Case Presentation

51 year old Hispanic male is referred recent onset dyspepsia. He is from southern Mexico and is generally healthy. His EGD is unremarkable, with mild erythema of the antrum; biopsies are obtained from the antrum and body, which confirm *H. pylori* infection and also reveal intestinal metaplasia.

Management would include:

a) Treatment of *H. pylori* infection.
b) Review of histology with pathologist.
c) Repeat EGD with further biopsies.
d) Surveillance EGD in 2-3 years.
Gastric cancer: **Epidemiology Summary 2017**

- The third leading cause of cancer mortality
- Annual incidence over one million
- Leading cause of infection-associated cancer mortality
  - *H. pylori* is a WHO Class I Carcinogen
- All-cause mortality worldwide: 14th
  - Will rise to 10th, given growing & aging populations
  - Consistent 2:1 male to female ratio
- Significant geographic variability offers the opportunity for scientific discovery & focused prevention
- High incidence regions include: Latin America, Eastern Asia, Eastern Europe

In the U.S., incidence rates are double in minorities

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**New Cancer Cases Attributable to Infection**

![Graph showing infection-attributable cancers in 2008.](image)

- **Total infection-attributable in 2008:**
  - 23% in LMICs
  - 7.4% in HICs
  - *H. pylori*: 6.2% of cancers
Global Cancer 5-year survival (UICC 2014, NCI 2014)

Gastric cancer “Rim of Fire”?
Gastric Cancer Mortality in the Americas
Torres J & Morgan DR, Cancer Causes Control 2013
IARC 2010, GLOBOCAN 2010

• Incidence 2000-09, mean ASRs:
  - Males 36 (29-43), Females 14.5 (11-20)
• Patient population
  - Male : Female ratio, 2.1 : 1
  - Median age: 58 (youngest patient, 17)
  - Age distribution: <25 <35 <49
  - 5% 12% 25%
• Endoscopy yield: 1 cancer / 7-10 endoscopies
  - Pyloric obstruction: 30-40% with high mortality
• Pathology: 60% poor, 30% moderate, <10% well
Noncardia Gastric Cancer Age-Specific Incidence Rates: Whites

Anderson, W. F. et al. JAMA 2010;303:1723-1728
Gastric cancer incidence in the U.S. (SEERS data)
Kim GH, GIE 2016; Li FH, DigDisSci 2014; Miller BA, CCC 2008

Gastric Cancer Etiologic Model

Environment

Infection

Host

Cancer

Courtesy: MC Camargo
Gastric Cancer “Correa” Cascade

Polk DB, Nature Rev Cancer 2010;
Correa P, Gastro 2007
Correa P, Cancer Res 1992

Gastric Cancer Cascade and the Microbiome

Plottel and Blaser, Cell Host and Microbe
Four Molecular Subtypes of Gastric Adenocarcinoma


**Key Features of Four Molecular Classes of Gastric Cancer**

- Epstein-Barr virus positive (9% of cancers)
  - High levels of EBV genome
  - PIK3CA mutation in 82%, cell survival and growth
  - MET mutation in 32%, growth factor signalling
  - ERBB2 mutation in 18%, growth factor signalling
- Microsatellite instability (22% of cancers)
  - Hypermutation (> 11.4 mutations/Mb)
  - PIK3CA mutation in 64%, cell survival and growth
  - ERBB3 mutation in 55%, growth factor signalling
  - B2M mutation in 35%, HLA class 1 antigen presentation
- Genomically stable (20% of cancers)
  - CDH1 mutation in 38%, cell adhesion defects
  - MET mutation in 29%, growth factor signalling
  - RHOD mutation in 15%, GTPase activity
  - Diffuse +/− signet ring cell histology
- Chromosome instability (50% of cancers)
  - TP53 mutation in 71%, DNA repair
  - ERBB2 mutation in 30%, growth factor signalling
  - CDKN2A mutation in 29%, cell cycle regulation
  - PIK3CA mutation in 28%, cell survival and growth

**Genes commonly mutated (any molecular class)**

- TP53
- KRAS
- RNF43
- RASA1
- PTPRC
- CDH1
- MUC6
- ABCA10
- FAM46D
- SMAD4
- APC
- CTNNB1
- PLB1
- PIK3CA
- BCR
- MACF1
- CNGA4
- RHOD
- EYA4
- SMAD2
- EIF2C4
- ARID1A
- BNC2
- SOHLH2
- ERBB2 (HER2)
Incidence of gastric cancer among patients with gastric precancerous lesions: observational cohort study in a low risk Western population

Huan Song,1 Isabella Guncha Ekheden,1 Zongli Zheng,1 Jan Ericsson,2 Olof Nyrén,1 Weimin Ye1

Over 20 years:
1 in 256 with normal mucosa
1 in 85 with gastritis
1 in 50 with atrophic gastritis
1 in 39 with intestinal metaplasia
1 in 19 with dysplasia
GC Progression: Netherlands Cohort Study, 1991-2004
deVries AC, Gastro 2008

Risks and Predictors of Gastric Adenocarcinoma in Patients with Gastric Intestinal Metaplasia and Dysplasia: A Population-Based Study Li, AJG 2016
Gastric cancer prevention: Needed research

**Biomarkers:** There are no proven serum biomarkers for gastric cancer, gastric premalignant lesions, nor for the risk of progression of premalignant lesions. *H. pylori*, CagA and/or pepsinogen testing lack sensitivity and specificity

**Chemoprevention:** There are no existing agents for patients with precancerous lesions. *H. pylori* eradication may be helpful in patients with chronic gastritis, but is insufficient for atrophy or GIM

**Endoscopy technology.** Endoscopy screening programs have a significant impact (Japan, Korea). Needed: Novel imaging & cost-effective strategies
Missing rate for gastric cancer during upper gastrointestinal endoscopy: a systematic review and meta-analysis
Ana Rita Pimenta-Melo, Matilde Monteiro-Soares, Diogo Libânio and Mário Dinis-Ribeiro
European Journal of Gastroenterology & Hepatology 2016

Age <55
Female
Severe atrophy
Adenoma or ulcer
Limited #biopsies

Systematic Alphanumeric-Coded Endoscopy (SACE)
Emura F, Rev Gastro 2013

SACE
8 regions
28 areas
3 minutes
Systematic Alphanumeric-Coded Endoscopy (SACE)
Emura F, Rev Gastro 2013

- **SACE**
  - 8 regions
  - 28 areas
  - 3 minutes

Gastric cancer detection and EGD exam time
Teh JL, CGH 2015

![Graph showing high-risk lesions detection rates vs. mean procedure time for normal examination.](image)

- $R^2 = 0.554$
A multicenter prospective study of the real-time use of narrow-band imaging in the diagnosis of premalignant gastric conditions and lesions

Pimental-Nunez, Endoscopy 2016

Gastric biopsy mapping protocol

Dinis-Ribiero, Endoscopy 2012; Correa P, AJG 2010
Kaplan-Meier Analysis of Gastric Cancer Incidence by Extent of Gastric IM

Cumulative incidence

Year of follow-up

IM corpus

IM antrum

no IM

Subsets of Gastric Intestinal Metaplasia

Correa P, AJG 2010

Complete IM (small intestine)
Goblet cells, Paneth cells (arrow), and eosinophilic enterocytes with brush border (inset).

Incomplete IM (colon)
Intracytoplasmic mucin droplets, and absence of a brush border
Incomplete type of intestinal metaplasia has the highest risk to progress to gastric cancer: results of the Spanish follow-up multicenter study

Carlos A. González, José Miguel Sanz-Anquela, Osmel Compañón, Catalina Bonet, María Berdasco, Conxuelo López, Jorge Mendizabal, Ma Dolores Martín-Aranz, Enrique Rey, Elvira Powes, Laura Espinoza, Jesús Barroso, Angelines Torrecilla, Minam Cuetoescas, Ignasi Elies, Luis Buñol, Maddà Garmendia, Ángel Fernández, Guillermo Muñoz, Victoria Andreu, Ma Jose Pau, Sergio Laro, Ma Jose Ramírez, Study group, and Javier P. Gavert

Journal of Gastroenterology and Hepatology 31 (2016) 953–958

<table>
<thead>
<tr>
<th>Precursor lesion</th>
<th>HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>IM vs CAG</td>
<td>4.17</td>
<td>0.55 - 31.6</td>
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<tr>
<td>CIM vs CAG</td>
<td>2.50</td>
<td>0.30 - 20.5</td>
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<tr>
<td>IIM vs CAG</td>
<td>6.42</td>
<td>0.83 - 49.9</td>
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<tr>
<td>IIM vs CIM</td>
<td>2.57</td>
<td>1.06 - 6.26</td>
</tr>
</tbody>
</table>

Long-term follow-up of persons treated for *H. pylori* infection

![Graph showing long-term follow-up of persons treated for *H. pylori* infection](image-url)
Antral intestinal metaplasia post *H. pylori* eradication

Kong *et al.*, WJG, 2014

Corpus intestinal metaplasia post *H. pylori* eradication

Kong *et al.*, WJG, 2014
Gastric Intestinal Metaplasia Proposed Algorithm
Dinis-Ribeiro, Endoscopy 2012; Correa P, AJG 2010

Pathology report with IM in a gastric mucosa biopsy sample

Access for H. pylori infection (test with serology if biopsy is negative) and treat
Access extension and type of IM in original biopsies

Extensive IM or incomplete IM

Extensive or severe atrophy

Yes/unknown

No

Surveillance:
- Endoscopy with mapping in two to three years
- Consider repeat endoscopy in two to three years if extensive IM or incomplete IM persists

No surveillance required

Proposed algorithm for the management and surveillance of patients with gastric atrophy or gastric intestinal metaplasia.

GIM Detection: Endoscopy Caveats

• Detailed evaluation of the gastric mucosa
  • Systematic visual inspection of regions and areas
  • Adequate examination times (7 minute threshold?)
  • Satisfactory insufflation
  • Consider imaging enhancement
    • Magnification, chromoendoscopy, NBI

• Standardized gastric biopsy mapping (5 sites)
  • Coordination with pathology (e.g., incomplete GIM)
Management of Gastric Premalignant Lesions

- General screening & surveillance is not recommended in U.S. populations with a low risk of gastric cancer
- **Higher risk groups include:**
  - Family history of gastric cancer
  - Immigrants from high incidence areas
  - Consider: Non-white racial and ethnic groups
- **Gastric visual & biopsy “mapping”:**
  - Minimum of 2-4 antral and 2-4 corpus biopsies
- **Gastric biopsy “mapping” is indicated for:**
  - Initial endoscopy in high risk patients
  - Surveillance EGD in those with high risk lesions

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Management of Gastric Premalignant Lesions

- **Surveillance endoscopy may be warranted:**
  - GIM which is _extensive_ or _incomplete_ (q2-3 years)
  - Low grade dysplasia (<12 months)
- **High grade dysplasia** warrants definitive treatment

- **H. pylori eradication** is indicated for patients with precancerous lesions of the stomach
  - Consider _H. pylori_ serology if histology negative
  - Counsel regarding tobacco use & meat consumption

- **The future:** Improved biomarkers & imaging technology