Case. A gastric body polyp from a 66 year old woman.
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

Table 1 Location of pyloric gland adenoma (PGA) throughout the gastrointestinal tract based on a recent analysis of 373 patients with PGA in Bayreuth including 90 cases that were published elsewhere

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>2.7%</td>
</tr>
<tr>
<td>Bulb</td>
<td>8.3%</td>
</tr>
<tr>
<td>Antrum</td>
<td>3.8%</td>
</tr>
<tr>
<td>Corpus</td>
<td>54.1%</td>
</tr>
<tr>
<td>Cardia</td>
<td>17.4%</td>
</tr>
<tr>
<td>Oesophagus (in Barrett's)</td>
<td>2.4%</td>
</tr>
<tr>
<td>Remaining stomach</td>
<td>83.4%</td>
</tr>
<tr>
<td>Rectum</td>
<td>1.1% (4 cases)</td>
</tr>
<tr>
<td>Papilla of Vater</td>
<td>0.8%</td>
</tr>
<tr>
<td>Pancreatic duct</td>
<td>0.3%</td>
</tr>
<tr>
<td>Bile duct</td>
<td>4%</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>4.3%</td>
</tr>
<tr>
<td>BII, Billroth II</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Distribution of pyloric gland adenoma cases in Baltimore at Johns Hopkins Hospital

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>14.8%</td>
</tr>
<tr>
<td>Bulb</td>
<td>10.0%</td>
</tr>
<tr>
<td>Antrum</td>
<td>2.6%</td>
</tr>
<tr>
<td>Corpus</td>
<td>37.0%</td>
</tr>
<tr>
<td>Cardia</td>
<td>13.2%</td>
</tr>
<tr>
<td>Oesophagus (in Barrett's)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Papilla of Vater</td>
<td>1.5%</td>
</tr>
<tr>
<td>Pancreatic duct</td>
<td>3.7%</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

Vieth M, Montgomery EA. Some observations on pyloric gland adenoma: an uncommon and long ignored entity! J Clin Pathol. October 2014
Pyloric gland adenoma in duodenum

Pyloric gland adenoma – Ki-67

Pyloric gland adenoma, MUC5AC
Syndromic Pyloric Gland Adenoma?
In patients with familial adenomatous polyposis? (normal background mucosa seen; US population) – Have GNAS mutations just like sporadic ones
In patients with Lynch syndrome? (essentially all cases in this series had background of damaged gastric mucosa; Korean population)

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
Intestinal type
Gastric foveolar type
Pyloric gland adenoma
Oxyntic gland adenoma – evolving concept since very rare
Gastric adenoma, gastric foveolar type – pristine background mucosa, NO intestinal metaplasia anywhere. The cells have apical neutral mucin. In many ways equivalent to colorectal adenomas.

Pyloric gland adenoma - cells lack apical mucin caps and these arise in stomachs with pyloric metaplasia of the body mucosa.

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, Abraham View
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.
Gastric Adenoma

Intestinal type adenoma - the lesion arises in damaged background mucosa ("field effect") - whole stomach at risk

Gastric Adenoma, Gastric Foveolar Type

Background stomach not at risk

Gastric adenoma, gastric foveolar type - pristine background mucosa, NO intestinal metaplasia anywhere. The cells have apical neutral mucin. In Many ways equivalent to colorectal adenomas
Gastric Adenoma, Intestinal Type

Muc5AC  Muc6

Gastric Adenoma, Intestinal Type
Literature Confusion


These authors claim that having foveolar differentiation (MUC5AC) was bad.

Difference between that and the scheme just noted is that these patients ALL had background intestinal metaplasia in their stomachs so essentially the authors are saying if the background IM is of the incomplete type this is worse!

No need to waste your time doing silly MUC profiles on gastric dysplasia/neoplasia!

Oxytic gland adenoma

Rare

Same lesions have been termed “gastric adenocarcinoma of fundic type”, despite benign follow-up in the initial series. Our follow-up was also benign.

Limited numbers of cases reported to date so they are either benign of very low-grade/ unlikely to kill patients

Oxyntic gland adenoma, Ki-67 – only stains the gastric mucosa proliferative compartment over the lesion.

Super rare oxyntic gland adenocarcinoma/Chief cell adenocarcinoma.

MUC6 stain.
Case
A biopsy was performed of a gastric polyp and diagnosed as a “hyperplastic polyp”. The gastroenterologist called and pointed out that the diagnosis was wrong.

Gastric Peutz-Jeghers polyp

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).
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.

Gastric Hamartomatous Lesions
Peutz-Jeghers
Juvenile polyposis/
Cowden’s disease
(Cronkhite-Canada)

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 juvenile polyposis – note that the flat mucosa appears normal.

Syndromic gastric juvenile polyposis
Syndromic gastric juvenile polyposis in Italian patient

Real life - polyp from a patient with known juvenile polyposis - it cannot be separated from a hyperplastic polyp

Juvenile Polyp – nice flat mucosal surface

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>Peutz-Jeghers Polyp</th>
<th>Juvenile Polyp</th>
<th>Hyperplastic Polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelium</td>
<td>Unremarkable</td>
<td>Eroded or Normal</td>
</tr>
<tr>
<td>Pit and Gland</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>
</tr>
<tr>
<td>Architecture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamina Propria</td>
<td>Unremarkable</td>
<td>Edematous</td>
</tr>
<tr>
<td>Smooth Muscle</td>
<td>Short wispy or chunky bundles not connected to muscularis mucosae</td>
<td>Unremarkable</td>
</tr>
</tbody>
</table>

From Lam-Himlin et al
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 to female ratio is 3:2. Neither a familial association nor a genetic defect are known. Affects whole GI tract except esophagus.

The most common presenting symptoms include diarrhea, weight loss, nausea, vomiting, hypogeusia and anorexia. Mucoid diarrhea results in the depletion of the patients 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 80%.

Cronkhite-Canada Polyposis – the flat mucosa is ABNORMAL

Fundic Gland Polyps – Most common stomach polyp
2 distinct forms: sporadic and FAP-associated. Originally described in patients with FAP and believed to be a manifestation of that syndrome, now recognized to be the most common gastric polyps in individuals without FAP. Sporadic - 1-2% of routine upper endoscopic examinations, most common in middle-aged females. Small (a few millimeters and only rarely more than 1 cm), sessile, and dome-shaped. Not associated with inflammatory or atrophic background. Asymptomatic.
Fundic Gland Polyps

Sporadic may be single but are commonly multiple (usually a few polyps). Rarely patients without FAP will have carpeting of the body and fundus by numerous FGPs in a manner that resembles a polyposis syndrome.?

Sporadic Fundic Gland Polyps

Use of proton pump inhibitors and the development of FGPs.

Fundic Gland Polyps – FAP Associated v Sporadic

FAP-associated FGPs occur in a majority of patients with FAP (reported frequencies range from 12.5% to 100% of FAP patients, depending on the age at endoscopy) Equal gender distribution. Younger ages, including children More numerous than sporadic FGPs, and hence patients with FAP are more likely to have fundic gland “polyposis” Approximately 25% of FAP-associated FGPs demonstrate low-grade epithelial dysplasia. Dysplasia in sporadic FGPs can occur but is distinctly unusual AND HAS NO RISK OF PROGRESSION TO CANCER!!!!!!

Fundic Gland Polyps

Fundic Gland Polyps

Fundic Gland Polyps
Adenomas

In general, gastric adenomas are rarely truly “sporadic” lesions. Most arise in “dirty soil” (intestinal or pyloric metaplasia after damage). Gastric foveolar types and oxyntic gland adenomas are both very rare. 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.

<table>
<thead>
<tr>
<th>TYPE OF GASTRIC POLYP</th>
<th>LIKELY APPEARANCE OF BACKGROUND GASTRIC MUCOSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic polyp</td>
<td>Gastritis (autoimmune or environmental)</td>
</tr>
<tr>
<td>Syndromic/Hamartomatous polyp (juvenile or Juvenile polyposis type)</td>
<td>Normal</td>
</tr>
<tr>
<td>Menetrier’s disease</td>
<td>Abnormal, involving the entire gastric body but sparing the antrum</td>
</tr>
<tr>
<td>Gastritis–Canada syndrome</td>
<td>Abnormal, involving entire stomach</td>
</tr>
<tr>
<td>Gastric adenoma, intestinal type</td>
<td>Gastritis (autoimmune or environmental)</td>
</tr>
<tr>
<td>Gastric adenoma, gastric foveolar type</td>
<td>Normal</td>
</tr>
<tr>
<td>Gastric adenoma, pyloric gland type</td>
<td>Abnormal (autoimmune gastritis)</td>
</tr>
<tr>
<td>Gastric adenoma, oxyntic gland type</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Case

A 26 year old white male presented to our hospital to discuss the management of his known germline E-cadherin mutation. Otherwise healthy, striking family history of hereditary diffuse gastric cancer; father, paternal grandmother.

Case Report, Cont

The patient’s only sibling, his sister, underwent similar testing and also had the deleterious mutation. The patient has 2 uncles and an aunt. The aunt and one uncle both underwent CDH1 testing and were found to be carriers as well.
Follow-Up

The patient underwent a total gastrectomy and roux-en-Y anastomosis. His gastrectomy specimen demonstrated six foci of intramucosal adenocarcinoma of the diffuse type and numerous foci of in-situ carcinoma.
Intramucosal Carcinoma

Hereditary Gastric Cancer
Autosomal dominant
Gastric cancers develop in youth
Mutated CDH1 gene (E-cadherin), a tumor suppressor gene in all cells
“Second hit” initiates neoplasia
Accounts for up to 40% of familial gastric cancer cases

E-cadherin Mutations
About 40-70% (men) - 65-85% (women) develop gastric cancer by age 75
Females have a 40-50% cumulative risk of mammary lobular carcinoma by age 80
15 year old asymptomatic CDH1 mutation carrier. Formalin fixed stomach, showing barely discernible pale patches the body-antrum transitional zone.

Patterns of signet ring cell carcinoma in situ, non-invasive. Single signet ring cells on left, pagetoid spread pattern on right. The latter pattern is descriptive and does not imply the presence of an adjoining invasive component.

Mucosa
Muscularis mucosae
Submucosa

T1a
Tis

Early diffuse gastric cancers, invasion into lamina propria

Does Screening Work?
Not yet
Multiple random biopsies fail to detect lesions in most cases; enhanced detection methods increase the yield somewhat
ALL patients will harbor pockets of carcinomas in resections

Do I Need To Look For These in situ lesions in Everyone?
Probably not – not sure what they would mean
They are PROBABLY not present in the background mucosa in sporadic diffuse cancers [except no one has REALLY looked for them]
Any Pitfalls

Yes, Reactive cells at the gastric surface can appear similar to the in situ signet cells. The references in your handout have nice illustrations to help you if you get a case!
Scar-like gastric carcinoma

Sneaky gastric cancer

Subtle gastric carcinoma, high magnification

Gastric carcinoma - Abnormal amphophilic mucin color on PAS/AB – neither like that in goblet cells nor like neutral mucin of gastric foveolar cells or fundic glands

Pitfall alert – about a third of gastric adenocarcinomas express DOG1

Gastric adenocarcinoma - keratin stain
Gastric carcinoma – even a blush in the epithelium

**Immunohistochemistry Pitfalls for Stomach Malignant Neoplasms**

Remember that melanomas often are CD117+

Large cell lymphomas are often P63+

GISTs can express MELAN-A

*Keratin stains do not tell you if atypical cells in ulcer beds are reparative or neoplastic but E-cadherin can help with so-called “signet cell change”*

**Gastric Cancer Variants**

Clear cell pattern, squamous, mucinous, “lymphoepithelial”, and hepatoid all known Metastases are always a concern
Metastases

(Remember to always consider epithelioid gastrointestinal stromal tumor/GIST)
The common metastases – lobular breast, renal cell carcinoma, melanoma, hepatobiliary carcinoma
Clue – the background mucosa looks healthy
ALWAYS think of metastatic lobular carcinoma in women with “signet cell carcinoma”

- Metastatic lobular breast carcinoma - background pristine mucosa
- Metastatic lobular breast carcinoma - ER
- Metastatic renal cell carcinoma - BEWARE - appears similar to xanthoma!!
Metastatic renal cell carcinoma - BEWARE - appears similar to xanthoma!!! AND can have subtle keratin expression.

**HER2 (HER2/neu; ERBB2)**

1984

The new oncogene an erb-B-related gene encoding a 185,000-M, tumour antigen

- **HER2**: Human epidermal growth factor receptor 2
- **Neu**: Derived from a rodent neural tumor line
- **ERBB2**: Similarity of avian erythroblastosis oncogene 2 (ErbB 2)

**Mechanism of Trastuzumab Action**

- Antibody-dependent cellular cytotoxicity (ADCC)
- Interference with dimerization
- Increased endocytosis of the HER2 receptor
- Interferes with proteolytic cleavage of HER2 to a truncated active form

**HER2 in Cancer Treatment**

- 1998: Trastuzumab approved for treatment of HER2+ metastatic breast cancer
- 2010: Approved for treatment of metastatic gastric and GE-junction cancers
- Trastuzumab is potentially cardiotoxic and very expensive ($71,000 / course)
- Critical to identify which patients are most likely to respond using HER2 testing
HER2 for Breast had Quality Issues

- Poor reproducibility of HER2 testing
  - 18% of positive results could not be replicated (2002 NSABP central review)
- Initially non-standardized
  - IHC antibodies
  - Detection systems
  - Interpretation criteria
- Reagents and interpretation is now standardized for breast cancer


IHC Scoring Overview - Breast

Validated HER2 IHC Test

- POSITIVE
- EQUIVOCAL
- NEGATIVE
- NEGATIVE


ToGA – Trastuzumab for Gastric Cancer

Lancet 2010; 376: 687-97
Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

- Combination Chemo +/- Trastuzumab in HER2+ advanced gastric & GE adenocarcinomas
- HER2 positive (entry to trial):
  - IHC 3+ OR FISH positive
- Improved overall survival from 11.1 mo (chemo alone) to 13.8 mo (chemo + trastuzumab)

Wolff et al. (2011) J Clin Oncol 31:3887-90
Wolff et al. (2011) Arch Pathol Lab Med 135:201-08

Overall Survival in ToGA

HER2 Scoring in Gastric Cancer

Different Criteria from Breast Cancer

- HER2 detection validation study for ToGA
- Major differences from breast cancer scoring:
  - Incomplete membranous immunoreactivity
  - Higher rate of tumor heterogeneity
- Developed a modified IHC scoring system for gastric cancer (GCS)
Unlike breast cancer, gastric cancer HER2 membranous staining is usually incomplete.
- "circularity" of membranous staining NOT required for gastric cancer
- Basolateral, or lateral staining sufficient
* Use of breast cancer HER2 scoring may produce 50% false negative IHC

Gastric Scoring: 3+
Breast Scoring: 1+

Most gastric and GEJ adenocarcinomas have significant heterogeneity in IHC staining
Small biopsies may not be representative of the entire lesion
≥ 10% rule used for resections
For biopsies: ≥ 5 clustered cells are required

Common Algorithm HER2 IHC Scoring
GCS – Gastric Cancer Score

<table>
<thead>
<tr>
<th>HER2 Test</th>
<th>N (%): Range</th>
<th>Mean</th>
<th>N &gt; 2.0 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>61 (53)</td>
<td>0.70 - 1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>1+</td>
<td>29 (25)</td>
<td>0.8 - 5.3</td>
<td>1.6</td>
</tr>
<tr>
<td>2+</td>
<td>20 (17)</td>
<td>8.6 - 10.8</td>
<td>2.4</td>
</tr>
<tr>
<td>3+</td>
<td>6 (5)</td>
<td>2.5 - 16.2</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Overall, 16/116 (12%) of tumors were HER2 positive (either IHC 1+ or FISH 1+).

HER2 positive (entry to trial):
- IHC 3+ OR FISH positive
- Both tests performed on every case
**HER2 Testing Algorithms**

ToGA did FISH and IHC on all patients
- US FDA Label
  - Protein Overexpression **OR** Gene Amplification
- European Medicines Agency
  - IHC3+ **OR** IHC2+ and FISH+
- NCCN Guidelines Panel for Gastric Cancer (2014)
  - IHC3+ **OR** IHC2+ and FISH+
- CAP (2014)
  - IHC3+ **OR** IHC2+ and FISH+

**Tumor Heterogeneity and Implications for Biopsy Sampling Errors**

**CAP, NCCN, EMA Algorithm**

- Cost effective
- Identifies patients most likely to benefit from trastuzumab

- **Positive IHC3+**
- **Equivocal IHC2+**
- **Negative IHC1+**
- **Negative IHC0**

- **ISH**

No proven benefit even if FISH + ?
More tissue is better: encourage multiple biopsies from tumor (8-10 is best). Retest resection specimens (if available) and material from metastatic sites. Consider ISH analysis even if IHC is negative (0/1+).

Pre-Analytical Issues

- Only use 10% Neutral Buffered Formalin
- Fixation 6-72 hours
- Ischemic time of less than 3 hours
- No Decalcification - Destroys DNA
- Beware of “rush” protocols
- No Bouin’s – 1 hour of Bouin’s will turn a HER2 FISH negative

Mohammed et al. (2019) Am J Clin Pathol

Thank You