Nonneoplastic Gastric Pathology
(Will cheat a Bit and Include Endocrine Lesions)
Elizabeth Montgomery

Stomach!
We will begin with a whirlwind tour of the things that we can encounter in gastric biopsies and then review a focused case with differential diagnosis.

A Few Benign Pitfalls
Crushed mucosa with sloughed mucous neck cells
Erosive gastritis/gastropathy including iron pill gastritis
“Signet cell change”
Gastric Xanthoma

Disclosure Statement
Dr. Montgomery reports no relevant financial relationships with commercial interests.
Pitfall - Iron pill gastritis with reactive changes

Pitfall - Iron pill gastritis with reactive changes

Pitfall - Iron pill gastritis with reactive changes - iron stain

Pitfall - “Signet cell change” in ischemic columnar mucosa; cells lose their cohesion and slough into the lumen whilst “rounding up”

Pitfall - “Signet cell change” in ischemic columnar mucosa; cells retain E-Cadherin expression

Remember that “signet cell change” is very different from the in situ signet ring cell cancers in patients with CDH1 (the gene encoding for e-cadherin) germline mutations
Pitfall – crushed mucosa with prominent mucus neck cells – note the the sloughed single cells are not within lamina propria but “floating” and seen in gland lumina.

The real thing – signet cell carcinoma - the bad cells are firmly in the lamina propria so not seen in the lumina.
And now a whirlwind of things we encounter on biopsies..... Some rare and some common
Proto pump inhibitor effect

Sarcina ventriculi Patient with diabetes and slow gastric emptying - note exudate and organisms at low power

Sarcina ventriculi

Sarcina ventriculi gastritis
Gram positive, anaerobic, sugar-fermenting bacterium, *S. ventriculi* was first observed in the human stomach in 1842 by Goodsir. Readily found in soil and is known to cause a similar type of gastric injury in animals. Delayed gastric emptying and carbohydrate stasis in association with acidic gastric juices may provide an ideal culture medium for the organism.

Sarcina Ventriculi gastritis
Studied patients all had underlying delayed gastric emptying (one had a bezoar) from diabetic neuropathy, narcotic use, and pyloric stenosis secondary to malignancy. The organism may simply colonize pre-existing lesions but there are too few cases to draw firm conclusions as to whether the organism is truly a pathogen.

Packets of 4, 8 or more cells with characteristic flattening

Lymphocytic gastritis – Most common association - Celiac disease followed by H. Pylori

Lymphocytic gastritis

Sarcina ventriculi

Lymphocytic gastritis – Most common association - Celiac disease followed by *H. Pylori*
Lymphocytic gastritis – Most common association – Celiac disease followed by H. Pylori

Collagenous Gastritis

Associated with various autoimmune diseases in both children and adults. We have seen it associated with medications (eg Benicar/Olmesartan)

Early studies proposed 2 clinicopathologic subtypes:

1. children (18 y of age or younger) presenting with severe anemia, nodular gastric mucosa, and isolated gastric disease; and
2. adults with chronic watery diarrhea that is associated with diffuse collagenous involvement of the gastrointestinal tract.


Collagenous gastritis – poorly understood and sometimes resolves by itself - presents with watery diarrhea just like collagenous colitis

Collagenous gastritis in gastric body. Is something missing (you betcha – parietal cells)
Collagenous gastritis associated with autoimmune gastritis

- Chromogranin stain showing enterochromaffin like (ECL) cell hyperplasia

Granulomatous gastritis - pattern - can be Crohn’s disease but always requires correlation with clinical findings

Cytomegalovirus gastritis - note that the EPITHELIAL cells are often affected in the stomach

Russell body gastritis - usually a curious incidental finding and only sometimes associated with plasma cell disorders
Syphilis Gastritis

Not well studied and correlation with HIV status is not well established in the literature (which consists mostly of case reports). The key is that it tends to present in young adults with diffuse erosive gastritis or lesions that mimic carcinoma and lymphoma.
Epstein Barr virus gastritis – mimics lymphoma

EBV in situ hybridization

EBV gastritis - note nuclear hybridization in the exuberant mixed lymphoid infiltrate
Case
A 68 year old woman with dyspepsia underwent upper endoscopy and had some gastric biopsies. The endoscopist thought the mucosa was atrophic and also saw a polyp.
Diagnosis
Autoimmune gastritis
Hyperplastic polyp

Esophagus, Stomach, and Duodenum: Normal Anatomic Outlines and Relationships

Normal Antral Mucosa with Gastric Lumen (LUM), Foveolae (FOV), and Antral Glands (AG) Indicated

H&E Mucus (PAS)

Normal Oxyntic Mucosa with Foveolae (FOV), Parietal Cells (PC), and Chief Cells (CC) Indicated

Major Endocrine Cell Types of the Stomach and Their Products - Immunostain Demonstrations
A few Comments on Helicobacter pylori Gastritis

Two Australians win Nobel Prize in Medicine
Awarded for work on peptic ulcer disease

Helicobacter pylori: Curved Organisms (HP) with Flagellae Over Gastric Epithelium

Prevalence of Helicobacter pylori Infection in Developing vs. Developed Countries

Variant form - Helicobacter helmanii
Reacts with H. pylori immunostain
Similar clinical profile to H pylori
Pediatric cases possible over-represented
Consequences of H. pylori infection

Many are asymptomatic
“dyspepsia”
Peptic ulcer
Atrophy and intestinal metaplasia of mucosa
Increased risk for intestinal type adenocarcinoma
MALT lymphoma
Link to autoimmune gastritis in susceptible host

Duodenal and “Pre-Pyloric” Ulcers

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Duodenal Ulcer with Brunner Gland (BG) Hyperplasia, Pancreatic Penetration and Exposed Artery

Eradication of H. Pylori in Recurrent Duodenal Ulcer

Benign Gastric Ulcer - Lesser Curve, Transitional Zone

Environmental Metaplastic Atrophic Gastritis

- Suspected causative factors:
  - H. pylori infection
  - Dietary: High salt; smoked foods; nitrates; poor fruit and vegetable intake
  - Others:
    - Smoking
H. Pylori associated Metaplastic Atrophic Gastritis (Stemmermann’s Technique; stained for alkaline phosphatase)

H. Pylori Organisms Have Specific Affinity for Gastric Mucous Cells But Not Intestinal Absorptive Cells

Carcinoma in Environmental Metaplastic Atrophic Gastritis (EMAG)


Autoimmune gastritis

Metaplastic Atrophic Gastritis (MAG) Autoimmune vs. H.pylori Types
Autoimmune vs. Environmental Metaplastic Atrophic Gastritis

**Autoimmune MAG (AMAG)**

- **Etiology/Pathogenesis:**
  - Inherited predisposition
  - Autoimmune-induced damage
    - Parietal cell antibodies
    - Intrinsic factor antibody
    - *H. pylori* organisms usually absent

- **Pathology:**
  - **Body (ONLY)**
    - Diffuse metaplasia; mucosa thin
    - Loss of oxyntic glands ("atrophy")
  - **Antrum**
    - No metaplasia; hyperplasia
  - Endocrine
    - G-cell hyperplasia
    - ECL cell hyperplasia

**Autoimmune Metaplastic Atrophic Gastritis (AMAG) vs. Normal Mucosa**

**Autoimmune Metaplastic Atrophic Gastritis (AMAG)** - Autopsy

**Oxyntic Mucosa: Autoimmune Metaplastic Atrophic Gastritis (AMAG) - Intestinal and Pyloric Metaplasia**

**Autoimmune MAG (AMAG) Clinical Correlations**

- Achlorhydria or marked hypochlorhydria
- B-12 malabsorption
- Serum gastrin - high levels
- Gastric cancer: risk increased 7 fold
- Gastric ulcer: not a problem (no acid!)

We used to think this was a Northern European disease but it is equal opportunity. Female prevalence holds regardless of race.
Gastric Polyps and Neoplasms Associated with Autoimmune Gastritis

1. Hyperplastic polyps
2. Adenomas (intestinal and pyloric gland types)
3. Gastric carcinomas
4. Well differentiated neuroendocrine (carcinoid) tumors

Gastric Polyp

Any projection above the adjacent mucosal surface.
reactive/inflammatory, hamartomatous, or neoplastic in nature.
The classification of gastric epithelial polyps can be challenging histologically, but can have important consequences both for the clinical management of the polyp itself as well as implications about the remainder of the patient’s gastric mucosa.

Gastric Polyps – Why the Fuss

Dysplastic (pathologically equivalent to neoplastic) or non-neoplastic.
Implications of various types of polyps for the remainder of the patient’s gastric mucosa.
Unlike colonic polyps (most of which are isolated findings in an otherwise normal background mucosa) many gastric polyps arise in association with either inflammatory/atrophic gastritis or in association with inherited polyposis syndromes.
Correct classification of gastric polyps, even innocuous-appearing polyps, may sometimes provide important clues as to abnormalities in the surrounding stomach.
Hyperplastic polyps

Common gastric epithelial polyps (second most common overall after fundic gland polyps).
Few mm to many cm (one hyperplastic polyp resected at Johns Hopkins was 9 cm in diameter)
May be mistaken endoscopically for carcinoma.

Hyperplastic Polyps

Hyperplastic polyps may arise anywhere in the stomach
Slight preference for the antrum
20% multiple
Considered to be non-neoplastic lesions (though many molecular alterations reported)
It is unusual for hyperplastic polyps to arise in normal stomachs.

Hyperplastic Polyps - Associations

Most strongly associated with atrophic gastritis of either autoimmune or environmental (e.g., Helicobacter pylori-associated) types
post-antrectomy state
chemical/reactive gastropathy
following therapy for gastric antral vascular ectasia (“watermelon stomach”).

Endoscopic Appearances – “Watermelon stomach”
Hyperplastic Polyps - Associations

Patients with hyperplastic polyps are at an increased risk for synchronous or metachronous adenocarcinomas arising in the stomach outside of the polyp.

Hyperplastic Polyps

True dysplasia arising in hyperplastic polyps is uncommon. Dysplasia in hyperplastic polyps reported in <2% to 19% of cases in the literature.

In a review of 160 patients with gastric hyperplastic polyps, we found dysplasia in only 4%. Adenocarcinomas are occasionally reported in these polyps but this is unusual; we found adenocarcinoma within a hyperplastic in only one (0.6%) of 160 patients.
When we diagnose a gastric hyperplastic polyp in a patient who has not had corresponding biopsies of the non-polypoid mucosa, we often add a note in the pathology report indicating that biopsies of the non-polypoid antrum and body may be helpful in further assessment.

Extensively documented association. Autoimmune gastritis is suggested histologically when biopsies show corpus-predominant gastritis, glandular atrophy, and intestinal metaplasia.
Type 1 carcinoid arising in gastric body of 50+ woman with history of type 1 diabetes

The background gastric body lacks parietal cells

Type 1 carcinoid arising in gastric body of 50+ woman with history of type 1 diabetes

The flat oxyntic mucosa surrounding Type 1 carcinoid

Intestinal metaplasia

ECL cell hyperplasia

(pseudo)pyloric metaplasia

ECL cell hyperplasia, the precursor to the carcinoid that will never kill the patient

ECL Hyperplasia – Type 1 Carcinoids

When Does It Stop Being ECL Cell Hyperplasia and Become Carcinoid?

Extensive useless literature on hyperplasia-dysplasia-neoplasia involving use of micrometers

Some use a cut-off of 0.5 mm as “carcinoid”

Our definition – if the endoscopist sees a bump it’s a carcinoid

It is pointless to measure minute lesions – they never hurt the patients…… even as full fledged carcinoids
Multiple Gastric Carcinoids – sometimes antrectomy is needed to remove the source of the excess gastrin.

Problems

Many pathologists don’t know how to diagnose autoimmune gastritis/pernicious anemia pattern. Many internal medicine/family practice colleagues have no idea that they need to give their patients vitamin B12 when the diagnostic line in the pathology report says “autoimmune gastritis” and think their patients have uncomplicated iron deficiency anemia - the high gastric pH does not allow for iron absorption. Many surgery colleagues want to perform aggressive resections for such tumors.

Another Type 1 carcinoid of the gastric body. There is no background oxyntic mucosa.

Type 1 carcinoid, Chromogranin stain. Note the ECL cell hyperplasia in the background.

We avoid doing ki-67 stains in Type 1 carcinoids since they are essentially always indolent and results such as this one don’t mean anything - metastases are rare for type 1 carcinoids and deaths are exceptional.
Time to Talk About Type 2 Carcinoid
Slide A is from the duodenum and slide B is from the stomach.
What syndrome can you dream up to explain these findings?
Diagnosis – Zollinger-Ellison Syndrome with a duodenal gastrinoma and a gastric carcinoid tumor/WDNET of ECL cell type
Type 3 Gastric NET

No autoimmune backdrop, no Zollinger Ellison (no gastrinoma)  
In other words, no hypergastrinemia  
More aggressive than type 1 with about a third dying of disease and metastases in about 70%  
\textit{(metastases are rare for type 1 and deaths are exceptional)}  
data poor on type 2 but they are indolent

For this lesion, we need more information to subtype it – if we know it’s antral then it is type 3

Another Type 3 carcinoid in a patient with normal serum gastrin. The background is normal oxyntic mucosa. This lesion is spindly and reminiscent of a gastrointestinal stromal tumor.
Type 3 carcinoid – note the intact parietal cells

Type 3 carcinoid – Cam 5.2 saves the day...

Type 3 carcinoid – and others – pitfall alert - note weak AE1/3

Type 3 carcinoid – chromogranin stain – no ECL cell hyperplasia in adjoining mucosa

True high grade gastric neuroendocrine lesions can also be very rarely encountered and are most often metastases from the lung; this was primary in the antrum.
What Do We Need to Assure?

Be sure you know how to diagnose autoimmune gastritis!!!! Many pathologists do not know how!!!!!! We see autoimmune gastritis in about 2% of our gastric biopsies “in house” at Johns Hopkins – if this diagnosis is never in your path reports you are not recognizing the pattern.

We have begun to report autoimmune gastritis as “autoimmune gastritis/pernicious anemia pattern” with a note about risk for iron deficiency and pernicious anemia and various tumors.

Hyperplastic Polyps - Ddx

1) conditions of generalized gastric mucosal hyperplasia (Menetrier’s disease) and/or inflammation (Cronkhite-Canada syndrome)
2) hamartomatous polyps and syndromes involving the stomach.
Ménétrier’s Disease
Marked foveolar hyperplasia with abundant mucus production
Glandular atrophy
Edematous but typically uninflamed lamina propria
Most commonly limited to the body and fundus.
Knowledge of the endoscopic appearance of giant folds, hypoproteinemia, and peripheral edema, as well as lack of intervening normal mucosa can help to distinguish Menetrier’s disease from hyperplastic polyp; however, the changes may be histologically indistinguishable based on a single biopsy.

Pathogenesis
Overproduction of transforming growth factor alpha (TGF alpha) has been documented could account for decreased acid production, hyperplasia of surface mucous cells, oxyntic atrophy, and increased mucin production.
Transgenic mice that overproduce TGF alpha have features of Ménétrier’s disease, including foveolar hyperplasia, increased mucin content.
TGF alpha is one of six ligands that bind to the epidermal growth factor receptor, and increased production of any of these ligands may contribute to Ménétrier’s disease.

Novel Treatment
Thank you