Syndromic serrated lesions of the colon

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Outline

• Serrated polyposis: updated criteria, pathologist’s role

• Serrated lesions/polyps of the colon: updated nomenclature and histological criteria

• Serrated lesions/polyps in genetic syndromes of the GI tract
What’s new in serrated polyposis
Why were the criteria updated?

• 2010 criterion 2 (Any number of serrated polyps proximal to the sigmoid colon in an individual who had a first-degree relative with SP) not used

• 50% of CRC in serrated polyposis patients from the rectosigmoid

• Include distal polyps in the definition with some restriction for size and number of rectal polyps
Updated 2019 WHO criteria

<table>
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<tr>
<th>Criterion 1</th>
<th>( \geq 5 ) serrated lesions/polyps proximal to the <strong>rectum</strong>, all being ( \geq 5 \text{ mm in size} ), with ( \geq 2 ) being ( \geq 10 \text{ mm in size} )</th>
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<td>Criterion 2</td>
<td>( &gt; 20 ) serrated lesions/polyps of any size but distributed throughout the <strong>large bowel</strong>, with ( \geq 5 ) being proximal to the <strong>rectum</strong></td>
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- Polyp count is cumulative over multiple colonoscopies
- Any histological subtype of serrated lesion/polyp is included in the final polyp count
Clinical features of serrated polyposis

• Risk of CRC: 15-30%

• CRC risk increased if:
  • Fulfillment of both diagnostic criteria
  • > 2 serrated lesions/polyps proximal to splenic flexure
  • At least 1 SSLD
  • At least 1 advanced conventional adenoma

• Risk of serrated polyposis in first-degree relatives: 5%

• CRC risk in first-degree relatives: 5x

• Management:
  • Refer to specialised centres
  • Colonoscopic clearance
  • 1-2 yearly surveillance colonoscopy
Role of the pathologist in the diagnosis

• Make the diagnosis if all information is available

• Suggest the diagnosis if criteria are likely to be fulfilled
  • Comment: “Depending of polyp location and size, the patient may fulfil one of the criteria for serrated polyposis. The revised 2019 WHO criteria are (1) at least 5 serrated polyps proximal to the rectum all ≥ 5 mm, with at least two ≥ 10 mm and (2) > 20 serrated polyps of any size but distributed throughout the large bowel, with at least 5 proximal to the rectum.”

• Look for and sample polyps in surgical resection specimens for CRC
Right hemicolecetomy for synchronous CRCs
Colectomy for high polyp burden
5th WHO classification of serrated lesions/polyps

- Hyperplastic polyp (HP)
  - Microvesicular type
  - Goblet cell type
    - Mucin poor type
- Sessile serrated lesion (SSL)
- Sessile serrated lesion with dysplasia (SSLD)
- Traditional serrated adenoma (TSA)
- Serrated adenoma unclassified
Sessile serrated lesion (SSL)

- SSA and SSP no longer recommended
- A single unequivocal architecturally distorted serrated crypt is sufficient:
  - Asymmetrical dilatation of basal third of the crypt
  - Horizontal growth along the muscularis mucosae
  - Serration extending into the crypt base
- Not enough for SSL diagnosis
  - Mild symmetrical crypt dilatation
  - Occasional branched crypts
  - Goblet cells in the crypt bases
Asymmetrical dilatation of the crypt base
Serration extending into the crypt base
Asymmetrical proliferation
Unequivocal SSL crypt in a 2 mm lesion
Not an SSL
Mucosal prolapse changes in HP
Perineurial-like stromal proliferation in HP
SSL versus HP

- Well-oriented tissue section is essential
- HP is a diagnosis by exclusion when no SSL crypt is present
- Proximal HPs do exist but are usually small (< 10 mm)
- SSLs can be diminutive polyps (< 5 mm)
- Distal colonic SSLs do exist; rectal SSLs are rare
- Superimposed mucosal prolapse changes in HP and SSL
Sessile serrated lesion with dysplasia

- Most advanced and clinically relevant type of serrated lesion
- Main precursor lesion of *BRAF*-mutated CRC
- Varied morphological patterns of dysplasia
- Abrupt transition from SSL
- Dysplasia in SSLD is not graded
- Loss of MLH1 expression in 75%
SSL with dysplasia - villiform
SSL with dysplasia – MLH1 loss
Adenocarcinoma – BRAF mutated MMR deficient
SSL with serrated dysplasia
SSL with serrated dysplasia
SSL with serrated dysplasia is the main pattern associated with retained MLH1
SSL with serrated dysplasia – positive BRAF V600E IHC
Adenocarcinoma – *BRAF* mutated MMR proficient
This is NOT (low grade) serrated dysplasia
This is SSL dysplasia NOS with loss of MLH1
Area of dysplasia can be very small
Area of dysplasia can be difficult to identify
Tip: Look for abrupt change in mucin content
SSL with minimal deviation dysplasia
SSL with minimal deviation dysplasia – MLH1
Hypermucinous pattern in SSLD
Mucinous carcinoma - BRAF mutated MLH1 deficient
The diagnosis of traditional serrated adenoma

• Two of the following 3 features are required and sufficient:
  1. Slit-like serration
  2. Typical cytology
  3. Ectopic crypt formations

• Mucin-rich TSAs lack typical cytology
• Flat TSAs often lack ectopic crypt formations
• 50% of TSAs have a precursor polyp: HP or SSL
• TSA can be diminutive in size
Distal protuberant TSA
Mucin-rich TSA
Small villiform TSA
Proximal flat TSA
Small distal flat TSA
TSA versus SSL(D)

• TSA biologically less advanced than SSLD
• If TSA features present in an SSL, it is reported as TSA not SSLD
• TSA is not low grade serrated dysplasia
• Serrated adenoma unclassified
  • For lesions difficult to classify as SSL or flat TSA
  • Not for HP versus SSL
  • Sparingly used
This is NOT (low grade) serrated dysplasia

This is a flat TSA arising from an SSL
This is NOT (low grade) serrated dysplasia

This is a protuberant TSA arising from an SSL
Advanced TSA

- Superimposed dysplasia can develop in TSA
- Usually resembles the dysplasia of conventional adenoma
- The significance of low-grade dysplasia is not clear
- High-grade dysplasia represents an advanced stage and should be summarised as “TSA with high-grade dysplasia”
- Nearly always retain MLH1 expression
TSA with high-grade dysplasia
Serrated adenocarcinoma from TSA – MMR proficient
Is serrated polyposis a genetic syndrome?
What is the role of \textit{RNF43} in serrated polyposis?

- \textit{RNF43} is a negative regulator of the WNT signalling pathway
- Initial reports of germline variants in serrated polyposis families
- Mutation testing from large series of serrated polyposis patients found a $<2\%$ prevalence
- Currently no role for \textit{RNF43} mutation testing in clinical practice
Serrated polyps/lesions in GIT genetic syndromes

• *MUTYH*-associated polyposis:
  • 18% *MUTYH* biallelic mutation carriers fulfilled serrated polyposis criteria (Boparai et al. Gut 2013)
  • But conventional adenomas are often predominant

• Cowden syndrome:
  • 24% *PTEN* mutation carriers fulfilled serrated polyposis criteria (Heald et al. Gastroenterology 2010)
  • But CS-type hamartomatous polyps are always present and often predominant

• Juvenile polyposis syndrome (*SMAD4, BMPR1A*):
  • But juvenile polyps are always present

The role of genetic testing for typical serrated polyposis patients is uncertain
Summary

• Improve consistency and reproducibility of serrated lesions/polyps
• More research necessary for evidence-based guidelines
• Serrated polyposis remains poorly understood
• Serrated lesions/polyps sometimes a secondary component in MAP, Cowden syndrome, juvenile polyposis