Intestinal Inflammation and Colorectal Cancer

Falk Symposium
Sevilla-Spain
2007
How to deal with dysplasia and adenomatous polyps in IBD?

Paula Chaves and Paula Borralho
Lisboa
How to deal with dysplasia and adenomatous polyps in IBD?

- The importance of identifying dysplasia.
- The distinction between low-and high-grade dysplasia.
- Adenomatous polyps arising in colitis.

What is dysplasia?
How to deal with dysplasia and adenomatous polyps in IBD?

Dysplasia is the unequivocal neoplastic transformation of an epithelium.

*Inflammatory Bowel Disease Morphology Study Group, 1983*

..... it is the first morphological step of the neoplastic process in an epithelium.

... these epithelia began its neoplastic transformation.
How to deal with dysplasia and adenomatous polyps in IBD?

Why is dysplasia so important in IBD?

Because IBD is a premalignant condition predisposing to colorectal neoplasia.

How do we know this?
How to deal with 
dysplasia and adenomatous polyps in IBD?

- Crohn BB, Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific).
  

  
  *Am J Pathol 1949.*

- Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis.
  
  *Gut 1967.*
How to deal with dysplasia and adenomatous polyps in IBD?

- Dysplasia was then regarded as the presence of atypical architectural and cytological features.
- It included all the morphological alterations associated with inflammation, degeneration, regeneration as well as neoplastic transformation.

- It considered 3 grades:
  - Mild
  - Moderate
  - Severe
How to deal with dysplasia and adenomatous polyps in IBD?

This has atypical features but...

... is this neoplastic or reactive?
How to deal with dysplasia and adenomatous polyps in IBD?

- In the early 1980s it was urgent:
  - To address the spectrum of all reactive changes.
  - To separate them from neoplastic features.
  - A definition and grading system for dysplasia.
How to deal with dysplasia and adenomatous polyps in IBD?

**IBD MORPHOLOGY STUDY GROUP, 1983**

**DEFINITION**
- Dysplasia is the unequivocal neoplastic transformation of an epithelium.

**GRADING**
- Negative *(reactive changes, with no neoplasia)*
- Positive *(with intraepithelial neoplasia)*
  - Low-grade
  - High-grade
- Indefinite *(I don't know)*
How to deal with dysplasia and adenomatous polyps in IBD?

Negative
How to deal with dysplasia and adenomatous polyps in IBD?

Low-grade dysplasia

High-grade dysplasia
How to deal with dysplasia and adenomatous polyps in IBD?

Indefinite
How to deal with dysplasia and adenomatous polyps in IBD?

## INTEROBSERVER VARIABILITY

<table>
<thead>
<tr>
<th>Author</th>
<th>Specimens</th>
<th>Pathologist</th>
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How to deal with dysplasia and adenomatous polyps in IBD?

**THE VIENNA CLASSIFICATION**

- Negative
- Indefinite
- Non invasive low grade neoplasia
- Non invasive high grade neoplasia
  * High grade dysplasia
  * Non-invasive carcinoma
  * Suspicious of invasive carcinoma
- Invasive neoplasia
  * Intramucosal carcinoma
  * Submucosal carcinoma
How to deal with dysplasia and adenomatous polyps in IBD?

WHAT'S NEW IN VIENNA CLASSIFICATION?

Dysplasia → Intraepitelial Neoplasia

Non invasive high grade neoplasia
* High grade dysplasia
* Non-invasive carcinoma = carcinoma in situ
* Suspicious of invasive carcinoma

Invasive neoplasia
* Intramucosal carcinoma
* Submucosal carcinoma
How to deal with dysplasia and adenomatous polyps in IBD?

Now, we know that dysplasia is an intraepithelial neoplasia and that it must be classified in two grades...

... how shall we use this knowledge in IBD patients?
How to deal with dysplasia and adenomatous polyps in IBD?

RISK OF NEOPLASIA IN CROHN'S DISEASE

- **Dysplasia**
  - Adjacent to Ca in 40-100%
  - More common close to tumor
  - 2-16% of patients without carcinoma

- **Carcinoma**
  - Risk Similar to UC
  - Involved and uninvolved areas
  - Dysplasia-carcinoma sequence
How to deal with dysplasia and adenomatous polyps in IBD?

RISK OF NEOPLASIA IN UC

- **Dysplasia**
  - 5% incidence/10 years
  - 25% incidence/20 years

- **Carcinoma**
  - 3-43% incidence/25-35 years
    - 5-10% incidence/20 years
    - 10-20% incidence/30 years
  - 1-2%/year after 10 years
How to deal with dysplasia and adenomatous polyps in IBD?

RISK FACTORS IN ULCERATIVE COLITIS

- Disease duration (> 10 years)
- Disease extent
- Primary sclerosing cholangitis
- Early age of onset
- Family history of colon cancer
How to deal with dysplasia and adenomatous polyps in IBD?

We must look for dysplasia in patients with long-standing extensive IBD disease.
How to deal with dysplasia and adenomatous polyps in IBD?

- The importance of identifying dysplasia.
- The distinction between low-and high-grade dysplasia.
How to deal with dysplasia and adenomatous polyps in IBD?

Why is it important to distinguish between low-grade and high-grade dysplasia in IBD patients?
How to deal with dysplasia and adenomatous polyps in IBD?

**NATURAL HISTORY OF FLAT DYSPLASIA**

- **Low grade**
  - Co-existent carcinoma: 9%
  - Progression to HGD/CA: 30-54%

- **High grade**
  - Co-existent carcinoma: 40-67%
  - Progression to CA: 40-90%

Bernstein et al, Lancet 1994
How to deal with dysplasia and adenomatous polyps in IBD?

**MANAGEMENT OF IBD PATIENTS WITH FLAT DYSPLASIA**

Flat dysplasia

- Low grade
  - Unifocal
    - Surveillance
    - Local resection
    - Colectomy??
  - Multifocal
    - Synchronous
      - Colectomy
  - High grade
    - Colectomy
How to deal with dysplasia and adenomatous polyps in IBD?

In all cases of dysplasia assessment, the diagnosis must be confirmed by at least 2 expert GI pathologists

(AGA and ACG)
How to deal with dysplasia and adenomatous polyps in IBD?

How can pathologists distinguish between low-grade and high-grade dysplasia in IBD patients?

We use architectural and cytologic features...

but...

...how do we make the distinction between the two grades?
How to deal with dysplasia and adenomatous polyps in IBD?

Architectural and cytologic changes: tubular or villous features, nuclear stratification, ↑ N/C ratio and hyperchromatic nucleous.

Polarity is not lost.
How to deal with dysplasia and adenomatous polyps in IBD?

Intense architectural and cytologic changes: “back to back” configuration of glands, cribriform aspects.

High grade dysplasia

Loss of polarity
How to deal with dysplasia and adenomatous polyps in IBD?

The integrity of the basal membrane is probably lost.

Suspicious of invasive carcinoma...

...Probably intramucosal carcinoma.
How to deal with dysplasia and adenomatous polyps in IBD?

- The importance of identifying dysplasia.
- The distinction between low- and high-grade dysplasia.
- Adenomatous polyps arising in colitis.
How to deal with dysplasia and adenomatous polyps in IBD?

What do we know about the gross morphologic features of dysplastic lesions arising in IBD patients?
How to deal with dysplasia and adenomatous polyps in IBD?

**DYSPLASIA IN IBD**

- IBD-associated dysplasia may arise in two gross patterns:
  - "Flat" (endoscopically undetectable)
  - "Raised" (endoscopically detectable)
  ["Dysplasia-associated lesions or masses" (DALMs)]

- Polypoid dysplastic lesions in IBD may be:
  - DALMs
  - Adenomas
How to deal with dysplasia and adenomatous polyps in IBD?

Is it possible to distinguish between sporadic adenomas arising in IBD patients and DALMs?
How to deal with dysplasia and adenomatous polyps in IBD?

Clinical, pathological and molecular features distinguishing Adenomas from DALMs

How to deal with dysplasia and adenomatous polyps in IBD?

Villous architecture, inflammation and admixture of N/D glands.
How to deal with dysplasia and adenomatous polyps in IBD?

**ADENOMA**

Tubular architecture, no inflammation, no admixture of N/D glands
How to deal with dysplasia and adenomatous polyps in IBD?

**IBD NEOPLASIA/SPORADIC NEOPLASIA**

<table>
<thead>
<tr>
<th>GENE</th>
<th>IBD</th>
<th>SPORADIC</th>
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<tbody>
<tr>
<td>Kras</td>
<td>early, frequent</td>
<td>early, frequent</td>
</tr>
<tr>
<td>P53 (17P)</td>
<td>early</td>
<td>late</td>
</tr>
<tr>
<td>LOH 17P</td>
<td>early</td>
<td>late</td>
</tr>
<tr>
<td>LOH 9P (P16)</td>
<td>early</td>
<td>rare</td>
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<td>LOH 3P (50%)</td>
<td>early</td>
<td>rare, late</td>
</tr>
<tr>
<td>APC (5q)</td>
<td>late</td>
<td>early</td>
</tr>
<tr>
<td>P27</td>
<td>early</td>
<td>late</td>
</tr>
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</table>
How to deal with dysplasia and adenomatous polyps in IBD?

But...........

... is it possible to reliably differentiate sporadic adenoma from polypoid dysplasia in an individual IBD patient?

No.
How to deal with
dysplasia and adenomatous polyps in IBD?

DALM’S HISTORICAL PERSPECTIVE

- Dawson IMP, Pryse-Davies. The development of carcinoma of the large intestine in ulcerative colitis.


   “polypoid lesions” indistinguishable from adenomas in 9 out the 17 patients included.
How to deal with dysplasia and adenomatous polyps in IBD?


- 12/112 patients with long-standing UC had DALMs.
- 7/12 (58%) patients with DALMs had carcinoma.
How to deal with dysplasia and adenomatous polyps in IBD?

  
  *Dig Dis Sci 1983.*

  
  *Dis Colon Rectum 1984.*

- Rosenstock E, Farmer RG, Petras R et al. Surveillance for colonic carcinoma in ulcerative colitis.
  
  *Gastroenterology 1985.*
How to deal with dysplasia and adenomatous polyps in IBD?

• In the 1980s, given the strong association with cancer, the presence of DALM constituted a strong indication for colectomy.
• But the studies were quite divers with regard to:
  • criteria for dysplasia
  • gross features of DALMs
  • type of material (biopsies/resections)
  • clinico-endoscopic features.
How to deal with dysplasia and adenomatous polyps in IBD?

- It became evident that DALMs were a heterogeneous population of tumours that may endoscopically appear as plaques, masses, sessile nodules or polyps, the cancer risk being not equal among the divers subtypes.
How to deal with dysplasia and adenomatous polyps in IBD?

**POLYPOID DYSPLASIA IN IBD**

- May be:
  - DALMs (Adenoma-like/Non Adenoma-like)
  - Adenomas
How to deal with dysplasia and adenomatous polyps in IBD?

**DALM**

<table>
<thead>
<tr>
<th>Adenoma-like</th>
<th>Non Adenoma-like</th>
</tr>
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<tbody>
<tr>
<td>Sessile/Pedunculate</td>
<td>Mostly sessile</td>
</tr>
<tr>
<td>Well circumscribed</td>
<td>Poorly circumscribed</td>
</tr>
<tr>
<td>Smooth surface</td>
<td>Irregular surface</td>
</tr>
<tr>
<td>Visible borders</td>
<td>Indistinct borders</td>
</tr>
<tr>
<td>Non-ulcerated</td>
<td>Ulcerated</td>
</tr>
<tr>
<td>No stricture</td>
<td>Stricture</td>
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Morphologically
How to deal with dysplasia and adenomatous polyps in IBD?

Pedunculate, well circumscribed polyp with a smooth surface and visible borders

Adenoma
How to deal with dysplasia and adenomatous polyps in IBD?

Sessile, poorly circumscribed lesion with irregular surface and indistinct borders...

Non Adenoma-like DALM
How to deal with dysplasia and adenomatous polyps in IBD?

Sessile, well circumscribed lesion with a smooth surface...

Adenoma-like DALM
How to deal with dysplasia and adenomatous polyps in IBD?


How to deal with dysplasia and adenomatous polyps in IBD?

Polypoid dysplasia

Adenoma-like

Outside colitis
- Polytectomy
- Surveillance

Inside colitis
- Polytectomy
- Absence of flat dysplasia
- Surveillance

Non Adenoma-like

Colectomy
How to deal with dysplasia and adenomatous polyps in IBD?

Conclusion

If it looks like an adenoma

It probably is!

Odze 2004