Intraepithelial Lymphocytes in the Gastrointestinal Tract: To Celiac Disease and Beyond

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Current Issues in Anatomic Pathology
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Outline
• Celiac disease and lymphocytosis of the small bowel
  • Clinical features
  • Histopathology
  • Differential diagnosis
• Intraepithelial lymphocytes elsewhere in the GI tract
  • Esophagus
  • Stomach
  • Colon
• Other conditions with GI tract lymphocytosis
  • Drugs (esp. immune checkpoint inhibitors)

Disclosures
• BHB Therapeutics (spouse is co-founder)

Did you know...
• “Sprue” is an Anglicized form of the Dutch word “sprouw,” a term applied in 1669 to a chronic diarrheal disease of unknown etiology accompanied by aphthous ulcers that was prevalent in Belgium
Celiac disease and other gluten-related disorders

- **Celiac disease (CD)**
  - Non-IgE immune-mediated
  - Triggered by dietary gluten ingestion
  - In genetically susceptible individuals
- **Non-celiac gluten sensitivity (NCGS)**
  - Patients develop intestinal and extraintestinal symptoms after gluten exposure
  - Do NOT meet criteria for CD or WA
- **Wheat allergy (WA)**
  - Hypersensitivity reaction to wheat proteins mediated via mast cell activation and immune mechanisms that are both IgE-mediated and non-IgE mediated
  - Affects 0.5-4% of the population

Celiac disease

- Virtually unknown condition in mid-20th century
- Seroprevalence currently ~1% in European and US populations
- But majority of these individuals have not been diagnosed with celiac disease
- Early diagnosis is challenging in children and adults
- Presentation of diagnosed CD has been changing, with shift toward older individuals with milder disease
- Increased awareness
- Better diagnostics
- Earlier detection through serologic testing
- Environmental factors (e.g., increased wheat consumption)

Celiac disease: Definition and diagnosis

- Immune-mediated systemic disorder
- Elicited by gluten and related prolamins (plant storage proteins)
- Occurs in genetically susceptible individuals

  - Characterized by:
    - **CLINICAL**: Variable combination of gluten-dependent clinical manifestations
    - **SEROLOGIES**: CD-specific antibodies
    - **GENETICS**: HLA-DQ2 and HLA-DQ8 haplotypes
    - **HISTOPATHOLOGY**: Enteropathy

Celiac disease: Clinical features in adults

- Increase in median age at diagnosis to 3rd-4th decades
- Female : Male = 3:1
  - Females diagnosed at a younger age
  - Females present more frequently with constipation, bloating, and iron deficiency anemia
  - Females (and elderly) tend to have more associated autoimmune conditions
- ~40% of patients at diagnosis are overweight/obese
- Incidence of CD diagnosed in those >65 years has been increasing
  - Elderly men > women
  - Most common symptom = anemia
  - Micronutrient deficiencies may be only presenting sign
  - GI symptoms less prevalent and, if present, tend to be mild
Celiac disease: Clinical features

**Adults**
- >50% w/ GI symptoms and weight loss at presentation
- Diarrhea most common
- Bloating
- Aphthous stomatitis
- Alternating bowel habits
- Constipation
- GERD
- Persistent vomiting
- Chronic abdominal pain

**Children**
- “Classic” – malabsorption, diarrhea, wasted buttocks
- Vomiting and abdominal distension – esp. children <1 yr of age
- Failure to thrive
- Iron-resistant anemia (usually older children)
- Short stature (usually older children)
- Pubertal delay
- Personality problems
- Dermatitis herpetiformis
- Dental enamel hyperplasia
- Epilepsy with cerebellar calcification

Celiac disease: Conditions with increased prevalence of CD in childhood

- Type I diabetes mellitus
- Autoimmune thyroiditis
- Down syndrome
- Turner syndrome
- Williams syndrome
- Selective IgA deficiency
- Juvenile chronic arthritis
- Autoimmune liver disease

Causes of protracted diarrhea in infants

**Normal villus architecture**
- Transport defects
  - Chloride-bicarbonate exchanger (chloride-losing diarrhea)
  - Sodium-hydrogen exchanger (congenital sodium diarrhea)
- Ileal bile acid receptor defect
- Sodium-glucose cotransporter (glucose-galactose malabsorption)
- Micronutrient deficiency
  - Acrodermatitis enteropathica (zinc deficiency)
- Enzyme deficiency
  - Enterokinase deficiency
  - Congenital short bowel
  - Enteroendocrine cell dysgenesis/enteric anendocrinosis

**Villus atrophy**
- Microvillus inclusion disease
- Tufting enteropathy
**Autoimmune enteropathy**
- IPEX syndrome
- Celiac disease
- Infectious and post-infectious enteropathy
- Allergic enteropathy
- Idiopathic

Celiac disease: Serologies

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-gliadin antibody, IgA</td>
<td>80-90</td>
<td>85-90</td>
</tr>
<tr>
<td>Anti-gliadin antibody, IgG</td>
<td>75-85</td>
<td>75-98</td>
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<tr>
<td>Anti-endomysial antibody, IgA</td>
<td>85-98</td>
<td>95-97</td>
</tr>
<tr>
<td>Tissue transglutaminase (TGG) antibody, IgA</td>
<td>90-98</td>
<td>95-97</td>
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<tr>
<td>Deamidated anti-gliadin peptide (DGP) antibody, IgA</td>
<td>80-95</td>
<td>86-93</td>
</tr>
<tr>
<td>DGP antibody, IgG</td>
<td>80-98</td>
<td>86-97</td>
</tr>
</tbody>
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- Serologic tests need to be performed in patients when they are not on gluten restriction
- Sensitivities for all markers decrease among patients with no/mild symptoms
- None are entirely specific for CD and can be spuriously elevated in other immune-mediated disorders
Celiac disease: Genetics

- HLA-DQ2 and HLA-DQ8
  - Present in >95% of CD patients
  - Present in 30-40% of population

⇒ HIGH NEGATIVE PREDICTIVE VALUE:
  Lack of these permissive haplotypes essentially excludes CD

Celiac disease: Histopathology

- Intraepithelial lymphocytosis (constant feature)
- Variable villus atrophy with crypt hyperplasia
- Lymphoplasmacytic inflammation of lamina propria
  - Granulocytic infiltrates (neutrophils and eosinophils);
    neutrophilic/eosinophilic cryptitis not prominent
- Increased crypt apoptosis
- Reactive epithelial changes
- Associated gastrointestinal lymphocytosis

Celiac disease: Biopsies - how many and where?

- Most studies recommend at least 4 samples to exclude CD
- At least one from duodenal bulb recommended, with submission in different containers
  - 10% of patients with CD have involvement of bulb only
    - "Ultra short celiac disease"
    - Particularly children
  - 10% of patients with CD have normal bulb and diagnostic changes more distally

Celiac disease: The problem with the bulb...

- Can be difficult to interpret biopsy
  - Brunner gland hyperplasia
    - Villi normally broad and short overlying Brunner glands
  - Peptic injury common (up to 80%)
  - Can show associated lymphocytosis and villus atrophy
  - Heterotopias (usually gastric)
    - Can have lymphoid aggregates with lymphocytosis overlying aggregates
Celiac disease: Histopathologic classification schemes

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>IEL Vili (V)</td>
<td>Crypts (C)</td>
<td>V:C ratio</td>
<td>IEL Vili (V)</td>
</tr>
<tr>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Type 1</td>
</tr>
<tr>
<td>Increased</td>
<td>Normal</td>
<td>Hyperplastic</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Increased</td>
<td>Marked atrophy</td>
<td>Hyperplastic</td>
<td>&gt;3</td>
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<tr>
<td>Increased</td>
<td>Flat</td>
<td>Hyperplastic</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Normal</td>
<td>Flat</td>
<td>Hyperplastic</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

Celiac disease: Our practice

- Counting of intraepithelial lymphocytes is performed on H&E
- Often provide a range
- Descriptive diagnosis given with differential diagnosis in comment
  - Marsh (or other) classification not performed unless specifically requested
  - Canned comments available for use/ modification:
  1. Focal mild intraepithelial lymphocytosis with normal villus architecture (focally >30 IEL / 100 epithelial cells)
  2. Intraepithelial lymphocytosis with normal villus architecture (>30 IEL / 100 epithelial cells)
  3. Intraepithelial lymphocytosis with villus atrophy

DDx of lymphocytosis with normal villus architecture

- Gluten-related disorders (celiac disease, non-celiac gluten sensitivity, wheat allergy)
  - Dermatitis herpetiformis
  - First-degree relatives
  - Partially treated celiac disease
- Non-gluten food hypersensitivity (e.g., cow’s milk, soy products, fish, rice, chicken/egg)
- Infections (e.g., Giardia, Cryptosporidium, H. pylori, tropical sprue)
- Bacterial overgrowth
- Drugs (e.g., NSAIDs)
- Immune dysregulation (e.g., Hashimoto thyroiditis, rheumatoid arthritis, SLE, etc.)
- Immune deficiency (e.g., IgA deficiency, CVID)
- Inflammatory bowel disease
- Lymphocytic and collagenous colitis
- Graft-versus-host disease
- Pre-infiltrative intestinal T-cell lymphoma
- Idiopathic (including irritable bowel syndrome)

Case 1

- 44-year-old woman with history of heavy alcohol use who presents with an 8-month history of intermittent watery diarrhea and unintentional weight loss of 17 pounds over the past year.
- Endoscopy normal
• **Intraepithelial lymphocytosis with normal villus architecture (≥30 IEL)**

  The duodenal biopsy shows normal villus architecture and increase in intraepithelial lymphocytes (40-50 IELs per 100 crypt epithelial cells). The changes may represent symptomatic, latent or treated celiac disease. Correlation with clinical and serologic findings is necessary to confirm the diagnosis of celiac disease. Increased intraepithelial lymphocytes with normal villous architecture can also be seen with dermatitis herpetiformis and in first-degree relatives of patients with celiac disease. Other reported associations include systemic autoimmune disorders, NSAIDs, Crohn disease, *H. pylori* gastritis, peptic duodenitis, and infections like Giardia, tropical sprue and spontaneous bacterial overgrowth.

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**Duodenal lymphocytosis canned comment (2)**

**Case 1: Follow-up**

- **Stool Cx:** No Salmonella, Shigella, or Campylobacter isolated; Normal enteric gram negative flora absent
- **Stool O&P:** Numerous Blastocystis hominis; no cryptosporidium or cyclospora; poorly preserved sample
- **Stool Giardia Ag:** Negative

Clinically thought to be due to **bacterial overgrowth**
Case 2

- 27-month-old ex-38-week girl with Down syndrome
- Always had difficulties with increased stooling and inability to gain weight
- Has been hospitalized in multiple times for severe diarrhea
- Severe failure to thrive (FTT) – less than 3rd percentile for growth charts
- Not taking any lactose-containing products at presentation; eats a large amount of food but is picky about the type of food she eats (oranges, yogurt, oatmeal, rice, wheat toast, muffins, donuts)

Duodenal lymphocytosis canned comment (3)

- Intraepithelial lymphocytosis with villus atrophy
  - The duodenal biopsy shows patchy/mild/marked/subtotal/total (choose) villus atrophy with increased intraepithelial lymphocytes (40-60 IELs lymphocytes per 100 epithelial cells). While the biopsy in this case is characteristic of celiac disease, histologic findings alone are not diagnostic and correlation with clinical presentation and laboratory tests, such as tissue transglutaminase and/or anti-endomysial antibody, is necessary to confirm the diagnosis of celiac disease.
  - Additional considerations include hypersensitivity reactions to other proteins (soy, milk, egg), infections like Giardia, tropical sprue and severe bacterial overgrowth, chronic malnutrition, and rarely drugs like NSAIDs.
### Case 2: Follow-up

- **Labs:**
  - Increased serum IgA (180; reference range 14-159)
  - Positive TTG (>100; reference range <20)

- **Diagnosed with celiac disease**
- **Registered dietician consult for gluten-free diet**

### Duodenal lymphocytosis canned comments (1)

- **Focal mild intraepithelial lymphocytosis with normal villus architecture (focally >30 IEL)**
  - The duodenal biopsy shows normal villus architecture and focal increase in intraepithelial lymphocytes ([# IELs per 100 crypt epithelial cells]). The finding is of unclear clinical significance. The changes may fall within the spectrum of asymptomatic, latent or treated celiac disease. Correlation with clinical and serologic findings is necessary to confirm the diagnosis of celiac disease. Increased intraepithelial lymphocytes with normal villous architecture can also be seen with dermatitis herpetiformis and in first-degree relatives of patients with celiac disease. Other reported associations include systemic autoimmune disorders, NSAIDs, Crohn disease, H. pylori gastritis, peptic duodenitis, and infections like Giardia, tropical sprue and spontaneous bacterial overgrowth.

### Celiac disease: Other histopathologic features

- **Neutrophils common**
  - >25% of adult biopsies
  - >50% of pediatric biopsies
  - Usually seen as scattered infiltrates in lamina propria
  - Cryptitis is not typically a prominent feature (but seen more often in bulb)

### DDx of villus atrophy with lymphocytosis

- **Acid**
  - Peptic injury
  - H. pylori gastritis
- **Infection**
  - Bacterial overgrowth
  - Tropical sprue
  - Giardiasis
  - Viral, including HIV
  - Whipple disease
  - Coccidian, including cryptosporidium
- **Medications**
  - Olmesartan and related agents
  - Idelalisib
- **Altered immunity**
  - Gluten-related disorders (celiac disease, non-celiac gluten sensitivity, wheat allergy)
  - Food allergies (cereals, milk, eggs, etc.)
  - Collagenous sprue
  - Common variable immunodeficiency (CVID)
  - Autoimmune enteropathy
  - Inflammatory bowel disease
  - Eosinophilic gastroenteritis
  - Morbid obesity
Case 3

- Consult case with limited initial history:
  - 27-year-old woman who presents with epigastric pain, nausea, and diarrhea
Case 3: Dx

- For both duodenum and terminal ileum:
  - Intraepithelial lymphocytosis (>40 IEL/100 epithelial cells) with partial villus atrophy

- Additional history obtained from gastroenterologist:
  - Patient had recently returned from an extended (~2 years) stay in Ecuador

 ≥ Raised possibility of tropical sprue

**Tropical sprue**

- **Definition:**
  - Chronic diarrheal disease involving small intestine, possibly of infectious origin (may be related to bacterial overgrowth; no specific infectious agent known)
  - Characterized by malabsorption of nutrients, esp. folic acid and vitamin B12

- **Geography:**
  - Occurs in the tropics in a narrow band north and south of the equator to 30° latitude
  - In the Western hemisphere, particularly prevalent in Haiti, Dominican Republic, Puerto Rico, and Cuba; rare/absent in Jamaica and Bahamas
  - Also common in India, Pakistan; less common in Burma, Indonesia, Borneo, Malaysia, Singapore, and Vietnam
  - Uncommon in Africa, China, and Middle East
  - Only rare cases reported in U.S.

- **Affects indigenous populations as well as visitors who stay for > 1 month**
  - Seldom seen in travelers who visit an endemic area for < 2 weeks

≥ Histologically identical to celiac disease, but greater involvement of ileum

**What about collagenous sprue?**

- **Shares clinical and histologic features with celiac disease**
  - Some patients have history of CD before developing collagenous sprue

- **Middle-aged to elderly females**

- **Symptoms:**
  - Malabsorption – diarrhea, weight loss
  - Abdominal pain

- **Associated with:**
  - Celiac disease
  - Collagenous gastritis and lymphocytic gastritis
  - Collagenous colitis and lymphocytic colitis

- **Course:**
  - ~50% respond to a combination of gluten-free diet and immunosuppressive tx
  - Many have progressive worsening and may die from malnutrition
Case 4

• 4-week-old ex-35-week male infant who presented with fever and ongoing diarrhea and dehydration
  • Failure to thrive; ongoing poor weight gain during hospitalization.
  • PICU course complicated by acute kidney injury, coagulopathy, and thrombocytopenia
  • Continued copious diarrhea despite attempting multiple different types of formula and also being NPO on TPN.
  • All infectious studies were negative.
  • Abdominal ultrasound and echocardiogram unremarkable except for an atrial septal defect.

Causes of protracted diarrhea in infants

- Normal villus architecture
- Transport defects
  - Chloride-bicarbonate exchanger (chloride-losing diarrhea)
  - Sodium-hydrogen exchanger (congenital sodium diarrhea)
- Ileal bile acid receptor defect
- Sodium-glucose co-transporter (glucose-galactose malabsorption)
- Microvillus inclusion disease
- Microvillus atrophy
- Tufting enteropathy
- Autoimmune enteropathy
- IPEX syndrome
- Celiac disease
- Infectious and post-infectious enteropathy
- Allergic enteropathy
- Idiopathic
Case 4: Dx

- Superficial portion of small intestinal mucosa with likely villus atrophy and focally prominent intraepithelial lymphocytes
- Paneth cells and goblet cells present, but few
- Enteroendocrine cells present, against enteroendocrine cell dygenesis/enteric anendocrinosis

**Additional work-up not shown:**
- Electron microscopy showed no ultrastructural abnormalities, against microvillus inclusion disease
- IHC for CD10 and EpCAM/MOC31 reportedly positive/intact expression, against tufting enteropathy

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Case 4: Follow-up

- Genetic testing positive for FOXP3 gene mutation
  Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome
- Patient started on immunosuppression
  - Tacrolimus
  - Methylprednisolone
  - Anti-thymocyte globulin
  - Rituximab
  - Weekly IVIG
- Biopsy performed post-initiation of immunosuppression while undergoing work-up for bone marrow transplant
Autoimmune enteropathy (AIE)

- Most frequent disorder leading to infantile intractable diarrhea
- Most present in infancy/first year of life
- Strong male predilection and family history
- Frequent extraintestinal involvement
- Various circulating autoantibodies
  - e.g., anti-enterocyte antibodies, anti-goblet cell antibodies
  - Role in dx questioned (association, no causative?)
  - Also seen in HIV, IBD
- May be more helpful in older children/adults (infants produce little IgG in first 3 months of life)
- IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome is best characterized form of AIE (mutations in FOXP3 gene)
- APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) syndrome (mutations in AIRE gene) involved in T-cell regulation

AIE: Clinical

- Secretory diarrhea
- Dermatitis
- Various endocrine disorders
- Infectious complications due to loss of functional gut barrier, central lines, underlying immunodeficiency, immunosuppression
- Immunosuppressive medications, bone marrow transplant

- ADULT ONSET DISEASE clinically looks like CD unresponsive to gluten-free diet
  - Protracted diarrhea
  - Weight loss
  - Malnutrition

AIE: Histopathology

- Characteristic absence/severe decrease in goblet and Paneth cells (also enteroendocrine cells)
  - Seen only in a minority of cases
  - Immune-mediated destruction
  - Rapid regeneration that does not allow complete differentiation
### Comparison of histopathologic features

<table>
<thead>
<tr>
<th>Celiac disease</th>
<th>Autoimmune enteropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• IELs present in surface and crypts</td>
<td>• IELs more prominent at crypt base</td>
</tr>
<tr>
<td>• Neutrophils infrequent (crypt abscesses rare)</td>
<td>• Neutrophils readily identified (crypt abscesses frequent)</td>
</tr>
<tr>
<td>• Surface &gt; crypt injury</td>
<td>• Crypt &gt;&gt; surface injury</td>
</tr>
<tr>
<td>• Crypt epithelial apoptosis uncommon</td>
<td>• Crypt epithelial apoptosis common (GVHD-like)</td>
</tr>
<tr>
<td>• Proximal small intestine most severely affected</td>
<td>• Stomach and colon often affected</td>
</tr>
</tbody>
</table>

### Lymphocytes in the colon

- "Normal"
  - Density of lymphocytes highest in proximal colon → decreases distally
    - Lamina propria
    - IELs
  - Published normal range is 5-12 IELs/100 epithelial cells

- Intraepithelial lymphocytosis
  - Celiac disease
  - Autoimmune disease
  - Drugs

### “Microscopic colitis”

- Obsolete term, yet clinicians continue to use it
- Most often refers to lymphocytic colitis (LC) and collagenous colitis (CC), but also encompasses:
  - Post-infectious colitis
  - Drug (NSAID) colitis
  - Inflammatory bowel disease in remission
  - Eosinophilic colitis
Lymphocytic colitis (LC): Histopathology

- Increased IELs (we use >20 IELs/100 epithelial cells)
- Surface epithelial injury/disarray
- Increase in lamina propria inflammation (lymphoplasmacytic, eosinophilic)
- No thickening of subepithelial collagen
- Normal crypt architecture

- May be patchy
- More common in right colon (essential to biopsy!)

Collagenous colitis (CC): Histopathology

- Thickened subepithelial collagen
  - Irregular → “Dripping candle wax”
  - Entrapment of capillaries, fibroblasts, and inflammatory cells
  - No minimum thickness requirement, although some have advocated >10 μm
  - Do not confuse with thickened basement membrane
- Surface epithelial injury/disarray/sloughing
- Increase in lamina propria inflammatory cells (lymphoplasmacytic and eosinophilic)
- Intraepithelial lymphocytosis
LC and CC: Other histopathologic features

- Ileal involvement
- Paneth cell metaplasia (44% of CC, 14% of LC)
- Focal crypt architectural distortion (<10% of CC/LC)
- Cryptitis and crypt abscess formation (30-40%)
- Surface erosion/ulceration


- 14% of all patients with microscopic colitis (LC or CC) harbored a second lymphocytic disorder of the GI tract
- Duodenal intraepithelial lymphocytosis (DIL) was most common > celiac disease (CD) > lymphocytic gastritis (LG)
- LG and CD had stronger associations than DIL with microscopic colitis

LC and CC: Clinical

- Typical presentation is in a middle-aged or elderly woman with watery diarrhea
- All age groups can be affected, including children
- LC more common (~3x) than CC
- Endoscopy almost universally normal

- Tx:
  - Antidiarrheal, salicylates, bismuth
  - Immunosuppressive agents

- Course is typically intermittent relapsing
  - Most (>90%) resolve in 3 years
  - Histologic changes can persist
  - No histologic predictors of outcome

LC and CC: Association with drugs

- 10-35% of cases associated with medications
- Clozapine
- Lansoprazole
- NSAIDs
- Rantidine
- Ticlopidine
- Cyclo-3-fort
- Acarbose
- Fluazamide
- Immune checkpoint inhibitors
But wait, don’t we have more GI organs…?

Lymphocytic gastritis: Histologic findings
- Intraepithelial lymphocytosis (>25 IELs per 100 epithelial cells)
  - Infiltration of gastric surface and foveolar epithelium
  - Predominantly CD8-positive T-cells
  - No lymphoepithelial lesions
- Foveolar and crypt hyperplasia
- Increased lymphoplasmacytic inflammation in lamina propria
- Inflammation often seen throughout stomach (~75%)
  - Body-limited gastritis more commonly due to H. pylori infection
  - Antral-limited gastritis more commonly due to celiac disease

Lymphocytic gastritis
- Etiology/Pathogenesis:
  - Celiac disease (40%)
    - 10-45% of patients have lymphocytic gastritis
    - Particularly in children
  - Helicobacter pylori infection (20%)
  - 4-10% of patients have lymphocytic gastritis
  - Allergy, NOS
  - Drugs
    - Ticlopidine
    - Immune checkpoint inhibitors
  - Crohn disease
  - HIV infection
  - Idiopathic (20%)
What about collagenous gastritis?

- More common in adults > children
  - **Adults:**
    - Heterogeneous disease often with other GI tract involvement (e.g., lymphocytic colitis)
    - May have underlying autoimmune disease (e.g., Sjogren syndrome) affects to which may be similar to lymphocytic/collagenous colitis
  - **Children:**
    - Abnormalities limited to stomach

- **Histologic findings:**
  - Increased subepithelial collagen
  - Surface epithelial injury/sloughing
  - Intraepithelial lymphocytosis (patchy)
  - Lamina propria inflammation
  - Glandular atrophy

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**Stomach**

5 y/o boy with protein S deficiency and iron deficiency anemia; all other bx’s normal (esophagus, duodenum, ileum, colon)

> Collagenous gastritis

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**Lymphocytic esophagitis: Dx**

- No established criteria for diagnosis
- No minimum number of lymphocytes
  - 10-15 lymphocytes/HPF considered normal
  - Lymphocytic esophagitis shows wide variation (up to 100/HPF)

> I have never made this diagnosis nor seen anyone else make this diagnosis...

- Some suggest making a diagnosis only when:
  - Numerous lymphocytes with clustering and evidence of injury (dyskeratotic epithelial cells)
  - Intercellular edema
  - Other etiologies excluded (GERD, eosinophilic esophagitis, Candida)
  - Endoscopic findings suggest a diffuse mucosal abnormality
Lymphocytic esophagitis: DDx

- Children
- Crohn disease

- Adults
  - Clinical significance unclear (often asymptomatic)
  - Variety of immune-mediated disorders (lichen planus)
  - Other forms of esophagitis feature lymphocytes
    - GERD
    - Allergic esophagitis
    - Candida esophagitis

Immune checkpoint inhibitors (ICI)

- Anti-CTLA-4 antibody → Ipilimumab
- Anti-PD-1 antibodies → Nivolumab, pembrolizumab
- Anti-PD-L1 antibodies → Atezolizumab, avelumab, durvalumab

- Increasingly used to treat several different types of cancer
  - Melanoma
  - NSCLC
  - RCC
  - Gastric or GEJ adenocarcinoma
  - Classical Hodgkin lymphoma
  - SCC of the head and neck
  - Urothelial carcinoma
  - Merkel cell carcinoma
  - Solid tumors that are MSI-high

Immune checkpoint inhibitors (ICI)

- Enhance anti-tumor activity which leads to systemic loss of tolerance
- Diarrhea and colitis are among the most frequent causes of tx-related deaths in pts treated with ICI
  - 31% of toxic deaths are due to GI events
  - Relative risk of enterocolitis in patients on anti-PD-1 therapy is 0.20 compared to anti-CTLA-4 tx

Drugs: Immune checkpoint inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Anti-CTLA-4 (ipilimumab)</th>
<th>Anti-PD-1 (nivolumab, pembrolizumab)</th>
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<tbody>
<tr>
<td>Incidence of diarrhea/colitis</td>
<td>10.2% / 5.7%</td>
<td>22.1% / 0.7%</td>
</tr>
<tr>
<td>Incidence of high-grade diarrhea/colitis</td>
<td>7.4% / 4.1%</td>
<td>2% / 0.4%</td>
</tr>
<tr>
<td>Immunopathologic features</td>
<td>Predominance of colonic mucosal CD4+ T-cells, High TNF-α secretion</td>
<td>Predominance of colonic mucosal CD8+ T-cells</td>
</tr>
<tr>
<td>Time to onset after first infusion</td>
<td>1 month</td>
<td>2 – 4 months</td>
</tr>
<tr>
<td>Time to resolution of enterocolitis</td>
<td>0.5 – 1.6 months</td>
<td>1.1 – 4.2 months</td>
</tr>
<tr>
<td>Response rate to corticosteroids</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>


ICI: Clinical presentation

Anti-CTLA-4 (ipilimumab)
- Diarrhea
- Abdominal pain
- Nausea, vomiting
- Hematochezia and fever (less frequent)
- Symptoms reminiscent of Crohn disease
  - Oral aphthous ulcers
  - Anal lesions (fissures, fistulas, abscesses)

Anti-PD-1 (nivolumab, pembrolizumab)
- Diarrhea
- Abdominal pain
- Nausea
- Oral and anal lesions not reported

ICI: Endoscopic findings

Anti-CTLA-4 (ipilimumab)
- Erythema
- Erosion/ulceration (up to 79%)
- Luminal bleeding
- Extensive colitis (proximal to splenic flexure) in > 2/3
- Continuous inflammation in 45-75%
- Ileitis (12%) – can be present without concomitant colitis

Anti-PD-1 (nivolumab, pembrolizumab)
- Erythema
- Erosions/ulceration
- Luminal bleeding
- Endoscopic findings patchy in 75%
- Rare patients reported to have “necrotizing gastritis”

ICI: Histopathology

- Active colitis (lamina propria neutrophils, cryptitis, crypt abscesses)
- +/- features of chronic IBD (e.g., mononuclear cell infiltration, granulomas, basal plasmacytosis, crypt architectural abnormalities)
- Crypt epithelial apoptosis (42%) and crypt atrophy/dropout
- Microscopic colitis (lymphocytic and collagenous colitis)
- Stomach and duodenum involvement (55% in anti-CTLA-4 tx) – typically patchy
  - Mild activity
  - Crypt distortion
  - Focal/heterogeneous villus atrophy
  - Increased lamina propria eosinophils and mononuclear cells
  - Brunner gland hyperplasia
- Esophageal involvement reported in anti-PD-1 tx
Random colon

History of metastatic renal cell carcinoma, on nivolumab

Esophagus

History of metastatic rectal adenocarcinoma and collagenous colitis, on nivolumab

Duodenum

→ CC or nivolumab??
History of Crohn disease and multifocal hepatocellular carcinoma, on nivolumab ➔ Crohn disease and/or nivolumab??
We are not planning an entire trip around YOU!

Yes we are.

There's more than just food there! Architecture, landmarks, scenery!

Those are just the things you do to kill time between meals!