Mixed Polyps

Collision between hyperplastic polyp and adenoma

Dysplasia in a Hyperplastic Polyp

Mixed Polyps

Collision between hyperplastic polyp and adenoma - minority

Dysplasia in a sessile serrated lesion - majority
Loss of MLH1 expression in serrated lesions

Associated with development of dysplasia

No detectable *MLH1* mutation

Epigenetic *MLH1* silencing due to promoter methylation

Results in Microsatellite Instability (MSI) – change in length of repetitive sequences
e.g. –CACACACA–

Usually part of a more global DNA methylation (CIMP)
Leggett B & Whitehall V. Gastroenterology 2010; 138: 2088-100
CIMP

CpG Island Methylation Phenotype

DNA methylation of cytosine residues in dinucleotide CpG clusters or ‘islands’

CpG islands present in promoter regions of 40% of mammalian genes

Examine 5 marker genes (CACNA1G, CDKN2A (p16), CRABP1, MLH1, NEUROG1)

CIMP-High (4-5 genes methylated)
CIMP-Low (1-3 genes methylated)
Some genes inactivated in CIMP-High Colorectal Tumours

MLH1
P16
IGFBP7
SFRP

CDX2
TLR2
MCC
?APC
Nomenclature

Mixed polyp

Sessile serrated adenoma

Sessile serrated lesion with cytological dysplasia (low grade or high grade)
Serrated Adenocarcinoma

- 12-15% colorectal cancer
- Mainly in right colon but some in rectum
- Serrated, mucinous (including signet-ring) or trabecular growth pattern
- Abundant eosinophilic cytoplasm
- Preserved polarity
- Chromatin condensation of nuclei
- No ‘dirty’ necrosis
- Arise adjacent to serrated lesions
Serrated Adenocarcinoma

• With Microsatellite Instability
  – Arise in SSLs
  – More proximal tumours
  – Tumour budding inconspicuous
  – Lymphoid reaction
  – Better prognosis (70% 5-year survival)

• Microsatellite ‘stable’ (MSS)
  – Poor prognosis (30% 5-year survival)
  – More tumour budding
  – Some arise in SSLs (proximal tumours)
  – Others arise in TSAs (distal tumours)

**BRAF mutation (V600E)**

<table>
<thead>
<tr>
<th>Type of Polyp</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvesicular hyperplastic polyps</td>
<td>70-80%</td>
</tr>
<tr>
<td>Sessile serrated lesions</td>
<td>80-90%</td>
</tr>
<tr>
<td>Mixed Polyps</td>
<td>40-100%</td>
</tr>
<tr>
<td>Traditional serrated adenomas</td>
<td>~60%</td>
</tr>
<tr>
<td>Conventional adenomas</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>All colorectal cancers</td>
<td>15-30%</td>
</tr>
<tr>
<td>Lynch Syndrome cancers</td>
<td>0%</td>
</tr>
<tr>
<td>MSI-high non-Lynch cancers</td>
<td>76%</td>
</tr>
</tbody>
</table>
CIMP-High

- Microvesicular hyperplastic polyps: 47%
- Sessile serrated adenomas (SSLs): 70-76%
- SSLs with cytological dysplasia: 80%
- Conventional adenomas: 15%
- All colorectal cancers: 30%
- Lynch Syndrome cancers: 0%
- Serrated cancers: 90%
Serrated Neoplasia Pathway(s)

J.R. Jass (1952-2009)
Figure 4. Mitogen-activated protein kinase (MAPK) pathway activation, which results from BRAF mutations, is accompanied by an initial proliferative burst, followed by up-regulation of p16INK4a and increased secretion of insulin-like growth factor binding protein 7 (IGFBP7), resulting in cellular senescence. Silencing of either p16INK4a or IGFBP7 via methylation in cells with CpG island methylator phenotype (CIMP) could facilitate escape from senescence and progression to sessile serrated adenomas (SSA).
'Right Sided’ Serrated Neoplasia

*BRAF* mutation

No *KRAS* or *APC* mutation

DNA methylation (CIMP – CpG Island Methylation Phenotype -high)

Å *p16* and *IGFBP7* inactivation
  Å Escape from senescence

Å *MLH1* inactivation
  Å Microsatellite instability

Å silencing of *MCC* and other Wnt-pathway genes
  Å WNT signalling activation (aberrant ©-catenin)
Normal mucosa

$BRAF$ mutation

Proximal microvesicular hyperplastic polyp

$BRAF$ mutation $\rightarrow$ CIMP

Sessile serrated lesion

$MLH1$ promoter methylation $\rightarrow$ MSI

Sessile serrated lesion with cytological dysplasia

?Accelerated progression

$BRAF$ mutant, MSI-high, methylation-rich non-Lynch “serrated” carcinoma
‘Left Sided’ Serrated Neoplasia

Traditional serrated adenoma

No $BRAF$ or $APC$ mutation

$KRAS$ mutation frequent

DNA methylation (CIMP) occurs, but ‘low’

Inactivation of $MGMT$ (DNA repair gene)

$MLH1$ expression retained

Microsatellite stable
‘Left sided’ Serrated Neoplasia Pathway

Normal mucosa

KRAS mutation

Hyperplastic polyp
(Goblet cell type)

CIMP MGMT inactivation

Traditional serrated adenoma

+ TP53 mutation + Chromosomal instability

KRAS mutant, MSS, methylation-rich distal serrated carcinoma