Epithelial and lymphoid neoplasms of the stomach

2017

Epidemiology

- The worldwide incidence of gastric cancer has declined rapidly over the recent few decades, however, this trend reflect the decreasing incidence of cancers arising in the distal stomach and intestinal type.
- Proximal cancers arising in the gastro-esophageal junction have in fact been increasing in incidence (related to Barrett esophagus and GERD ?); (different etiology)

GERD

- Gastroesophageal reflux disease: transient relaxation of lower esophageal sphincter causes reflux of acid and bile into the distal esophagus
- Complication of GERD: Barrett’s e. (glandular metaplasia in distal e. due to acid injury)
  - ulceration with stricture formation
  - glandular dysplasia with risk for adenocarcinoma.

Prevention modalities in cancer

- Treatment of gastroesophageal reflux disease decreases the risk for developing adenocarcinoma arising from Barrett’s esophagus

GASTRIC CANCER - epidemiology

- Incidence varies with geography: lower rates in North America, Northern Europe and Africa, and highest rates in Japan, East Asia and East Europe
- Males > females
- Average age at diagnosis: in seventh decade of life

Epidemiology

- Once the second most common cancer worldwide, stomach cancer has dropped to fourth place, after cancers of the lung, breast, and colon and rectum. However, stomach cancer remains the third most common cause of death from cancer.
- The World Health Organization estimates that in 2012, gastric cancer accounted for 723,000 deaths worldwide.
Risk factors

Environmental factors
- Diet: rich in nitrates, salt, smoked foods, and complex carbohydrates

Protective factors
- Diet rich in fresh fruits and vegetables are associated with reduced cancer risk through their antioxidant properties

Environmental risk factors
- Cigarette smoking is associated with a 2 to 3 times increased risk for gastric cancer

Risk factors
- A history of prior gastrectomy

Hypochlorhydria, bile reflux and gastritis in the residual gastric stump
- Low socioeconomic status
- Autoimmune gastritis (Pernicious anemia)

Autoimmune gastritis
- An immune-mediated chronic gastritis where the antibodies are directed against parietal cells and intrinsic factor, resulting in loss of oxyntic cells, hypochlorhydria and vitamin B deficiency
- 5% of all cases of chronic gastritis
- Affects individuals of northern European or Scandinavian descent
- Mainly white women in their fifties or sixties

Autoimmune gastritis
- Loss of parietal cells (which secrete acid and intrinsic factor)
- Deficient acid production – hyperplasia of antral gastrin-producing cells
- Lack of intrinsic factor – decreased ileal absorption of vit B12 – megaloblastic anemia
- Reduced serum concentration of pepsinogen reflects chief cell loss
Autoimmune gastritis
Clinical symptoms

• Abdominal pain
• Weight loss
• Pernicious anemia
• Rarely: subacute degeneration of the spinal cord related to vitamin B12 deficiency
• Other immune-related disorders such as Hashimoto thyroiditis, type 1 diabetes mellitus, adrenal insufficiency

Autoimmune gastritis
Laboratory findings

• Serum gastrin – elevated
• Gastric pH – alkaline or neutral (achlorhydria)
• Vitamin B12 level – reduced
• H pylori serology – usually negative
• Antiparietal and intrinsic factor antibodies - positive

Autoimmune gastritis
Endoscopic findings

• Thinning of body mucosa with prominent submucosal vascular pattern, which becomes visible as a result of mucosal atrophy

Autoimmune gastritis

• Body fundic mucosal biopsy in a patient with longstanding autoimmune gastritis. Chief cells and parietal cells are not seen, while chronic inflammation is readily identified

Gastric cancer - risk factors

• *Helicobacter pylori* infection (increases the risk for both intestinal and diffuse type)
• The risk is significantly increased if the *H. pylori* infection is acquired in childhood or is present for greater than 10 years prior to diagnosis of cancer
• *H. pylori* infection may also be associated with the risk seen in people with blood group A.

Risk of Gastric Cancer and Peptic Ulcers in Relation to ABO Blood Type: A Cohort Study
Am J Epidemiol 2010

• “Blood group A was found to be associated with gastric cancer. Strikingly, for peptic ulcers an increased risk has been shown for blood group O.”
• Using the Scandinavian Donations and Transfusions (referred to as “SCANDAT”) database, the authors established a cohort of Swedish and Danish blood donors with known blood type and followed these for the occurrence of gastric cancer and peptic ulcers. Altogether, 1,089,022 donors were followed for up to 35 years, during which 688 gastric cancer cases and 5,667 peptic ulcer cases occurred.
**Helicobacter pylori gastritis**

- In developing countries up to 75% of population over 25 years of age are infected
- In developed countries the overall prevalence is over 30%, exceeding 60% in adults over 60
- H pylori is a flagellated, gram-negative rod
- The WHO has classified H pylori as a class I human carcinogen of gastric cancer

- The intestinal type of non-cardia gastric cancer is generally thought to arise from *Helicobacter pylori* infection, which initiates a sequence that progresses from chronic non-atrophic gastritis to atrophic gastritis, then intestinal metaplasia, and finally dysplasia. This progression is known as Correa's cascade.

**H pylori gastritis**

- Clinical symptoms: abdominal pain, nausea, vomiting, dyspepsia, weight loss, iron-deficiency anemia
- Microscopic findings: marked lymphoplasmacytic inflammation, erosions, lymphoid aggregates (follicles, hyperplasia)

**H pylori gastritis**

- Antral mucosa with chronic active gastritis (HE)
- Helicobacter pylori
- (Giemsa)

**Prevention modalities in cancer**

- Treatment of *H. pylori* infection decreases risk for developing lymphoma and adenocarcinoma of the stomach

**H pylori gastritis**

- Over time, *H. pylori* gastritis progresses to
  - Pangastritis -
  - Multifocal atrophic gastritis -
  - Intestinal metaplasia -
  - Reduced acid secretion -
  ---- increased risk of gastric adenocarcinoma
Intestinal metaplasia

- Intestinal metaplasia of gastric mucosa with sulfomucin-secreting goblet cells

Intestinal metaplasia in gastric antral mucosa

- The open arrows point to residual antral type epithelium, whereas the solid arrows point to the intestinal metaplasia associated areas that have replaced the normal antral type glandular epithelium.

Gastric cancer - risk factors

Epstein-Barr virus (EBV)-the exact pathogenesis remains unknown

- Approximately 10% of gastric adenocarcinomas are associated with EBV infection
- EBV-positive tumors tend to occur in the proximal stomach and most commonly have a diffuse morphology

Genetic alterations

The vast majority of gastric cancers occur sporadically, but patients with

- Li-Fraumeni syndrome
- Germline mutation in adenomatous polyposis coli APC genes

All have increased risk for developing familial, diffuse gastric cancer

- Loss of E-cadherin function is involved in the development of familial, diffuse gastric cancer

Signs and symptoms of gastric cancer

- Most symptoms of gastric cancer reflect advanced disease...
  Indigestion
  Nausea or vomiting
  Dysphagia
  Postprandial fullness
  Loss of appetite
  Melena or pallor from anemia
  Hematemesis
  Weight loss
  Enlarged lymph nodes such as Virchow nodes (ie, left supraclavicular)

Diagnosis. Testing

Serum tumor markers such as CEA and CA 19-9:

- Elevated CEA in 45-50% of cases;
- Elevated CA 19-9 in about 20% of cases
Gastric cancer - gross findings

Location
• in the pylorus and antrum (50-60%)
• cardia 25%
• the body or fundus 15-25%

Type of growth
• Exophytic
• Flat
• Ulcerated

Endoscopic image of elevated and ulcerate gastric adenocarcinoma

Ulcerated gastric cancer

Exophytic gastric cancer

Microscopic findings

• 95% of gastric cancers are adenocarcinomas

The Lauren classification system
• intestinal subtype
• diffuse

Microscopic findings

Lauren classification
• Intestinal subtype histologically resembles colorectal adenocarcinoma (well-formed glands lined by columnar epithelial cells. Intraluminal mucin is often present
Microscopic findings
Lauren classification

Diffuse-type gastric adenocarcinoma is composed of individual or poorly formed nests of cells growing in an infiltrative pattern

• Cells take on a signet-ring cell appearance with the intracytoplasmic mucin pushing the nucleus of the cell to the periphery
• The amount of mucin may be highly variable

Gastric adenocarcinoma, diffuse type signet ring cell carcinoma

Gastric adenocarcinoma, mucinous type

Linitis plastica

• A strong desmoplastic response to the tumor cells may be present, contributing to the firm, rigid wall – a "leather bottle" stomach, termed linitis plastica.

Microscopic findings
Lauren classification

• Some tumors show features of both intestinal and diffuse types and thus are classified as mixed types
**WHO classification**

- Gastric adenocarcinoma:
  - Papillary
  - Tubular
  - Mucinous
  - Signet-ring cell
  - Adenosquamous
  - Undifferentiated
- These may be further classified into moderately or poorly differentiated

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**Hepatoid adenocarcinoma (HAC)**

- a rare type of extrahepatic tumor that has a morphological similarity to hepatocellular carcinoma (HCC)
- an extremely poor prognosis
- occurs in older people - the average patient age is 63.5 years, and the male-to-female ratio is 2.32:1.
- the most common location is the antrum (60.2%)

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**Gastric hepatoid adenocarcinoma (alpha-fetoprotein secreting)**


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**Gastric cancer - treatment and prognosis**

- The depth of invasion and the extent of nodal and distant metastasis at the time of diagnosis is the most powerful prognostic indicators for gastric cancer
- When possible, surgical resection remains the preferred treatment
- 5-year survival rate for advanced gastric cancer is below 20%

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**Early gastric cancers**

- are defined as those confined to the mucosa and submucosa of the stomach regardless of lymph node status (with or without regional lymph node metastases)
- 5-year survival rate can exceed 90% (even if lymph node metastases are present !)

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**Japanese classification of early gastric cancer**

- Early gastric cancer (EGC) is defined as invasive gastric cancer that invades no more deeply than the submucosa, irrespective of lymph node metastasis (T1, any N)
Early gastric cancer

- Have been identified in Japan, where there is active screening of patients at high-risk for gastric cancer

Gastric cancer - prognosis

- Poor prognostic indicators include:
  - Older age
  - Proximal location
  - Venous and/or lymphatic invasion
  - CEA levels greater than 10ng/mL

  The best predictor of prognosis is the pathologic stage

Gastric adenoma

- Adenomas almost always occur on a background of chronic gastritis with atrophy and intestinal metaplasia; by definition adenomas exhibit epithelial dysplasia
- The risk of adca is related to the size of the lesion (>2cm)
- Overall carcinoma may be present in up to 30% of gastric adenomas

Tubulovillous adenoma with low grade dysplasia

- On the left dysplastic epithelium.
- On the right normal epithelium for comparison

Gastric lymphoma

- 5% of all gastric malignancies are primary lymphomas
- Extranodal marginal zone B-cell lymphoma
  - (In the gut these tumors are referred to as arising in mucosa-associated lymphoid tissue - MALT)
- Associated with H.pylori gastritis (prolonged lymphoid proliferations)
- Most common location – gastric body

Gastric lymphoma

- Indolent behavior in low-grade lesions with excellent prognosis (5-year-survival rates 91%)
- Minority of lesions transform to high-grade B-cell lymphomas

- The fifth and sixth decades of life
- Endoscopically: ulcerated (single or multiple), polypoid, edematous or infiltrated folds
Gastric MALT lymphoma

- Treatment
  - Eradication of H pylori
  - Surgery

Immunohistochemical features

- Gastric adenocarcinomas are cytokeratin(CK), epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA) positive
- CK7/CK20 profiles vary considerably, with the majority being CK7 positive and CK20 negative

Current Perspectives on Gastric Cancer.
Gastroenterol Clin North Am 2016SEP; 45(3)

- Gastric cancer (GC) is third leading cause of cancer-related death.
- Only 28.3% of new GC cases survive more than 5 years.
- Although incidence has declined in the United States, an increase is estimated for 2016.
- Risk factors include sex (risk is higher in men), Helicobacter pylori infection, heredity, and lifestyle.

Current Perspectives on Gastric Cancer.
Gastroenterol Clin North Am 2016SEP; 45(3)

- GC is usually diagnosed between the ages of 60-80 years.
- Prognosis of GC is largely dependent on the tumor stage at diagnosis and classification as intestinal or diffuse type; diffuse-type GC has worse prognosis.

Mortality reduction from gastric cancer by endoscopic and radiographic screening.
Cancer Sci 2015 Dec;106(12). Hamashima C

- This study indicates that endoscopic screening can reduce gastric cancer mortality by 67% compared with radiographic screening. This is consistent with previous studies showing that endoscopic screening reduces gastric cancer mortality.