Case Presentations:
Gastric Epithelial Lesions and
The Company They Keep

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http://pathology2.jhu.edu/beweb
see also case reviews on Pathology Web:
http://pathology2.jhu.edu

Case 1

• 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, Case 1

- Autoimmune gastritis
- Hyperplastic polyp
Normal Oxytic 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

UNIDENTIFIED CURVED BACILLI IN THE STOMACH OF PATIENTS WITH GASTRITIS AND PEPTIC ULCERATION

BARRY J. MARSHALL  J. ROBIN WARREN
Departments of Gastroenterology and Pathology, Royal Perth Hospital, Perth, Western Australia
Two Australians win Nobel Prize in Medicine
Awarded for work on peptic ulcer disease

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

*Helicobacter pylori*: Routine Stains for Detecting and Verifying Bacillary and Coccoid Forms

Prevalence of *Helicobacter pylori* Infection in Developing vs. Developed Countries
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

Chronic Active H. pylori Gastritis with Neutrophils (PMN's) in Gland

Duodenal and “Pre-Pyloric” Ulcers

Duodenal Ulcer with Brunner Gland (BG) Hyperplasia, Pancreatic Penetration and Exposed Artery
Eradication of *H. Pylori* in Recurrent Duodenal Ulcer

![Graph showing probability of remaining in remission (Y-axis) over weeks after treatment (X-axis). The graph compares antibiotics and placebo groups with a significance level of P<0.001.]

Benign Gastric Ulcer - Lesser Curve, Transitional Zone

![Image of a gastric ulcer specimen with labeled parts: Body, Ulcer, Antrum, Anterior Speculum. Scale bar: 5 cm.]

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

H. Pylori and Gastric Cancer Risk: Two Meta-analyses

<table>
<thead>
<tr>
<th>Studies Analyzed (n)</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>2491</td>
<td>3959</td>
<td>7887</td>
<td>4334</td>
</tr>
<tr>
<td>% H. pylori positive (serology)</td>
<td>80.0</td>
<td>62.2</td>
<td>74.1</td>
<td>57.4</td>
</tr>
</tbody>
</table>

Carcinoma in Environmental Metaplastic Atrophic Gastritis (EMAG)

Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial.
Autoimmune gastritis

Metaplastic Atrophic Gastritis (MAG)

Autoimmune vs. H. pylori Types

Autoimmune vs. Environmental Metaplastic Atrophic Gastritis

Autoimmune MAG (AMAG)

- Etiology/Pathogenesis:
  - 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) - Autopsy

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

Autoimmune Metaplastic Atrophic Gastritis (AMAG) vs. Normal Mucosa

Autoimmune MAG (AMAG) Clinical Correlations

• Achlorhydria or marked hypochlorhydria
• B-12 malabsorption
• Serum gastrin - high levels
• Gastric cancer: ?? risk increased
• 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

- Any projection above the adjacent mucosal surface.
- Reactive/inflammatory, hamartomatous, or neoplastic.
- 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 gastritides 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.

Adenomas

- If lesion produces a polyp, it is referred to as an adenoma and the dysplasia graded whereas flat lesions are termed “dysplasia”.
- Background pathology is important just as for hyperplastic polyps.

Gastric Adenomas

- Abraham et al: defined them as “intestinal” or “gastric” type.
- Intestinal-type (containing at least focal goblet cells and/or Paneth cells),
- gastric-type (lined entirely by gastric mucin cells on PAS/alcian blue stain), or indeterminate.

Adenomas

- Intestinal-type adenomas were significantly more likely than gastric-type adenomas to show high-grade dysplasia ($p < 0.0001$), adenocarcinoma within the polyp ($p = 0.016$), intestinal metaplasia in the surrounding stomach ($p < 0.000001$), and gastritis ($p = 0.002$).
- Patients with intestinal-type adenomas more likely to have separate adenocarcinomas
Adenomas

- Gastric adenomas are rarely truly "sporadic" lesions.
- In any individual patient complete removal of the adenoma should be performed, and biopsy of the surrounding gastric mucosa is useful to understand the clinicopathologic context of the adenoma.
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
Hyperplastic Polyps - Associations

• Patients with hyperplastic polyps are at an increased risk (approximately 6%) 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.
Hyperplastic Polyps

- 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.

Hyperplastic Polyps and Autoimmune Gastritis

- Extensively documented association.
- Autoimmune gastritis is suggested histologically when biopsies show corpus-predominant gastritis, glandular atrophy, and intestinal metaplasia.
Antrum – 68 yo woman

Gastrin Stain

Hyperplastic polyp

Body
Autoimmune Gastritis, Continued

- The diagnosis of autoimmune gastritis is of clinical consequence in that carcinoid tumors that arise in response to prolonged hypergastrinemia (e.g., secondary to autoimmune gastritis or Zollinger-Ellison syndrome) differ in their behavior, prognosis, and management from sporadic gastric carcinoids:
  - smaller, less infiltrative, often multiple, almost never metastasize, and (in the case of autoimmune gastritis) frequently respond to antrectomy to remove the source of gastrin stimulation.

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, and 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.
Ménétrier's Disease

- Hypertrophic gastropathy
- Giant folds
- Hypoalbuminemia
- Foveolar hyperplasia
- Hypochlorhydria

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

Case 2

- A biopsy was performed of a gastric polyp and diagnosed as a “hyperplastic polyp”. The gastroenterologist called and helpfully pointed out that my diagnosis was wrong.
**Peutz-Jeghers Polyposis**

- Autosomal-dominant condition - germline mutations in the *LBK1/STK11* gene on chromosome 19p13.3,
- Polyposis and distinctive melanin pigmentation around the lips, buccal (cheek) mucosa, and sometimes eyelids and hands. Because the pigment may fade after puberty, the syndrome is not excluded—even if pigment is absent—in an adult presentation.

**Clinical Features of Peutz-Jeghers Syndrome**

- Average age at diagnosis 23 to 26 years
- Benign complications predominate in early decades
  - Intussusception and obstruction
  - Torsion, infarction and bleeding
  - Anal prolapse
- Malignancy more common after 4th decade
  - Average age at diagnosis of cancer 40 to 50 years
- 95% combined incidence of cancer after age 65 (GI and non GI primary – breast, ovary, pancreas)
Pathologic Features of Peutz-Jeghers Syndrome

- Hamartomatous polyps located throughout the gastrointestinal tract

- Distribution of polyps:
  - 78% small bowel (jejunum > ileum)
  - 42% colon
  - 38% stomach
  - 28% rectum

Gastric Peutz-Jeghers Polyps

- Unlike the small bowel polyps which show prominent arborization of the muscularis mucosae, gastric Peutz-Jeghers polyps are composed mostly of dilated or branching mucus-filled pits and may have relatively inconspicuous smooth muscle.
- Occasional examples of gastric Peutz-Jeghers polyps have the classic arborizing architecture with strands of smooth muscle, but most have less specific features (but some degree of smooth muscle proliferation).
Another perfect gastric Peutz-Jeghers polyp
normal site specific mucosa in a dirorganized
arrangement

Real Life - Polyp from a patient
with Peutz-Jeghers syndrome

Peutz-Jeghers
polyps in small
intestine – note that
the background flat
mucosa is normal
A perfect small bowel Peutz-Jeghers polyp – our data showed that even a single small bowel Peutz-Jeghers polyp probably means the patient has the syndrome.


Dysplasia in Peutz-Jeghers' polyps is uncommon.
Juvenile Polyposis

- Genetically heterogeneous condition in which some families have autosomal dominant germline mutations in the DPC4 gene on chromosome 18q21.
- Polyps in juvenile polyposis can be limited to the colon or can be generalized, involving the colon, small bowel, and stomach.
- Some patients appear to have juvenile polyposis predominantly confined to the stomach.

Gastric Hamartomatous Lesions

- Peutz-Jeghers
- Juvenile polyposis/Cowden’s disease
- Cronkhite-Canada

Dysplasia in Peutz-Jeghers’ polyps is uncommon

Gastric juvenile polyposis – note that the flat mucosa appears normal
Gastric juvenile polyposis – note that the flat mucosa appears normal.
Distinction between Gastric HP and Syndromic Polyps

- 1) The patient may have a previously characterized polyposis syndrome – Best Discriminator!!!!!!
- 2) There may be biopsies of the non-polypoid gastric mucosa showing an atrophic or inflammatory gastropathy of the type associated with the development of hyperplastic polyps
- 3) Hyperplastic polyps frequently show a more lobulated or villiform surface as compared to the often rounded surface of juvenile polyps
- 4) Hyperplastic polyps often contain a more prominent edematous, inflamed lamina propria as compared with Peutz-Jeghers polyps, which can sometimes but not always show smooth muscle arborization.

<table>
<thead>
<tr>
<th></th>
<th>Peutz-Jeghers Polyp</th>
<th>Juvenile Polyp</th>
<th>Hyperplastic Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epithelium</strong></td>
<td>Unremarkable</td>
<td>Eroded or Normal</td>
<td>Damaged with reactive or regenerative changes; chemical gastropathy changes.</td>
</tr>
<tr>
<td><strong>Pit and Gland Architecture</strong></td>
<td>Pits and glands are grouped or packeted with intervening septations of smooth muscle strands</td>
<td>Disorganized with varying sizes and shapes. Sometimes forms edematous club-shaped or irregular villiform structures</td>
<td>Surface of pits connect to deeper portions of glands in a linear trajectory. Glands and pits are generally small, regular and orderly although surface glands can appear disorganized and eroded.</td>
</tr>
<tr>
<td><strong>Lamina Propria</strong></td>
<td>Unremarkable</td>
<td>Edematous Granulation tissue common</td>
<td>Unremarkable or inflamed</td>
</tr>
<tr>
<td><strong>Smooth Muscle</strong></td>
<td>Short wispy or chunky bundles not connected to muscularis mucosae</td>
<td>Unremarkable</td>
<td>Long sweeping bundles; Connects with muscularis mucosae</td>
</tr>
</tbody>
</table>
Cronkhite-Canada Polyposis

- Diffuse polyposis occurring in patients with unusual ectodermal abnormalities, including alopecia, onychodystrophy (this means fingernails that are falling apart) and skin hyperpigmentation.
- Europeans and Asians - mean age at onset of 59 years.
- Male to female ratio is 3:2.
- Neither a familial association nor a genetic defect are known.
- Affects whole GI tract except esophagus.

Cronkhite-Canada Polyposis

- The most common presenting symptoms include diarrhea, weight loss, nausea, vomiting, hypogeusia and anorexia.
- Mucoid diarrhea results in the depletion of the patient's protein reserves such that the patient loses his (usually) hair and nails.
- Potentially fatal complications, such as malnutrition, gastrointestinal bleeding and infection, often occur, and the mortality rate has been reported to be as high as 60%.
Case 3

- Large gastric body polyp in a 72 year old woman with long history of autoimmune gastritis
Pyloric Gland Adenoma (PGA)

- Elster 1976
  - Described adenoma-like hyperplasia of mucoid glands
- Borchard et al and Watanabe et al 1990
  - Separately described similar lesions
  - Term “pyloric gland adenoma” mentioned in 1990 WHO classification of gastric tumors
- Case reports of similar lesions in:
  - Gallbladder
  - Main pancreatic duct
  - Duodenum
  - Cervix uteri
Pyloric Gland Adenoma

- Adults (73+/-12.8 years),
- Women (75%).
- In stomach, mostly in body (64%), often found in patients with autoimmune gastritis (36%).

Clinical Features of JHU PGAs

<table>
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<tr>
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<th>No. (%)</th>
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<tbody>
<tr>
<td><strong>Gender distribution</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (64%)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (36%)</td>
</tr>
<tr>
<td><strong>Mean Age (range)</strong></td>
<td>71.2 (47-85)</td>
</tr>
<tr>
<td><strong>Adenoma location</strong></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>17 (46%) (13F, 2M)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>18 (48%) (9F, 7M)</td>
</tr>
<tr>
<td>GE junction</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Background Mucosal Changes and in Gastric PGA

- 9 cases with surrounding mucosa available for assessment:
  - 3 with autoimmune metaplastic and atrophic gastritis (AMAG)
  - 5 with intestinal metaplasia
Pyloric gland adenoma – Ki-67

Pyloric gland adenoma – MUC 6
Gastric Adenoma, Gastric Foveolar Type

Pyloric gland adenoma, MUC5AC

Gastric Foveolar Type Adenoma

PAS/Alcian Blue
Case 4

- A 63 year old woman with a *history of a thin melanoma* and heartburn underwent upper endoscopy. A small gastric nodule was biopsied
Is this a melanoma??

**GI Tract Langerhans’ Cell Histiocytosis (LCH)**
- Proliferative histiocytic disease of unknown etiology and pathogenesis.
- Abnormal proliferation of bone marrow-derived Langerhans cells and may affect any age group.

**LCH - Three clinicopathologic syndromes**
- Unifocal disease (formerly solitary eosinophilic granuloma)
- Multifocal, unisystem disease (formerly Hand-Schuller-Christian disease)
- Multifocal, multisystem disease (formerly Letterer-Siwe disease).
LCH - General

- Treatment guidelines by the Histiocyte Society have subcategorized multisystem disease as either low-risk or high-risk.
- Low-risk patients: skin, bone, lymph node and pituitary gland;
- High-risk patients: spleen, liver, bone marrow and lung.
- The designation of high-risk implies poor response to therapy and worse prognosis.

GI Tract LCH

- Exceedingly rare - most often found in male children with high-risk multisystem disease.
- Younger than 2 years at presentation
- Symptoms: vomiting, abdominal pain, intractable diarrhea, malabsorption, bloody stool, protein-losing enteropathy and even intestinal perforation.
- Poor prognosis - no specific chemotherapeutic regimen of clear benefit.

GI Tract Langerhans cell histiocytosis

- In adults, LCH of the GI usually BUT NOT ALWAYS is an incidental innocuous process
- Usually involves the colon where it presents as a colon polyp and most patients do well following polypectomy
Adult colonic Langerhans cell histiocytosis – polypectomy – infiltrate in submucosa or lamina propria

Adult colonic Langerhans cell histiocytosis – S100 protein

Adult colonic Langerhans cell histiocytosis – polypectomy – CD1a