NEXT GENERATION LEARNING

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USCAP
Creating a Better Pathologist
Hereditary Gastric Cancer

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Disclosures

Dr. Bastiaan de Boer declares he has NO conflict of interest to disclose.
Case History A

• 18yo Male
• Family history of gastric polyposis and gastric cancer
• At endoscopy “carpet-like” gastric polyposis involving the fundus and corpus with sparing of the antrum
• Biopsy of a dominant 35mm polyp reported as low grade dysplasia
• Total gastrectomy
Gastrectomy: polyposis with a dominant 35mm polyp
Polyposis
Dominant Polyp
Case History B

- 30yo Female
- Family history of gastric cancer
  - youngest affected relative age 30
- Surveillance endoscopy: NAD
- Random biopsy
Surveillance endoscopy, random biopsy
Laparoscopic total gastrectomy
One of four microscopic foci (0.2-1mm)
Invasive poorly cohesive (signet ring) adenocarcinoma
Heritable GI cancer syndromes

- Li-Fraumeni syndrome
- Lynch syndrome
- Peutz-Jeghers syndrome*
- Hereditary breast and ovarian cancer (BRCA 1&2)
- MUTYH-associated adenomatous polyposis (MAP)*
- Familial adenomatous polyposis (FAP)*
- Juvenile polyposis syndrome*
- PTEN hamartoma tumour syndrome (Cowden syndrome)*
- Familial gastric polyposis*
- Hereditary diffuse gastric cancer (HDGC)
- Familial intestinal gastric cancer
- Gastric adenocarcinoma and proximal polyposis syndrome (GAPPS)*
Case A: Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS)

- First described in 2012
  - Australian and Nth. American kindred
- Autosomal dominant gastric polyposis syndrome
- Typical gastric phenotype may be evident from 10 years
- Earliest gastric cancer at 33
Case A: Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS)

Macroscopic findings

- Multiple (usually >100) often “carpet-like” polyps
- Predominantly <10mm in size
- Exclusive involvement of the gastric body and fundus
- Sparing of the lesser curve and antrum
- No duodenal or colorectal polyposis
“Carpet-like” polyposis
Microscopic findings

Types of polyps
- Fundic gland-like polyps
  - +/- areas of dysplasia
- Hyperplastic polyps
- Adenomatous polyps
- Mixed FGP-like/ adenomatous and hyperplastic polyps
- Adenocarcinoma of intestinal type
Earliest lesions: “hyperproliferative aberrant pits”
Fundic gland-like polyps
Foveolar hyperplasia/ adenoma
Adenomatous polyp

Adenocarcinoma
GAPPS

Underlying genetic defect
• Point mutation in the Promoter 1B of the APC gene*
• Not associated with other heritable GI polyposis syndromes

Management
• Endoscopic surveillance
• Prophylactic gastrectomy (±/ large polyp, ±/ dysplasia)
• Therapeutic gastrectomy (biopsy proven carcinoma)

* Personal communication
Case B: Hereditary Diffuse Gastric Cancer

First described in 1998 (New Zealand Maori kindred)
- Autosomal dominant with incomplete penetrance
- Diffuse (signet ring) gastric adenocarcinoma
- Also risk of lobular breast carcinoma in women
- Age of cancer onset 14 - 85
Microscopic findings

- Precursor lesion (Tis): signet ring cells lining the glands or as pagetoid spread.
- Multifocal (1 – 100s) T1a invasive signet ring carcinoma throughout.

HDGC

Underlying genetic defect
- Germline CDH1 mutation:
  - Calcium Dependant Adhesion protein gene on Chr 16q22.1
  - E-cadherin protein is the gene product

Management
- Surveillance
- Prophylactic gastrectomy (age 20)
- Curative gastrectomy in biopsy +ve patients
Heritable GI cancer syndromes

- Li-Fraumeni syndrome
- Lynch syndrome
- Peutz-Jeghers syndrome*
- Hereditary breast and ovarian cancer (BRCA 1&2)
- MUTYH-associated adenomatous polyposis (MAP)*
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<table>
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<th>Syndrome</th>
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<th>Gene</th>
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<td>TP53 gene</td>
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<td>GAPPS</td>
<td>Chr 5q21</td>
<td>Promoter 1B of APC gene</td>
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THANK YOU