ESMO Preceptorship

Gastric cancer

Brussels
4 - 5 September 2015
Gastric cancer
Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Pathology and carcinogenesis

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ESMO Preceptorship – Gastric Cancer
Pathology and carcinogenesis
Normal gastric mucosa

\[ H. \text{pylori} \]
Salt?

Superficial gastritis

Chronic inflammation

Recruitment of bone marrow–derived stem cells

Higher gastric pH
Bacterial overgrowth and nitrate reduction

Intestinal metaplasia and SPEM

Atrophic gastritis

Salt?

\[ \beta\text{-Carotene?} \]

Dysplasia

N-nitroso carcinogens
Chronic inflammation and reactive oxygen species

Carcinoma
Helicobacter pylori and gastric carcinogenesis

- Normal gastric mucosa
- Chronic gastritis
- Chronic atrophic gastritis
- Intestinal metaplasia
- Gastric carcinoma

Other host and environmental factors

Helicobacter pylori

Environmental factors
- diet
- smoking

Host susceptibility polymorphisms
- IL-1β T/T
- IL1-RN *2/*2
- TNF-α A -308*A

CagA; VacA...
BabA; SabA
Risk of gastric cancer development

*Helicobacter pylori* infection
Epstein Barr
Diet
Smoking

**Gene-environment interaction**

- *Helicobacter pylori* infection
- Epstein Barr
- Diet
- Smoking

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori virulent genotypes (vacA; CagA)</td>
<td>15 to 17</td>
</tr>
<tr>
<td>IL-1 gene polymorphism</td>
<td>3.3</td>
</tr>
<tr>
<td>H. pylori virulence &amp; IL-1B polymorphism</td>
<td>87</td>
</tr>
</tbody>
</table>

Machado *et al.* Gastroenterology 121: 823, 2001
Figueiredo *et al.*, JNCI 94: 1680, 2002

- Polymorphisms: Mucin genes, Pro-inflammatory genes
- Mutations in “low” or “high” penetrant genes

ESMO Preceptorship — Gastric Cancer Pathology and carcinogenesis
1. Gastric carcinogenesis (the role of *H. pylori* & the other gastric microbiota)

2. Molecular features of gastric carcinoma and its precursor lesions

3. Hereditary gastric carcinoma

4. Conclusions: a tentative, global picture

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**The role of the gastrointestinal microbiome in *Helicobacter pylori* pathogenesis**

Alexander Sheh and James G Fox*

Division of Comparative Medicine; Massachusetts Institute of Technology; Cambridge, MA USA

Keywords: *Helicobacter pylori*, gastric, stomach, microbiota, cancer, hypochlorhydria, bacterial colonization

The discovery of *Helicobacter pylori* overturned the conventional dogma that the stomach was a sterile organ and that pH values < 4 were capable of sterilizing the stomach. *H. pylori* are an etiological agent associated with gastritis, hypochlorhydria, duodenal ulcers, and gastric cancer. It is now appreciated that the human stomach supports a bacterial community with possibly 100s of bacterial species that influence stomach homeostasis. Other bacteria colonizing the stomach may also influence *H. pylori*-associated gastric pathogenesis by creating reactive oxygen and nitrogen species and modulating inflammatory responses. In this review, we summarize the available literature concerning the

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**Stomach Anatomy**
The stomach displays a diverse microbiota when *H. pylori* is absent or low in abundance.

**H. pylori** negative stomach

- Firmicutes: 47%
- Actinobacteria: 1%
- Bacteroidetes: 11%
- Proteobacteria: 30%
- Fusobacteria: 1%
- Others: 1%
- <1%

**H. pylori** positive stomach

- Firmicutes: 96%
- Actinobacteria: 2%
- Bacteroidetes: 1%
- Proteobacteria (H. pylori): 1%
- Others: 1%
The stomach displays a diverse microbiota when *H. pylori* is absent or low in abundance.

Resident or transient populations of ingested microbes?

Andersson *et al.*, PLoS ONE 2008
Any story about a human’s microbes tends to invoke impressive numbers. Take the 10 trillion or so microbial cells living in the gut, which exceed the number of human cells by 10 to 1. Between them, they harbour millions of genes, compared with the paltry 20,000 estimated in the human genome. To say that you are outnumbered is a massive understatement.

But that might not be a bad thing. There is strength in numbers; so much so, in fact, that some biologists regard a human as a ‘super-organism’ — a community that adds up to more than the sum of its parts. The body itself is merely one, albeit encompassing, component.

Mammals are metagenomic in that they are composed of not only their own gene complements but also those of all of their associated microbes.

Evolution of Mammals and Their Gut Microbes

NATURE Vol 453 29 May 2008

METAGENOMICS

THE INSIDE STORY

SCIENCE VOL 320 20 JUNE 2008
Human metagenome

Intestinal microbiome (genetic diversity)

Human genome (genetic variations)

Which bacteria and their genes are involved in the interactions?

Which human genes are involved in the interactions and respond to bacterial signals?

Bacterial components and metabolites

What components in the diet affect intestinal microbiota?

Diet

Health

Disease
Classification of gastric cancer
Gastric cancer is very heterogeneous.
4-1 Gastric carcinoma

Gregory Y. Lauwers
Fátima Carneiro
David Y. Graham
Maria-Paula Curado
Silvia Franceschi
Elizabeth Montgomery
Masae Tatematsu
Takenori Hattori

4-1-02 - ICD-O Code

<table>
<thead>
<tr>
<th>Pathology Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>8140/3</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>8260/3</td>
</tr>
<tr>
<td>Tubular adenocarcinoma</td>
<td>8211/3</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Poorly cohesive carcinoma</td>
<td>8490/3</td>
</tr>
<tr>
<td>(Signet-ring cell carcinoma and variants)</td>
<td></td>
</tr>
<tr>
<td>Mixed carcinoma</td>
<td>8255/3</td>
</tr>
</tbody>
</table>

Intestinal carcinoma

• Elderly patients, mainly males
• Decreasing incidence everywhere
• Blood-born metastases

Diffuse carcinoma

• Young patients, mainly females
• Familial/hereditary conditioning
• Dissemination to the peritoneum
Other classifications with putative prognostic value:

- Goseki
- Kodama
- Carneiro

However, one should keep in mind that the most important prognostic factor is staging (in the stomach and other organs)
Sporadic cancer

Hereditary cancer

Precursor conditions/lesions

• Chronic gastritis
• Intestinal metaplasia
• Dysplasia

Histopathology

Molecular pathology

Genetic susceptibility
Chronic gastritis
**ESMO Preceptorship — Gastric Cancer**

**Pathology and carcinogenesis**

- *Helicobacter pylori* infection

- **Diffuse antral gastritis**
  - Asymptomatic 90%

- **Multifocal atrophic gastritis**
  - Asymptomatic 90%

- Host & environmental factors

  - **Duodenal ulcer**
    - Asymptomatic 90%

  - **Focal atrophy**

  - **Gastric ulcer**
    - Asymptomatic 90%

  - **IM**

  - **IM → Dysplasia → Gastric cancer**
Chronic gastritis

Antrum

Incisura

Gland atrophy and multifocal IM

Body
## Classification of chronic gastritis

### OLGA staging

<table>
<thead>
<tr>
<th>Atrophy Score</th>
<th>Corpus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Atrophy (score 0)</td>
</tr>
<tr>
<td>Antrum</td>
<td>STAGE 0</td>
</tr>
<tr>
<td></td>
<td>STAGE I</td>
</tr>
<tr>
<td></td>
<td>STAGE II</td>
</tr>
<tr>
<td></td>
<td>STAGE III</td>
</tr>
</tbody>
</table>

Fig. 3. The OLGA staging frame.

**Classification of chronic gastritis**

**OLGIM staging**

The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis

Liseite G. Capelle, MD, Annemarie C. de Vries, MD, PhD, Jelle Haringsma, MD, Frank Ter Borg, MD, PhD, Richard A. de Vries, MD, PhD, Marco J. Bruno, MD, PhD, Herman van Dekken, MD, PhD, Jos Meijer, MD

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**TABLE 2. Proposal for the OLGIM staging system**

<table>
<thead>
<tr>
<th>IM score</th>
<th>Not fat: no IM (score 0)</th>
<th>Mild IM (score 1)</th>
<th>Moderate IM (score 2)</th>
<th>Severe IM (score 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antrum (including incisura angularis)</td>
<td>No IM (score 0)</td>
<td>Stage 0</td>
<td>Stage I</td>
<td>Stage II</td>
</tr>
<tr>
<td></td>
<td>Mild IM (score 1)</td>
<td>Stage I</td>
<td>Stage I</td>
<td>Stage II</td>
</tr>
<tr>
<td></td>
<td>Moderate IM (score 2)</td>
<td>Stage II</td>
<td>Stage II</td>
<td>Stage III</td>
</tr>
<tr>
<td></td>
<td>Severe IM (score 3)</td>
<td>Stage III</td>
<td>Stage III</td>
<td>Stage IV</td>
</tr>
</tbody>
</table>

*IM, Intestinal metaplasia; OLGIM, operative link on gastric intestinal metaplasia assessment.*

*Capelle L et al. Gastrointest Endosc 71: 1150, 2010*
Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer (Prospective study – mean follow-up: 7.7 years)

| HP infection | + | + | _ |
| CAG           | _ | _ | + |

<table>
<thead>
<tr>
<th>Gastric cancer</th>
<th>Cases/incidence rate</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>7.13 (0.95-53.33)</td>
</tr>
<tr>
<td></td>
<td>19/107</td>
<td>14.51 (1.96-107.70)</td>
</tr>
<tr>
<td></td>
<td>24/238</td>
<td>61.85 (5.60-682.64)</td>
</tr>
<tr>
<td></td>
<td>2/871</td>
<td></td>
</tr>
</tbody>
</table>

*p=0.0007*

**Helicobacter pylori Eradication to Prevent Gastric Cancer in a High-Risk Region of China**

A Randomized Controlled Trial

Prospective, randomized, placebo-controlled, population-based primary prevention study of 1630 healthy carriers of *H. pylori* infection

<table>
<thead>
<tr>
<th>Overall</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> eradication</td>
<td>7 gastric cancers</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Patients without **precancerous lesions** on presentation

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. pylori</em> eradication</td>
<td>0 gastric cancers</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Wong BC et al. JAMA 291: 187, 2004
**H. pylori infection**

- Normal mucosa
  - Chronic superficial gastritis
  - Enhanced chronic inflammatory response
    - Chronic atrophic gastritis
      - Intestinal metaplasia
        - Dysplasia
          - “Intestinal” carcinoma

**H. pylori** strain virulence

- (vacA s1, m1, cagA+)

**Host susceptibility**

- (IL1B-511*T / IL1RN*2/*2)
- (TNFA-308*A)
Gastric dysplasia - WHO classification (2010)

LOW- AND HIGH-GRADE DYSPLASIA

- Minimal architectural disarray
- Mild/moderate cytological atypia
- Nuclei are elongated, polarised, basally located
- Mitotic activity is mild/moderate.

- Pronounced architectural disarray
- High nucleus:cytoplasm ratio
- Numerous mitoses, often atypical
- Nuclei frequently extend towards the luminal half of the gland
**MORPHOLOGIC TYPE**

**Intestinal type**
- Columnar cells
- Pencilate nuclei
- Hypercromatic nuclei

**Gastric type**
- Cuboidal cells
- Oval, vesicular nuclei
- Clear, eosinophilic cytopasm

Intestinal phenotype
Gastric/foveolar phenotype
## Comparison between grade and immunophenotypes

<table>
<thead>
<tr>
<th>Grade</th>
<th>Immunophenotype</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastric (n=24)</td>
<td>Intestinal(n=22)</td>
</tr>
<tr>
<td>High grade</td>
<td>15*</td>
<td>4</td>
</tr>
<tr>
<td>(n=25)</td>
<td>63%</td>
<td>18%</td>
</tr>
<tr>
<td>Low grade</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>(n=35)</td>
<td>37%</td>
<td>82%</td>
</tr>
</tbody>
</table>

* coexistent intramucosal carcinoma in 8 cases

**Gastric differentiation is associated with high-grade dysplasia and coexistence of intramucosal carcinoma.**

What about diffuse gastric cancer

*Helicobacter pylori* associated gastritis

“Intestinal” carcinoma

Diffuse carcinoma

(lessons from HDCG)
GASTRIC CANCER

Sporadic cancer

Hereditary cancer

Histopathology

Molecular pathology

Genetic susceptibility

Precursor lesions
New Chapter on: Hereditary diffuse gastric cancer

Definition
Hereditary diffuse gastric cancer (HDGC) is an autosomal-dominant cancer-susceptibility syndrome that is characterized by signet-ring cell (diffuse) gastric cancer and lobular breast cancer. The genetic basis for this syndrome was discovered in 1998 by Guilford et al. (1081), who identified germ-line mutations of the E-cadherin (CDH1) gene (MIM No. 192090) by linkage analysis and mutation screening in three Maori kindreds with multigenerational, diffuse gastric cancer in New Zealand.

MIM No.: 137215

Diagnostic criteria
In families with an aggregation of gastric cancer, the histopathology of the tumours is often unknown; these cases are designated as familial gastric cancer (FGC). When the histopathological type of one or more gastric cancers is known, discrete syndromes/diseases can be diagnosed; these include HDGC, familial diffuse gastric cancer (FDGC) and familial intestinal gastric cancer (FGIC) (379).

On the basis of clinical criteria, the International Gastric Cancer Linkage Consortium (IGCLC) in 1999 defined families with the HDGC syndrome as those fulfilling one of the following features:

1. Two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one being diagnosed before the age of 50 years; or
2. Three or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of diagnosis (379). Women in these families also have an elevated risk of lobular breast cancer (341, 1501, 1513, 2855, 3136).

IGCLC criteria for genetic testing, updated in 2009 (871) are shown in Table 4.2.01. An alternative genetically-based nomenclature, proposed by the New Zealand group, in which the term "HDGC" is restricted to families with germ-line mutations in the CDH1 gene (1081, 1082).

The IGCLC definition for HDGC will be used for the remainder of this section (871).

Epistemology
The vast majority of gastric cancers are sporadic, but approximately 1–3% result from an inherited predisposition (870, 2296, 2439).

The prevalence of HDGC is uncertain, partly due to the recent identification of this syndrome. In a review of 439 families with aggregation of gastric cancer (2395), CDH1 mutations were preferentially observed in families fulfilling the clinical criteria for HDGC (36.4%). In FDGC, the frequency of germline mutations in CDH1 was much lower (12.5%) (2395). CDH1 mutations have not been found in families with weaker histories of gastric cancer; however, mutation rates of up to 10% have been described in individuals with no family history but DGC diagnosed at less than age 35 years, from populations with a low incidence of gastric cancer (1501, 3136).

There are striking population-specific differences regarding the fraction of families with aggregation of gastric cancer and frequency of CDH1 germ-line mutations. In countries with a low incidence of gastric cancer, the frequency of germline alterations in the CDH1 gene is > 40%, while in countries with a moderate or high incidence of gastric cancer, the frequency of alterations in CDH1 is about 20% (2396). These observations in moderate- or high-incidence countries are probably related to clustering of gastric cancer attributable to environmental risk factors (lifestyle, diet) and/or variation in genes conferring a weak susceptibility (2396).

Localization
Most index cases with HDGC present with cancers that are indistinguishable from sporadic diffuse gastric cancer, often with fritile plaques, which can involve all topographical regions within the stomach.

Systematic complete mapping of total gastrectomies from asymptomatic carriers
GASTRIC CARCINOMA

- Sporadic (90%)

- Familial Aggregation (10%)
  - Familial Gastric Cancer (FGC)
  - Familial Intestinal Gastric Cancer (FIGC)
  - Familial Diffuse Gastric Cancer (FDGC)

- Hereditary (1%)*
  - Hereditary Diffuse Gastric Cancer (HDGC)

* Most caused by E-cadherin alterations
Intramucosal signet ring cell (diffuse) carcinoma
In situ (signet ring cell) carcinoma

Pagetoid spread of signet ring cells:
Two-layer structure: an inner layer composed of benign mucous cells and an outer layer of signet ring cells.

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>Tis</th>
<th>T1a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td><img src="image1.png" alt="A" /></td>
<td><img src="image2.png" alt="B" /></td>
</tr>
<tr>
<td>Muscularis mucos</td>
<td><img src="image1.png" alt="A" /></td>
<td><img src="image2.png" alt="B" /></td>
</tr>
<tr>
<td>Submucosa</td>
<td><img src="image1.png" alt="A" /></td>
<td><img src="image2.png" alt="B" /></td>
</tr>
</tbody>
</table>

Carneiro F, Charlton A, Huntsman D

ESMO Preceptorship — Gastric Cancer
Pathology and carcinogenesis
Development model of HDGC

Inactivation of second allele of CDH1

CDH1 germline mutation

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS): a new autosomal dominant syndrome.

Worthley et al; Gut 61:774-779, 2012
Proximal polyposis of the stomach
Proximal polyposis of the stomach:
- Fundic gland polyps (predominant)
- Hyperplastic (rare)
- Adenomatous (rare)
Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

ESMO Preceptorship – Gastric Cancer Pathology and carcinogenesis
Case report

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPs): a new autosomal dominant syndrome

D L Worthley,1 K D Phillips,2 N Wayte,3 K A Schrader,4 S Healey,5 P Kaurah,4 A Shukas,6 F Grimpin,7 A Clouston,7 D Moore,8 D Cullen,9 D Ormonde,9 D Mournk,10 X Wen,11 N Lindor,11 F Carneiro,11 D G Huntsman,4 G Chenevix-Trench,5 G K Suteres2

ABSTRACT

Objective The purpose of this study was the clinical and pathological characterisation of a new autosomal dominant gastric polyposis syndrome, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPs).

Methods Case series were examined, documenting GAPPs in three families from Australia, the USA and Canada. The affected families were identified through referral to centralised clinical genetics centres.

Results The report identifies the clinical and pathological features of this syndrome, including the predominant dysplastic fundic gland polyp histology, the exclusive involvement of the gastric body and fundus, the apparent inverse association with current Helicobacter pylori infection and the autosomal dominant mode of inheritance.

Conclusions GAPPs is a unique gastric polyposis syndrome with a significant risk of gastric adenocarcinoma. It is characterised by the autosomal dominant transmission of fundic gland polyposis, including areas of dysplasia or intestinal-type gastric adenocarcinoma, restricted to the proximal stomach, and with no evidence of colorectal or duodenal polyposis or other heritable gastrointestinal cancer syndromes. It includes MUTYH-associated polyposis (MAP), generalised juvenile polyposis syndrome (GJPS), Peutz Jeghers syndrome (PJS) and Cowden syndrome.5–6 However, FGPs are relatively rare in MAP, an autosomal recessive disorder, and GJPS and PJS are often characterised by the presence of specific hamartomatous (rather than purely dysplastic fundic gland) polyposis.5–6

Sporadic FGPs are usually innocuous, but familial FGPs can progress to dysplasia and gastric adenocarcinoma.7–8 Therefore, clinicians must distinguish patients with sporadic versus familial fundic gland polyposis so that additional scrutiny is provided for the latter without subjecting the majority of patients to needless investigation.

Here we describe a new autosomal dominant syndrome characterised by fundic gland polyposis and gastric cancer. We refer to the syndrome as gastric adenocarcinoma and proximal polyposis of the stomach (GAPPs). This report documents the detailed clinical and pathological features of GAPPs in a large Australian family and in two smaller North American families. We propose diagnostic criteria and management strategies for GAPPs and examine potential factors that may contribute to the pathogenesis.
Diagnostic criteria for GAPPS

i) **gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis**;

ii) >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first degree relative of another case;

iii) predominantly FGPs, some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma);

iv) an **autosomal dominant pattern of inheritance**.

Exclusions include other heritable gastric polyposis syndromes and use of PPIs. In patients on PPIs it is recommended to repeat the endoscopy off therapy.
Familial gastric cancer

- Sporadic (90%)

- Familial Aggregation (10%)
  - Familial Gastric Cancer (FGC)
  - Familial Intestinal Gastric Cancer (FIGC)
  - Familial Diffuse Gastric Cancer (FDGC)

- Hereditary (1%?)
  - Hereditary Diffuse Gastric Cancer (HDGC)
  - Gastric Adenocarcinoma and Proximal Polyposis of the Stomach - GAPPS (HIGC)
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