Familial Gastric Cancer: Making the Right Decisions at the Right Time

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Familial Gastric Cancer: Making the Right Decisions at the Right Time

Slides developed by the National Cancer Institute, and the NIH Clinical Center Nursing Department and used with permission.
Goals:

• Background and making a diagnosis of familial gastric cancer and HDGC

• The implications of the abnormal CDH1 gene in affected families

• Current management of familial gastric cancer
# Hereditary GI cancer syndromes WITHOUT polyposis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) (chromosomal locus)</th>
<th>Inheritance pattern</th>
<th>Component gastrointestinal neoplasms</th>
<th>Features other than component gastrointestinal neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoLoN syndrome</td>
<td>MLH1 (3p21)&lt;sup&gt;b&lt;/sup&gt; MSH2 (2p21)&lt;sup&gt;b&lt;/sup&gt; MSH6 (2p15)&lt;sup&gt;b&lt;/sup&gt; PMS2 (7p22)&lt;sup&gt;b&lt;/sup&gt; Others</td>
<td>AR</td>
<td>Childhood onset colon cancer; duodenal cancer; colon adenomas</td>
<td>Childhood onset brain tumors; leukemia; lymphoma; endometrial and ovarian cancers&lt;sup&gt;37&lt;/sup&gt; Features of neurofibromatosis (café-au-lait spots; neurofibromas)</td>
</tr>
<tr>
<td>FAMMM</td>
<td>CDKN2A/p16 (9p21)&lt;sup&gt;b&lt;/sup&gt; Others</td>
<td>AD</td>
<td>Pancreatic cancer</td>
<td>Melanoma; Dysplastic nevi</td>
</tr>
<tr>
<td>Familial Colorectal Cancer Type X</td>
<td>Unknown</td>
<td>Presumed AD</td>
<td>Colon cancer</td>
<td>Families meet Amsterdam I criteria but MSI stable&lt;sup&gt;61&lt;/sup&gt; None</td>
</tr>
<tr>
<td>Familial GIST</td>
<td>KIT&lt;sup&gt;b&lt;/sup&gt; and PDGFR (4q12)</td>
<td>AD</td>
<td>GIST</td>
<td>None; KIT: hyperpigmentation; mast cell tumors; dysphagia PDGFR: large hands</td>
</tr>
<tr>
<td>Familial intestinal gastric cancer</td>
<td>Unknown</td>
<td>AD</td>
<td>Intestinal gastric cancer</td>
<td>None&lt;sup&gt;62,63&lt;/sup&gt; None</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer</td>
<td>CDH1 (16q22.1)&lt;sup&gt;b&lt;/sup&gt; Others</td>
<td>AD</td>
<td>Diffuse gastric cancer; possible association with signet-ring colon cancer&lt;sup&gt;62-64&lt;/sup&gt;</td>
<td>Lobular breast cancer; None</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>CFT (7q31)&lt;sup&gt;b&lt;/sup&gt; PRSS1 (7q35)&lt;sup&gt;b&lt;/sup&gt; SPINK1 (5q32)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AD</td>
<td>Pancreatic cancer</td>
<td>None; Pancreatitis</td>
</tr>
<tr>
<td>Lynch syndrome (HNPCC)</td>
<td>MLH1 (3p21)&lt;sup&gt;b&lt;/sup&gt; MSH2 (2p21)&lt;sup&gt;b&lt;/sup&gt; MSH6 (2p15)&lt;sup&gt;b&lt;/sup&gt; PMS2 (7p22)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AD</td>
<td>Colon, gastric, duodenal and/or small bowel, hepatobiliary and pancreatic cancers</td>
<td>Endometrial and ovarian cancers; ureteral and/or renal pelvis cancers; glioablastoma</td>
</tr>
<tr>
<td>Muir-Torre syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MLH1 (3p21)&lt;sup&gt;b&lt;/sup&gt; MSH2 (2p21)&lt;sup&gt;b&lt;/sup&gt; MSH6 (2p15)&lt;sup&gt;b&lt;/sup&gt; PMS2 (7p22)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AD</td>
<td>Same as Lynch syndrome</td>
<td>Sebaceous gland carcinomas; extracolonic Lynch syndrome cancers&lt;sup&gt;65&lt;/sup&gt; Sebaceous gland epitheliomas and adenomas; keratoacanthomas</td>
</tr>
<tr>
<td>MEN1</td>
<td>MENIN (11q13)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AD</td>
<td>Gastroenteropancreatic endocrine tumors such as gastrinoma with Zollinger–Ellison syndrome, VIPoma, insulinoma and glucagonoma</td>
<td>Foregut carcinoids, anterior pituitary tumors; Parathyroid adenomas; facial angiofibromas, collagenomas, lipomas, meningoimas and ependymomas</td>
</tr>
<tr>
<td>Turcot syndrome&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MLH1 (3p21)&lt;sup&gt;b&lt;/sup&gt; MSH2 (2p21)&lt;sup&gt;b&lt;/sup&gt; MSH6 (2p15)&lt;sup&gt;b&lt;/sup&gt; PMS2 (7p22)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AD</td>
<td>Same as Lynch syndrome</td>
<td>Typically glioblastoma multifforme (other brain tumors reported), extracolonic Lynch syndrome cancers</td>
</tr>
</tbody>
</table>
Genetic predisposition to gastric cancer

Bevan S, Houlston RS, QJM 1999
E-cadherin germline mutations in familial gastric cancer

Followed since 1964!

Linkage analysis

International Gastric Cancer Linkage Consortium (IGCLC)
- within same year of 1998
- criteria to define hereditary diffuse gastric cancer
IGCLC in 2010, extended HDGC guidelines

- two cases of gastric cancer in which one case is histopathologically confirmed as diffuse and younger than 50 years,

- families with both lobular breast cancer and diffuse gastric cancer, with one diagnosed younger than 50 years, and

- probands diagnosed with diffuse gastric cancer younger than 40 years, with no family history of gastric cancer.
Lauren classification:  
**Intestinal** vs **diffuse gastric cancer**

1. Poorly differentiated
2. Signet ring cells
3. ‘linitis plastica’

Lauren classification: **Molecular Implications – two different Diseases**

**Intestinal-Type**
- APC Mutation
- p53 Mutation
- TP53 Mutation
- Reduced p27 Expression
- Reduced p53 Mutation/LOH
- c-myc Amplification
- CD44 aberrant Transcript
- Chromosome 17q LOH
- Cyclin E Overexpression
- Cyclin D1 Overexpression
- DCC258 Overexpression
- H. pylori
- Intestinal Metaplasia
- Genetic Instability
- Telomere Reduction
- CpG Methylation (p16, MGMT, MLH1)

**Diffuse-Type**
- Chromosome 17p1 LOH
- p53 Mutation/LOH
- Early Cancer Poorly Differentiated
- Early Cancer Well Differentiated
- Advanced Cancer Invasion Metastasis
- Advanced Cancer Invasion Metastasis
- Histone Deacetylation
- Telomerase Activation
- TRIST Expression

**Normal Epithelium**
- Intestinal Metaplasia
- H. pylori
- Genetic Instability
- Telomere Reduction
- CpG Methylation (p16, MGMT, MLH1)

**Adenoma**
- Early Cancer Well Differentiated
- Reduced p27 Expression
- Reduced p53 Mutation/LOH
- c-myc Amplification
- CD44 aberrant Transcript
- Chromosome 17q LOH
- Cyclin E Overexpression
- Cyclin D1 Overexpression
- DCC258 Overexpression

**Normal Epithelium**
- Early Cancer Poorly Differentiated
- Early Cancer Well Differentiated
- Advanced Cancer Invasion Metastasis
- Advanced Cancer Invasion Metastasis
- Histone Deacetylation
- Telomerase Activation
- TRIST Expression

**Normal Epithelium**
- Intestinal Metaplasia
- H. pylori
- Genetic Instability
- Telomere Reduction
- CpG Methylation (p16, MGMT, MLH1)
Screening for familial gastric cancer and HDCG

Sporadic gastric cancer

≥95% of all cases

Individuals at risk based on clinical history

Confirmation of histopathological diagnosis

HDGC ½  FDGC ¾ EODGC

Genetic counselling

Genetic testing (CDH1 gene screening)

Positive

Missense mutations

Analysis of pathogenicity of missense mutations

Non-pathogenic

Pathogenic

High risk carriers

Truncating mutations

Low risk carriers

Clinical surveillance

Prophylactic gastrectomy

Negative

Summary – I:

History of familial gastric cancer

IGCLC Screening guidelines: importance of family history

Not all familial gastric cancer patients harbor CDH1 mutations
E-cadherin (CDH1) mutations:

<table>
<thead>
<tr>
<th>Missense mutations</th>
<th>Splice site mutations</th>
<th>Truncating mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>27&gt;C</td>
<td>469T&gt;C; 469T&gt;G</td>
<td>1595C&gt;T</td>
</tr>
<tr>
<td>133C&gt;G</td>
<td>183T&gt;C; 186C&gt;T</td>
<td>1595delC</td>
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<tr>
<td>320C&gt;G</td>
<td>1873delC; 1876delC</td>
<td>1618delC</td>
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<tr>
<td>516C&gt;G</td>
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<td>520C&gt;G</td>
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<tr>
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<tr>
<td>715G&gt;A</td>
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<tr>
<td>802T&gt;G</td>
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<td>1618delC</td>
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<tr>
<td>8920&gt;A</td>
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<td>919A&gt;G</td>
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<td>1618delC</td>
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<tr>
<td>12230&gt;T</td>
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<td>1618delC</td>
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<tr>
<td>1243A&gt;C</td>
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<td>1748T&gt;G</td>
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<tr>
<td>1795A&gt;T</td>
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<td>1873delC; 1876delC</td>
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<td>1837-1837delC</td>
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<tr>
<td>2289C&gt;A</td>
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<tr>
<td>2442G&gt;C</td>
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<td>1618delC</td>
</tr>
<tr>
<td>24943&gt;A</td>
<td>1873delC; 1876delC</td>
<td>1618delC</td>
</tr>
</tbody>
</table>
E-cadherin function: regulation cell-cell adhesion

Induction of β-catenin signaling in cells harboring aberrant CDH1
The ‘unique’ T1a stage in HDGC

Guilford P, Hereditary Cancer in Clinical Practice, 2007
Multiple foci of T1a lesions in all prophylactic gastrectomy specimens

Difficult to detect endoscopically

Long latency - ? when and which lesions will grow

Do type (mutation vs missense) and/or location of mutation predict clinical course?

**Genotype – phenotype relationships in patients with HDGC**

Articles identified from search = **142**

Excluded articles if not published in English, if full text was unavailable = **Excluded 18**

Articles selected for full text review = **124**

Articles excluded = **94**
- No germline mutation reported = **64**
- No family pedigree published, family did not fit HDGC clinical criteria, age at diagnoses not reported = **24**
- Protein product of germline mutation unknown = **6**

Articles acquired from Pubmed search = **30**

Addition of articles included in review article that were not found with original search = **13**

Articles included in analysis = **43**
Genotype – phenotype associations

• Family members with missense mutations were
  – more likely to be affected by gastric cancer (increased clinical penetrance (>50%) (p=0.012)) and were more likely to
  – come from countries with a high overall risk of gastric cancer (p=0.0037 for early vs late truncation, p=0.0057 for extracellular vs intracellular truncation).

• Families in which the youngest affected family member was
  – younger than 30 years of age were found to have a higher incidence of other HDGC cancers including lobular breast and colon cancer (p=0.002).

• No statistically significant association between type of mutation
  – Age of presentation
  – Presence of other HDGC syndrome cancers
Summary - II:
The function of the CDH1 gene (tumor suppressor)

The unique T1a stage, incl. the ‘latency’

Novel genotype-phenotype studies might help select patients for better surveillance and therapy
Carriers of CDH1 mutations have an approximately 70% lifetime risk of developing diffuse gastric cancer.

Women with CDH1 mutations have an additional 20-40% risk of developing lobular breast cancer (ILC).

Carriers of CDH1 mutations also harbor a 5-10% risk of developing colon cancer.

→ what about the families no CDH1 mutation is detected?
Prophylactic total gastrectomy for HDGC:

**Alternative?**

Usually with methylene blue and congo red

**When?**

New genotype-phenotype correlations might help

Able to pick up ≥70% of lesions

At least once per year

Highly operator-dependent

Cases of missed cancers reported
Approach to ILC:
- LBC is less likely to form calcifications or discrete mass lesions -> mammography less effective, MRI breast recommended
- Breast surveillance recommended to begin at age 25
- LBCs are estrogen-receptor positive -> tamoxifen is an option for chemoprevention
- Prophylactic bilateral mastectomy has been performed but its role remains undefined

Approach to increased risk of colon cancer:
- Colorectal cancer screening should begin five to 10 years earlier than the earliest diagnosis of colorectal cancer in the family or by age 50, whichever is sooner.

In general:
- Multiple modalities for surveillance have been used, but all have proven ineffective for early detection of HDGC

Role of prophylactic gastrectomy:
- Offered to all carriers of inactivating CDH1 mutations
- It is critical that a total gastrectomy needs to be performed
- Prophylactic gastrectomy specimens are typically found to harbor early foci of DGC
- Close collaboration with nutritionist and PCP important
Summary – III:

- Prophylactic gastrectomy is the most effective ‘curative’ option to prevent gastric cancer

- Women harboring germline CDH1 mutation should be followed at a breast center and have early breast surveillance which includes MRIs

- Chromoendoscopy can – at the moment – not be recommended as an effective screening strategy

What about the other familial gastric cancer patients not harboring CDH1 mutations?
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome


Worthley DL, Gut, 2012
Considering the high lethality of metastatic gastric cancer and the unknown natural history of CDH1 mutation negative familial gastric cancer

- In the absence of a marker (e.g. CDH1 mutation status in HDGC) there is an increased role of endoscopic surveillance
- Patients with endoscopic abnormalities and a positive family history of familial gastric cancer should be offered total gastrectomy

A ‘specific’ role for nursing in this disease:
Rare disease, to date >100 families well described
To fill the void of information on the natural history (improved family history, identifying patients AT RISK which have not been screened yet)

As per:

Hereditary diffuse gastric cancer: lifesaving total gastrectomy for CDH1 mutation carriers.
Lynch HT, Lynch JF.
Thank you for the invitation!

Ina Chen
Joal D. Beane
Seth Steinberg

And our patients . . .

Questions?