anti-tissue transglutaminase or anti-endomysial tests are recommended. IgA based tests so yield false negative results in IgA deficient patients. IgG based tests exist for this situation.
Several biopsies should be obtained since characteristic features may be patchy.
Diagnosis of Celiac Disease
European Society of Paediatrics Gastroenterology Hepatology and Nutrition (ESPGHN)

1970: series of 3 small bowel biopsies
1. Initial abnormal biopsy while on gluten containing diet
2. Improved biopsy while on gluten free diet
3. Subsequent deterioration with gluten challenge

1990: Single biopsy
• Characteristic celiac disease lesions
• Unequivocal clinical response (commonly utilizing follow-up biopsy)

2012 and beyond: Nonbiopsy diagnosis?

A Modern Definition
An immune-mediated systemic disorder
Elicited by gluten and related prolamines
In genetically susceptible individuals
Characterized by:
1. CLINICAL: Variable combination of gluten-dependent clinical manifestations
2. SEROLOGY: Celiac disease specific antibodies
3. GENETIC: HLA-DQ2 and HLA-DQ8 haplotypes
4. HISTOLOGY: Enteropathy

Why the change in definition?
Developments over the past decade:
• Serologic tests with high accuracy
• HLA typing
• Histologic findings are nonspecific
  - Patchy
  - May occur only in bulb
  - High interobserver variability

Gastrointestinal and Hepatic Findings
Abdominal pain
Abdominal distention
Nausea / vomiting
Steatorrhea
Aphthous stomatitis
Cheilosis
Diarhea
Hepatic steatosis
Weight loss

Nongastrointestinal findings
Delayed puberty / short stature
Osteopenia / osteoporosis
Folate deficiency anemia
Recurrent spontaneous abortions
Thrombocytosis (hyperplasmin)
Infertility (male / female)
Anxiety / depression
Arthritis or arthropathy
Dental enamel hypoplasia
Anemia
Vitamin K deficiency
Polyneuropathy
Dilated cardiomyopathy
Clubbing
Egocytosis
Epilepsy

*Fissuring and dry scaling of the vermilion surface of the lips and angles of the mouth, a characteristic of riboflavin (Vit B2) deficiency.
**Associated conditions**

**GASTROINTESTINAL**
- Primary biliary cirrhosis (6%)
- IgA deficiency (7-10%)
- Cystic fibrosis (rare)
- Autoimmune metaplastic atrophic gastritis
- Autoimmune hepatitis (5%)

**NON-GASTROINTESTINAL**
- Congenital heart defects
- Type I diabetes (3-7%)
- Down's syndrome (10%)
- Autoimmune thyroiditis (3-5%)
- Sarcoidosis
- Schizophrenia
- Turner syndrome
- Rheumatoid arthritis
- Dermatitis herpetiformis
- Hypothyroidism
- Vasculitis
- Addison's disease
- Psoriasis
- Alopecia
- Recurrent pericarditis
- Recurrent pancreatitis

**HLA-DQ2 and HLA-DQ8**

30-40% of population have HLA-DQ2 and/or HLA-DQ8
CD develops in a minority of the population
>65% of patients with CD have the isoform DQ2 or DQ8
Inherited in families and geographically
Lack of these permissive haplotypes essentially excludes celiac disease.

**Microscopic features**

- Normal Mucosa
- Marsh type 0
- Increased intra-epithelial lymphocytes (IELs)
- Marsh type 1
- Increased lamina propria chronic
- Marsh type 2
- Crypt Hyperplasia
- Marsh type 3a, 3b, 3c
- Villous Blunting
- Mild
- Moderate
- Total Atrophy

Some observers suggest choosing 20 epithelial cells in the tip of a villus – if there are 6 associated lymphocytes Consider celiac serology – about 20% will be +

"latent" celiac disease pattern

"full-blown" celiac disease
Celiac Disease

We do not routinely stain for T cells in evaluating small intestinal biopsies but some authors have advocated this practice and suggested assessing for CD3 reactive cells in a “top-heavy” distribution (more prominent at the tips than at the bases of villi). These authors regret their publication!

Reality In Diagnosing Celiac Disease

Causes of Villous atrophy.
Celiac disease and the related condition dermatitis herpetiformis
Cow’s milk protein intolerance (pediatric), giardiasis
Peptic duodenitis
Crohn’s disease
Small bowel bacterial overgrowth (stasis and overgrowth usually of anaerobes)
Eosinophilic gastroenteritis
Radiation enteritis
Tropical sprue
Severe malnutrition
Lymphoma, graft versus host disease
Hypogammaglobulinemia/common variable immunodeficiency syndrome, and alpha chain disease.

What a biopsy lacks is as important as what it shows

Common Variable Immunodeficiency

Small bowel biopsies from these patients display villous atrophy and may have prominent intraepithelial lymphocytes as well as crypt apoptosis and even occasional granulomas, all features that suggest celiac disease and/or Crohn’s disease.

No plasma cells about 2/3 cases
Likely to harbor infectious agents (particularly giardia).
Giardiasis in patient with common variable immunodeficiency syndrome; no lamina propria plasma cells.

Immunocompetent giardiasis.
Collagenous sprue pattern in CVID

Autoimmune Enteropathy

Once again, what a biopsy lacks is as important as what it shows!!!!!!

Autoimmune Enteropathy – What’s missing – 2 things?????

Look Mama, no goblet cells or Paneth cells
Autoimmune Enteropathy

Severe villous injury – no response to diet
Circulating gut auto-antibodies or associated autoimmune conditions
Lack of severe immunodeficiency
Commonest in male children; adults and females can be affected

Autoimmune Enteropathy/IPEX/FOXP3 Deficiency

FOXP3 molecule governs generation of mature regulator T cells (Tregs) expressing CD4 and CD25
Mutations of the gene on the X chromosome produce a syndrome: Immune dysfunction, Polyendocrinopathy, Enteropathy, and X-linked inheritance (IPEX)
Probably other molecules involved as well
Auto-immune Enteropathy – after Treatment (steroids)

Prominent Small Bowel Apoptosis
- Autoimmune enteropathy
- GVHD
- Mycophenolate-associated
- Telomerase defects(!)
- Medications
- Viral infections

Telomere Maintenance Disorders

Several disorders of telomere maintenance cause human disease, which tends to affect organs with high cell turnover (including GI tract). Pulmonary fibrosis is characteristic. Esophageal stenosis, enteropathy, and enterocolitis are characteristic. Intestinal (large and small) samples show prominent apoptosis, villous blunting in small bowel.


Telomere-mediated disease, villous blunting.
Case -

Male infant with history of IUGR, microcephaly, with prolonged hospital course significant for failure to thrive, severe enterocolitis, immunodeficiency, recurrent culture-negative sepsis.
Our patient versus normal
“Refractory Sprue”
Subset of cases that defies current medical management and has a presentation resembling celiac disease and these are sometimes termed “refractory sprue”.
Robert et al reported ten cases of refractory sprue and found that five of the 10 refractory patients ultimately developed collagenous sprue as a distinct histologic marker of refractory disease.

Refractory Sprue
In other studies and in our experience, such cases may be clonal by gene rearrangement studies and related to T cell lymphomas, but these cases are also heterogeneous and rare so difficult to study well. Some such patients respond to steroids but others are managed with anti-neoplastic regimens or anti-TNF alpha.

Refractory Sprue
Negative celiac serology OR initially positive then negative
Poor response to gluten free diet
Sometimes clonal by T cell gene rearrangement studies
May be in a spectrum with so-called N-K cell enteropathy

Refractory Sprue
Cal be divided into two types:
Type 1 refractory sprue: CD3+, CD8+, no clonality on analysis of T cell receptor gene rearrangements
Type 2 refractory sprue: CD3+, loss of CD8, clonality on analysis of T cell receptor gene rearrangements

“Refractory Sprue” looks like celiac disease
Refractory sprue can have a collagenous sprue pattern.

Severely ill young woman; these lymphocytes were CD8 reactive.

Severely ill young woman; these lymphocytes were CD8 reactive.

IgA deficiency; looks normal.

IgA stains can also look normal.
IgA deficiency and celiac disease

Stasis/ Small bowel bacterial overgrowth

“Tropical Sprue”
Small intestine of individuals predominantly living in and less often visiting or returning from tropical areas with poor sanitation
Epidemics, particularly in rural areas with poor sanitation, visitors from developed countries to endemic regions
Ranges from asymptomatic structural and/or functional abnormalities of the gastrointestinal mucosa (subclinical enteropathy) to a fully symptomatic condition highlighted by malabsorption of nutrients with associated nutritional deficiencies
Responsive to broad spectrum antibiotic treatment suggests infection/s.

“Tropical Sprue”
The findings appear similar to those in celiac disease in terms of villous attenuation but with the addition of active inflammation and, at times, features of chronicity such as gastric mucin cell metaplasia and crypt distortion.
DDX – celiac disease and Crohn’s disease
Primary Lymphangiectasia

Usually diagnosed before the age of 3 years. Most patients have growth retardation.
Gastrointestinal complaints consist of diarrhea, vomiting, abdominal pain, and steatorrhea.
Secondary edema from protein-losing enteropathy and malabsorption may occur. The edema is usually generalized, but asymmetric edema is not uncommon.

Primary Lymphangiectasia

Small biopsies taken in these patients may be non-diagnostic - multiple dilated lacteals, a finding easy to overlook without knowledge of an often dramatic CT appearance.
The long-term course is variable, but is usually slow in progression with intermittent clinical remissions.
Reported medical treatments lymphangiectasia: high-protein, low-fat diet with added medium-chain triglycerides. Octreotides have been reported to decrease intestinal protein losses.
Subtle example of primary lymphangiectasia

Subtle example of primary lymphangiectasia

Microvillous Inclusion Disease
Intractable diarrhea of infancy
Autosomal recessive
Found in populations with abundant consanguity (e.g., tribal Arabs)
EpCam may be involved but the genetics are incompletely understood

Microvillous Inclusion Disease
The diagnosis criteria for microvillus inclusion disease include:
- Intractable watery diarrhea in early infancy
- Diffuse intestinal villous atrophy with no inflammatory reaction
- Apical microvillus inclusions of surface enterocytes identified under electron microscope (definitive diagnosis criterion)
- No evidence of infection, autoimmune disease, or allergy.
Microvillous Inclusion Disease

Tufting Enteropathy; has loss of EPCAM