Envoi SPECIALIST PATHOLOGISTS *inside insights*

Update No.12 - 2016 *Dr Greg Miller*

Update on gastric carcinoma

Traditionally, gastric adenocarcinoma has been classified using histologic morphology according to either the Lauren or WHO classification systems (Table 1). However, there is little difference in clinical outcomes between these subgroups. In contrast, it is becoming increasingly apparent that there are distinct molecular subtypes of gastric cancer that might better predict survival and may have treatment implications.

Table 1. Histologic classification of gastric adenocarcinoma

Lauren system	**WHO system**
Intestinal	Tubular
Diffuse	Papillary
	Mucinous
	Mixed
	Poorly cohesive

Molecular classification of gastric adenocarcinoma

1. **EBER positive** (2-20% of cases)
   - More common in males; body, fundus>antrum
   - Histology - prominent lymphoid infiltrate surrounding the tumour cells
   - *EBER-ISH* positive
   - Extreme hypermethylation (CIMP-H); often show amplification/staining for *PD-L1*
   - May have improved survival

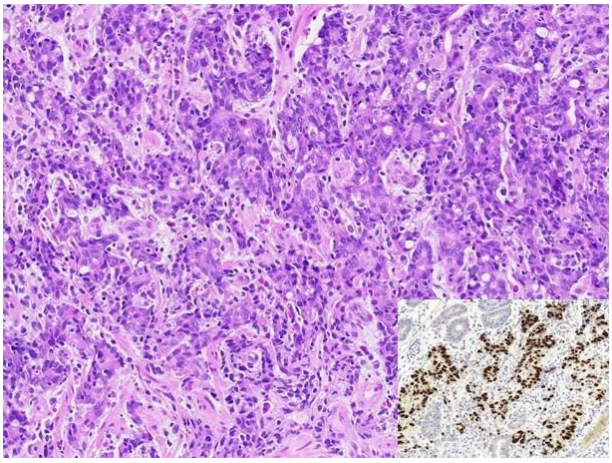


Fig. 1 Positive EBER –ISH in inset

2. **Mismatch repair deficient (MSI-H)** (8-25%)
   - More common in older females
   - Larger tumours; antral
   - Histology - intestinal phenotype
   - Loss of *MLH1*
   - Lower frequency of lymph node metastasis
   - May have improved survival

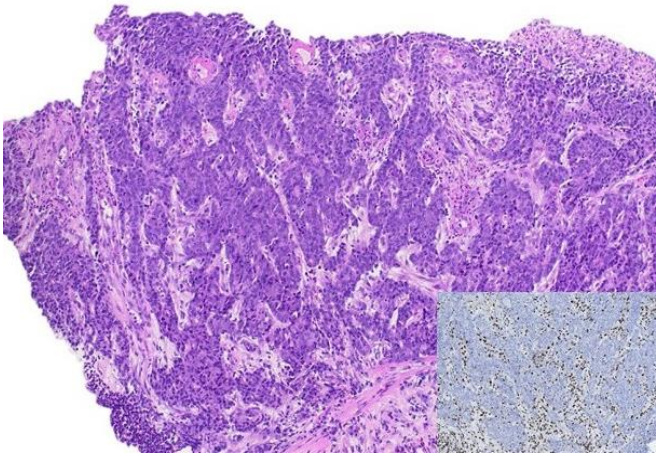
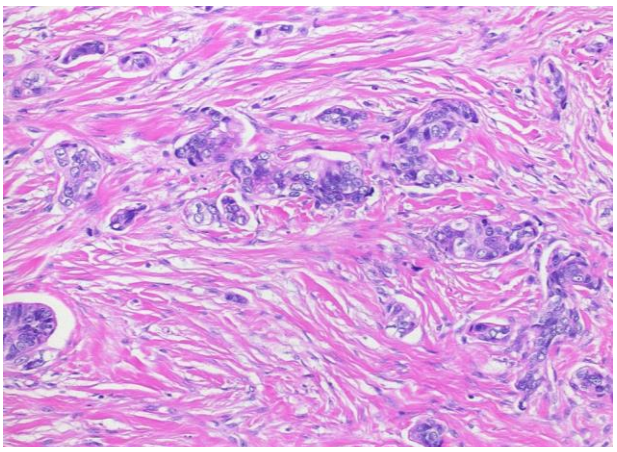
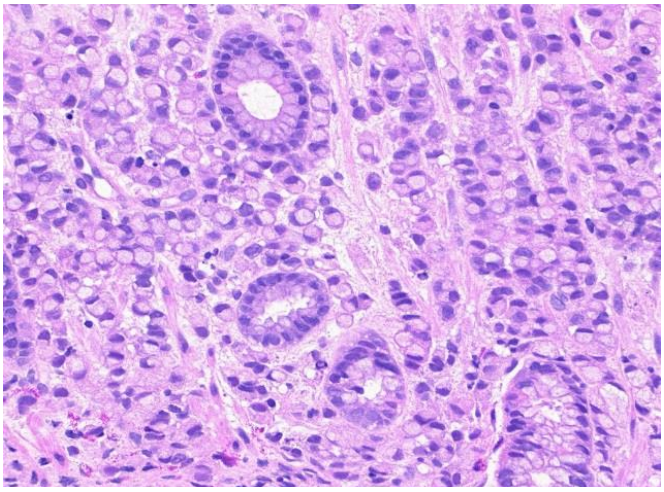


Fig 2. Loss of MLH-1 staining in inset

3. **Chromosomal instability (CIN)** (50%)
    - Most common subtype in adenocarcinomas of the GOJ
    - Histology - intestinal phenotype
    - P53 overexpression
    - Includes most HER-2 amplified cases



4. **Genomically stable** (15-20% of cases)
    - Younger age at diagnosis (median 59 years)
    - Histology – diffuse/poorly cohesive type
    - Aberrant e-cadherin staining



HER-2 and gastric cancer

- Her-2 is overexpressed in 7-34% of gastric/gastro-oesophageal junction adenocarcinomas
- Patient with locally advanced or metastatic gastric adenocarcinomas with overexpression of Her-2 by immunohistochemistry or in-situ hybridization (ISH) are eligible to receive trastuzumab (Herceptin)
- Her-2 positive tumours are usually of intestinal type; chromosomal instability with molecular profiling

Hereditary gastric cancers

- Familial diffuse gastric cancer
    - Autosomal dominant germline mutation in e-cadherin (CDH-1) gene
    - 1-3% of gastric cancers
    - Can occur in individuals as young as 14
    - Present with numerous foci of invasive signet ring cell (diffuse/poorly cohesive) type carcinoma
    - Prophylactic gastrectomy may be indicated in known carriers prior to the development of advanced gastric carcinoma
- Gastric adenocarcinoma and proximal polyposis syndrome (GAPPS)
    - Mutation in the promoter region of APC gene
    - Numerous fundic gland polyps in the gastric body with sparing of the lesser curve and antrum
    - Increased risk of developing gastric cancer

Further reading

Setia N et al. A protein and mRNA expression-based classification of gastric cancer. Mod Pathol. Epub 2016 April 1.
Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014; 513:202-9