HISTOPATHOLOGICAL AND MOLECULAR FEATURES OF ADENOMATOUS AND SERRATED COLON ADENOMAS, CHARACTERISTICS and OVERLAPPING FEATURES, CHALLENGES IN THE NOMENCLATURE

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Background on Adenomas of the Colon

• It is well established that colorectal cancer develops from a series of precursor epithelial polyps
  Conventional adenomas
  Serrated adenomas (since 1990s)
    Sesile serrated adenoma
    Traditional serrated adenoma (*possibly advanced form of SSA*)
• The criteria for diagnosing adenomas are well-defined
• However the overlapping features of these neoplastic lesions are not clear
Conventional adenomas (CAs)
Tubular Adenoma (TA), Tubulovillous adenoma(TVA), Villous Adenoma (VA)

- Epithelium with enlarged hyperchromatic nuclei with spindling and stratification and loss of polarity
- Decreased number of goblet and absorbtive cells
- Tubuler/villous/tubulovillous architecture
Sesile Serrated Adenoma (SSP/SSA/Now SSL)

- Serrated lesions contain goblet cells and microvesicular mucin droplets
- Growing horizontally along the muscularis mucosa
- Have dilated crypt base
- Asymmetric proliferation
Traditional Serrated Adenoma (TSA)

- Slit-like serration
- Tall columnar cells with intensely eosinophilic cytoplasm and pencillate nuclei
- Ectopic crypts along the side of villous projections
Aim of this study was to ....

- Settle the histopathological characteristics of adenomas
- Reveal/expose overlapping features of different adenoma types
- Document the molecular properties of these lesions
Materials and Methods

• 70 CAs, 35 SSA/Ps and 35 TSAs H&E stained slides were retrieved from archive and they are reclassified by 10 years experienced GI pathologist

• Demographics were collected from charts

• Macroscopic configurations of possessing sessile or polypoid structure were obtained from gross or endoscopy reports
Materials and Methods

- A **second histopathological reevaluation** was performed according to the **distinct criteria** of each adenoma type:
  - ✓ Tubular, villous, serrated architecture
  - ✓ Ectopic crypt, eosinophilic cytoplasm, pencillate nuclei
  - ✓ Dilatation of crypt base, presence of mucinous hypersecretion on the base and surface
  - ✓ Adenomatous dysplasia, serrated dysplasia
  - ✓ The degree of dysplasia

- Those criteria for each lesion first scored in
  - **the binary** system (present/ not present)
  - and
  - **the quartet system** (0: <10%, 1: 10-25%, 2: 25-75%, 3: >75%).

- **KRAS, NRAS, BRAF** mutation, **MSI analysis** and **MLH1 promoter methylation analysis** were performed.
Half of the conventional adenomas had focal serration, but only one had more than 25%
Eosinophilic cytoplasm ($n=30$), pencillate nucleus ($n=20$) and ectopic crypts ($n=23$) were not uncommon in CAs, but most of them are less than 25%
Only 26% (n=16) CAs have dilatation at the crypt base
Focal serrated dysplasia was seen only in 6 of the CAs
At least **focal adenomatous dysplasia** was seen in half of the **SSAs**
Ectopic crypts (n=4) and pencillate nucleus (n=5) were rare and focal in SSAs.
70% percent of the TSAs had **adenomatous dysplasia**, 14 cases had **serrated dyplasia**
More than half of TSAs had crypt base dilatation.
16 of the cases could not be classified in any group (11%). Hybrid/unclassified cases
All the unclassified cases had **serration** and **adenomatous dysplasia**, 75% of them had **crypt base dilatation**.
11 of 16 was sesile
## Molecular Features of Cases

<table>
<thead>
<tr>
<th></th>
<th>BRAF</th>
<th>KRAS</th>
<th>NRAS</th>
<th>MSI</th>
<th>MLH1-Methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (n=20)</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>SSA (n=10)</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>TSA (n=10)</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hybrid / Unclassified (n=10)</td>
<td>1</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</tbody>
</table>
One of the KRAS mutated SSA case had focal TSA features in recuts. Both the SSAs with KRAS mutation were hypermetilated.
Most of the hypermetililated cases had dysplastic changes
After detailed quartet system analysis....
Using 25% cut off for serration

χ²_{Pearson}(3) = 112.78, p = < 0.001, V_{Cramer} = 0.90, Cl_{95%} [0.83, 0.96], n = 140
Serration >25% percent and presence of >10% ectopic crypt or pencillate nucleus

\[ \chi^2_{\text{Pearson}}(12) = 221.31, \ p = <0.001, \ V_{\text{Cramer}} = 0.73, \ CI_{95\%} [0.67, 0.76], \ n = 140 \]
Neoplastic Colon Lesion with adenomatous dysplasia

Is Serration more than 25%?

Yes: Does the presence of ectopic crypt or pencillate nuclei is more than 10%?
  Yes: Traditional serrated adenoma
  No: Sesile serrated adenoma

No: Conventional Adenoma
7 cases can be moved from unclassified group to CA by using algorithm
All were KRAS mutated
By using algorithm 2 cases can be assigned from unclassified group to SSA.

Only one has molecular analysis and it was BRAF mutated.
7 hybrid cases classified as TSA by using this algorithm, 3 have KRAS mutation
In conclusion

- All histopathological findings can be seen in all types of adenomas
- **None of** these parameters are peculiar to a lesion
- **CAs** can have <25% of serration in most of the cases
- **SSAs** by a majority don’t have secondary architectural features, but adenomatous dysplastic changes can be seen
- **TSAs** are complex and the most difficult lesions to diagnose and differentiate both by histopathologic and molecular features
In conclusion........

- There was no established histopathological algoritm or cut off to differentiate these neoplastic lesions
- Thus the value 25% a cut off can be used to differentiate CAs from serrated lesions
- Displastic TSAs thought to be more advanced lesions. Therefore a lower thershold can be used to differantiate them
- In lesions with >25% serration, the presence of >10% pencillate nuclei and/or >10% ectopic crypt points to TSA
- This algoritm may be supported with more cases and concensus studies