Cancer as an infectious disease: Helicobacter Pylori and Gastric Cancer

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Objectives

Following this presentation, the participant will be able to:

- Identify the most common presenting complaints and differential diagnosis for gastric cancer
- Review the pathogenesis of *Helicobacter pylori* (H. Pylori) induced gastric carcinogenesis
- Describe the treatment of H. Pylori in gastric cancer
- Review the role of primary care in screening and surveillance
What is the Magnitude of the Problem?
Epidemiology of Gastric Cancer

- Incidence rates:
  - 2\textsuperscript{nd} leading cause of cancer death in the world
  - 14\textsuperscript{th} most common in Canada 2012
  - Estimated incidence: 3300 cases in 2012
  - 2:1 male: female
  - 7/100,000 population
  - 1 in 20 stomach ulcers are cancerous
  - only 1 in 5 gastric cancer patients will live more than 5 years

www.cancer.ca
Epidemiology (con’t)

- Mortality:
  - 2100 deaths in 2012
  - 4/100 000, but 7/100 000 in males, 1/100 000 females

www.cancer.ca
Global incidence of gastric cancer in men*

* The highest rates occur in Eastern Asia, South America, and Eastern Europe.
Age-Standardized Incidence Rates for Selected Cancers, Males, Canada, 1983-2012
Age standardized mortality rates for men for common cancers

www.cancer.ca
Age standardized mortality rates for common Cancers in Females

www.cancer.ca
Risk Factors for Gastric Cancer

- Diffuse Type Gastric Cancer:
  - Familial predisposition
    - Hereditary diffuse gastric cancer
Risk Factors for Gastric Cancer (cont’d)

- Diffuse type and Intestinal Type Gastric Cancer:
  - Environmental Factors
    - High sodium diet – salt and salt preserved foods
    - Nitroso compounds – exogenous and endogenous – increased risk of non cardia gastric cancer
    - Smoking
    - Obesity or being overweight – increased cardia gastric cancer
    - Alcohol – may be protective
    - Diet high in vegetable and fruit appears protective against intestinal type & cereal fibre appears protective against diffuse type
Risk Factors for Gastric Cancer: Environmental Factors (cont’d):

- **Helicobacter pylori** infection – most common cause & there is an association between salted food intake and increased persistent infection
- Epstein Barr virus – association between Nasopharyngeal Carcinoma and Gastric Cancer (mainly diffuse type but also intestinal)
- Socioeconomic factors – low SES – distal cancers increased, high SES – proximal cancer risk increased
- Gastric surgery – Bilroth II > risk than Bilroth I
- Reproductive hormones – lower risk in females with longer history of increased years of fertility
Host Risk Factors For Gastric Cancer

- **Blood group – Type A** 20% increased risk
- **Familial Risk**
  - Clustering of H. pylori in families, however some risk independent of H. pylori remains
- **Genetic syndromes:**
  - HNPCC, familial adenomatous polyposis, Li-Fraumeni syndrome, Peutz Jeghers syndrome
Host Risk Factors for Gastric Cancer (cont’d)

- Genetic polymorphisms
- Gastric polyps
- Hypertrophic gastropathy and immunodeficiency syndromes
- Gastric ulcer likely related to increased H. pylori infections
- Pernicious anemia – associated with 2 – 3 fold risk of gastric cancer, also associated with neuroendocrine (carcinoid) tumours
Studies Supporting H. Pylori as a Risk Factor?

- H. pylori identified in histologic analysis of cancerous and precancerous tissues
- Epidemiologic studies – strong correlation between H. pylori seropositivity and gastric cancer
- Case control and cohort studies found serologic evidence of H. pylori infection correlated with double the risk of gastric cancer
- Prospective studies of patients with H. pylori positive serology and negative serology – endoscopic evaluations sequentially – only H. pylori group gastric cancer diagnosed
Presentation

- Weight loss (58.1%) associated with:
  - Early satiety
  - Anorexia (50.9%)
  - Nausea and vomiting (20.7%)
- Abdominal pain (48.1%) – epigastric area, vague and mild initially then increasing and constant
- Dysphagia (16.6%) (proximal stomach cancer or GE junction)
- Anemia (26.6%)
- Epigastric mass palpable (33.3%)
- GI bleeding – hematemesis or melena (12.5%)

Goldsmith & Ghold, Am J Surg 1970
Dyspepsia

- Definition: poor or altered digestion
- Incidence rates in UK at 15.3/1000 person years
- Common Diagnoses within 1 year of presenting:
  - Irritable Bowel Syndrome (IBS) (OR 264)
  - Gastroesophageal reflux disease (GERD) (OR 62.8)
  - Peptic ulcer disease (PUD) (OR 27.2)

Wallander et al, Family Practice 2007
Approach to Evaluation of Dyspepsia
Dyspepsia

Red Flags:
- Age >45
- Weight loss
- Bleeding
- Anemia
- Dysphagia

Red Flags
- Endoscopic Evaluation
  - No Findings:
    - Consider: Pancreatic Cancer, Intra-abd malignancy, bowel ischemia, hepatoma, nonulcer or functional dyspepsia (diagnosis of exclusion)
  - Findings:
    - Crampy colicky pain increased with fried food or radiating to RUQ
      - Biliary colic
    - Male with history NSAID use, night pain, relief with food or antacids, prior history or family history PUD
      - Ulcer like dyspepsia
        - PUD Gastritis
      - Heartburn, regurgitation, ↑ with lying down or spicy food
        - Reflex like dyspepsia
      - Poorly localized, discomfort, increased with meals, associated with postprandial bloating, nausea and vomiting
        - Dysmotility like dyspepsia
          - IBS Gastroparesis

No Red Flags
- Treat accordingly
- Male with history NSAID use, night pain, relief with food or antacids, prior history or family history PUD
  - Ulcer like dyspepsia
- Heartburn, regurgitation, ↑ with lying down or spicy food
  - Reflex like dyspepsia
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Harrisons Internal Medicine
New onset Dyspepsia

Exclude by history GERD, medication use, biliary disease, IBS, aerophagia

Non-invasive Hp testing
- +

Anti Hp therapy
- Confirm eradication UBT
- Symptoms remain or recur

Empiric trial H2 blocker
- Refer to Gastroenterologist

>40 y/o Alarm symptoms

Or

Refer to Harrisons Internal Medicine
Differential Diagnosis of Dyspepsia

- Malignant:
  - Gastric, esophageal, pancreatic, bowel, biliary tract, liver, metastatic from lung, breast etc

- Non Malignant:
  - Small bowel/duodenum: PUD
  - Biliary: biliary colic
  - Esophageal: GERD
  - Intestinal: bowel ischemia
  - Functional: IBS, gastroparesis, functional dyspepsia (diagnosis of exclusion)
Helicobacter Pylori (H. pylori)

- First discovered in 1980’s, and proven causal association with gastritis and peptic ulcer shortly thereafter
- Colonizes gastric mucosa > 50% of human population – ↑prevalence in developing countries
- Increases risk of stomach cancer by 6 fold
Pathogenesis of H. pylori Infection and Gastric Cancer Development

- Majority of infected population with H. pylori is asymptomatic, some infected individuals develop:
  - Peptic ulcer
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
- A subset of colonized individuals may develop:
  - Corpus gastritis
  - Gastric hypochlorhydria
  - Gastric atrophy
  - Increased risk of gastric cancer
- Another subset may develop:
  - Antral-predominant gastritis
  - Gastric hyperchlorhydria
  - Increased risk of duodenal ulcer
Atrophic Gastritis

Metaplasia

Dysplasia

Gastric Cancer (intestinal type)
Pathogenesis of H. Pylori and Gastric Cancer

Harrisons Internal Medicine

1. Normal Gastric Mucosa
2. Acute H. Pylori Infection
3. Persistent chronic H. pylori infection
4. Antral Predominant Gastritis
5. Non Atrophic Pangastritis
6. Corpus Predominant Atrophic Gastritis
7. Intestinal metaplasia
dysplasia
8. Gastric ulcer
9. Asymptomatic H. pylori infection
10. MALT lymphoma
11. Duodenal ulcer

Gastric Cancer
Pathogenesis of H. pylori

Carcinogenesis:

• H. pylori strains: 2 types
• Type 1
  - Contains the cytotoxin-associated gene pathogenicity island (cag PAI) and express the CagA protein
  - Are the most common isolates and associated with more severe outcome of infection
  - Appears to alter host tumour suppression response resulting in increased carcinogenicity
  - Also has effect on immune responses
H. Pylori Carcinogenesis

- Type 2:
  - \textit{cag} negative
  - Most frequently associated with less toxic effects with asymptomatic gastritis
CagA Effects on Immune System and Role in Carcinogenesis

- T-regulatory cells (Treg) are able to suppress activation/proliferation of other T cells
- Crucial role in suppressing immune responses in autoimmune disease prevention, but also in controlling immune response to pathogens
- Suppression of CD4+ memory cells seen with the presence of H. pylori specific Treg
- Association between Treg, H. pylori infection, gastritis, peptic ulcer, and gastric adenocarcinoma
- Treg presence in gastric mucosa
  - suggests involved in suppression of mucosal immune responses & persistence of infection and modulating induction of gastritis

Ruggiero, P. Curr Opin Infect Dis 2012
H. Pylori Treatment after Diagnosis of Early Gastric Cancer

- Controversial:
  - Japanese group published in Lancet 2008:
  - 544 patients randomised to eradication therapy for H. pylori after endoscopic resection of gastric cancer or no eradication
  - HR for intention to treat group: 0.339 (95% CI 0.157-0.729; p=0.003) for metachronous gastric cancers

Fukase K et al. Lancet 2008
H. Pylori Eradication for Prevention of Gastric Cancer

- Meta analysis including 7 controlled trials in high risk countries for gastric cancer
- Significantly lower rates of gastric cancer (1.1 vs 1.7 percent)
  - RR 0.65, 95% CI 0.43-0.98
- Limitations of the trial:
  - only 2 studies were double blinded, and only 2 assessed gastric cancer incidence

Fuccio L. Ann Intern Med
Current Treatment Options

- **Triple therapy**
  - PPI, clarithromycin & amoxicillin
  - If allergic to penicillin: replace amoxicillin with metronidazole

- **Quadruple therapy**
  - PPI, bismuth, metronidazole, & tetracycline

- Test for eradication if symptoms recur
  - Second line therapy if positive
Role of Primary Care in Screening and Surveillance

- Insufficient data to recommend screening asymptomatic patients for *H. pylori* to prevent gastric cancer on a widespread basis
- Not cost effective
- Decisions to screen should be based on risk factors:
  - Race
  - Diet
  - Family history
Screening in High Risk Groups

- In Japanese Americans over 50 years, it is estimated that the cost effectiveness of screening is more effective than breast cancer mammographic screening.
- In Canada, there is no recommendation for screening of asymptomatic individuals.
- High risk could be considered for screening.
High Risk Groups in Canada?

- New immigrants from high risk parts of the world including Asia?
- First Nations Canadians?
- Helicobacter pylori Study Group in Canada recommended:
  - Canadian Aboriginals and recent immigrants are among populations in which the prevalence of H pylori infection remains high and, therefore, the health risks imposed by H pylori remain a significant concern.
  - In Canadian communities with a high prevalence of both *H pylori* and gastric cancer, there remains an opportunity to test the hypothesis that *H pylori* infection is a treatable risk factor for malignancy.

Jones N. Can J Gastroenterol  2012
References