Dysplasia (and serrated lesions) in IBD

Rodger Haggitt Memorial Lecture

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San Antonio

I have no conflicts or disclosures

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Editorial

Rodger C. Haggitt: A Biography

On June 28th of this year 1998, the world of pathology suffered a loss of incalculable magnitude. On this day, Dr. Rodger Haggitt was tragically lost to all of us, the consequence of a long battle with cancer. He is survived by his loving wife, but his dedication to the profession at the time of his death, and his legacy of excellence in such influence by Dr. William McGregor and ensured his career as an outstanding pathologist. In 1977, Dr. Haggitt returned to the University of Toronto, where he was in charge of surgical pathology. In 1981, he

MARY P. BRONNER, MD
CARL E. RUBIN, MD

THE HISTOMORPHOLOGIC PICTURE OF CHRONIC ULCERATIVE COLITIS (NON-SPECIFIC).

By Burkill B. Crohn, M.D.,
and
Herman Rosenberg, M.D.,


(From the Medical Department, Mount Sinai Hospital, New York City.)

Pt with “Non-specific ulcerative lesion” of the colon 14y+ duration.

No age but “his” disease.

...extensive polypoid colitis. In addition... growing in a mass of poly-p-like excrescences, a massive (rectal) carcinoma. Sections removed for histological examination showed the presence of adenocarcinoma.

THE CAUSES OF COLITIS, WITH SPECIAL REFERENCE TO ITS SURGICAL TREATMENT

WITH AN ACCOUNT OF 36 CASES

BY

P. LOCKHART MUMMERY, F.R.C.S.

Received April 5th, 1897—Read June 21st, 1897


Used the new electric proctosigmoidoscope
CANCER AS A CAUSE OF COLITIS

There were several (patients) in whom the symptoms were those of colitis rather than cancer, but I have not included them as there was at no time any doubt about the diagnosis, as a digital examination revealed the true state of affairs.

- **M46** Under treatment for ulcerative colitis. He had been passing blood and mucus for 2 years almost continuously. On examining him with the sigmoidoscope I found a small malignant growth, growing from the anterior wall of the sigmoid flexure about six inches above the upper end of the rectum. The mucous membrane above the growth was inflamed and resembled the condition seen in non-malignant cases of colitis.
- I excised the growth. A microscopical examination of the growth showed that it was an ordinary medullary carcinoma.

Goes on to talk about........

MULTIPLE ADENOMATA OF THE LARGE INTESTINE.

- This is a very curious condition and only a comparatively small number of cases have been recorded. These adenomata are present in great numbers; in some cases the entire mucosa of the large bowel is covered over with them.

Shields Warren & Sheldon (Charlie) Sommers

Neoplastic mucosal polyps are present in patients with ulcerative colitis to the same degree as in the general population, and have the same tendency to become malignant, accelerated, perhaps, by chronic inflammation. ....and eventually foci of precancerous epithelial hyperplasia develop in the unfavorable environment (4 cases).

? First description of "dysplasia" but no pics
The Scope of Dysplasia

1981 – State of the art (pathological chaos)

Multiple colonoscopic biopsies for surveillance
Emerging concept of DALMs

BUT
Nomenclature – Atypia = dysplasia OR reactive
Grades of dysplasia – Mild, moderate, severe = 5
Mild dysplasia also used for reactive changes
Dysplasia (“precancer”) = do colectomy

Formation of IBD dysplasia morphology study group.
1983 – Human Pathology Paper

Dysplasia in Inflammatory Bowel Disease:
Standardized Classification with Provisional Clinical Applications

ROBERT H. RIDGEL, MD,1 HARVEY GOLDMAN, MD,1
DAVID F. RANSCHOFF, MD,1 HENRY D. APPELMAN, MD,1
CECILIA M. FENOGlio, MD,1 RODGER C. HAGGITT, MD,1
CHRISTER AHREN, MD,17 PELAYO CORREA, MD,14
STANLEY R. HAMILTON, MD,14 BASIL C. MORSON, DM,15
SHELDON C. SOMMERS, MD,13 AND JOHN H. YARDLEY, MD,13

Definitions, Atlas

Rectal biopsy as an aid to cancer control in ulcerative colitis

B. C. MORSON AND LILLIAN S. C. PANG
From the Research Department, St. Mark’s Hospital, London

Gut 1967;8:423 - 434

EDITORIAL COMMENT: This is a very important paper as it provides the clinician with a new method of identifying patients with ulcerative colitis who may be particularly exposed to the risk of carcinoma. Rectal biopsies of flat masses may demonstrate a certain cellular pattern which has been shown to be particularly associated with carcinoma.

Prophylactic colectomy for cancer prevention was the standard of care

Grading system for epithelial changes (non-invasive) in IBD

Dysplasia – must be unequivocably neoplastic and capable of giving rise directly to an invasive carcinoma
Only 2 grades – High and Low (now everywhere)
Atypia – abolished or qualify as either regenerative or dysplastic

Action plans for all grades
Neg – regular follow up
IFD – need more info – early repeat Bx
LGD – early repeat or colectomy
HGD – colectomy
Allowed to say “I don’t know” (IFD) – kappas!
Interobserver variability study – need for 2nd opinion
Dysplasia is unequivocally neoplastic epithelium!

Q: How do we KNOW it is unequivocally neoplastic?

A: The Pathologists (“us”) say so
   (In my experience.... Its through the basement membrane.... blah blah blah)

B  The molecular guys say so - lots of mutations (p53, BRAF, p16, SOX2, Mayo panel), deletions, translocations, single nucleotide varaints, promoter Me etc.
   not always so easy

Well it seems to work  Doesn’t it???

The Vienna classification of gastrointestinal epithelial neoplasia

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative for neoplasia/dysplasia</td>
</tr>
<tr>
<td>2</td>
<td>Indefinite for neoplasia/dysplasia</td>
</tr>
<tr>
<td>3</td>
<td>Non-invasive low grade neoplasia (low grade adenoma/dysplasia) Intraepithelial neoplasia</td>
</tr>
<tr>
<td>4</td>
<td>Non-invasive high grade neoplasia</td>
</tr>
<tr>
<td>4.1</td>
<td>High grade adenoma/dysplasia</td>
</tr>
<tr>
<td>4.2</td>
<td>Non-invasive carcinoma (carcinoma in situ)*</td>
</tr>
<tr>
<td>4.3</td>
<td>Suspicion of invasive carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>Invasive neoplasia</td>
</tr>
<tr>
<td>5.1</td>
<td>Intramucosal carcinoma†</td>
</tr>
<tr>
<td>5.2</td>
<td>Submucosal carcinoma or beyond</td>
</tr>
</tbody>
</table>

*Non-invasive indicates absence of evident invasion.
†Intramucosal indicates invasion into the lamina propria or muscularis mucosae.

Preventing cancer in IBD

• Background
• Terminology & Definitions
• Problems with colitic cancers - DALMs
• Dysplasia
  – Endoscopic detection & Rx
  – Histological subtypes
  – Serrated lesions
  – Indefinite for dysplasia
  – Inflammation and repair
  – Dysplasia with inflammation
• Are we winning the battle?

Colitic cancers

• As Dukes said
• Can be conventional
  Often, flat, minimally raised, multiple
• If biopsied may have HGD (or worse), LGD, IFD, no dysplasia

Is it a DALM? Is it detectable?

LGD can give rise directly to invasive carcinoma.

Can carcinoma have no dysplasia on biopsy?

Inflammatory polyp-like DALM/Ca

The big myth

How it really works

No/min dysplasia → Low-grade dysplasia → High-grade dysplasia → Incipient invasion → Invasive Ca

No/min dysplasia → Low-grade dysplasia → High-grade dysplasia → Incipient invasion → Invasive Ca
Conclusion

We are (currently) never going to be able to detect or prevent all CRCs in IBD.

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Endoscopic identification of dysplasia

SCENIC guidelines

SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations)

Consensus statements provide unifying recommendations for the optimal surveillance & management of dysplasia in IBD.
Terminology for endoscopic findings in IBD - Modified Paris classification of dysplasia

**Visible dysplasia** (Identified on targeted biopsies)
- Polypoid (polyp) – projects >2.5mm
- Pedunculated (stalk), Sessile (no stalk)
- Non-polypoid - projects <2.5mm
  - Superficial elevated (raised), flat, depressed

**General descriptors**
- Ulcerated
- Borders
  - Distinct (distinguishable from surrounding mucosa)
  - Indistinct (indistinguishable)

**Invisible Dysplasia**
- Detected on random (non-targeted) biopsies (refer)
  - [incidental/unrecognized]

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**Dysplasia-Associated Lesion or Mass (DALM) Detected by Colonoscopy in Long-Standing Ulcerative Colitis: An Indication for Colectomy**

MICHAEL O. BLACKSTONE, ROBERT H. RIDDLE, B. H. GERALD ROGERS, and BERNARD LEVIN
Departments of Medicine and Pathology, University of Chicago, Pritzker School of Medicine, Chicago, Illinois

12 DALMs, 7 of which were actually invasive carcinoma
Pre-op Bx – No inv Ca, 2 - Severe dysplasia, 5 - Mild/mod Dys
An endoscopic lesion + dysplastic biopsy of any grade = DALM
Will only know if this is invasive or not when it is resected
- BUT – There were no endoscopic resection/ablation technique

Gastroenterology 1981;80:366-74

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**SCENIC Guidelines**

1. Detection of dysplasia (and carcinoma!!) is the immediate goal of surveillance colonoscopy.
2. Most dysplasia is visible
3. High-definition chromoendoscopy is best (No role for NBI)
4. After complete removal of endoscopically resectable polypoid OR non-polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy. (100% agreement; strong recommendation; very low-quality evidence)
5. Colectomy if not resectable endoscopically + IPAA (? Role of segmental excision)

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**DYSPLASTIC ENDOSCOPIC LESION / MASS IN UC**

? Resectable endoscopically
- Yes
  - Polypectomy
  - Not possible
- No - Possible Ca
  - ? Colectomy

a) Polypectomy, b) Bx Base
b) or c) negative
- Continued surveillance
  - b) and c) negative
  - + Surveillance run for Dysplasia

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If you can’t let it go, just do not equate it with = colectomy
Why biopsy around the base? What is the yield? Implication

Low Rate of Dysplasia Detection in Mucosa Surrounding Dysplastic Lesions in Patients Undergoing Surveillance for Inflammatory Bowel Diseases

Joan R. van Houwelingen, Erik Molenaar, Evelien Dijkstra, Andrea E. van de Meeden-de Jong, G. Johan A. Opperhans, Cyriel Y. Fersasky, Peter D. Siemenek, and Bas Oldenburg

Clinical Gastroenterology and Hepatology 2017;15:222-229

- 7/140 Bx - 5% 5/136 (3.7%) if LGD

Incomplete Polyprop Resection During Colonoscopy-Results of the Complete Adenoma Resection (CARE) Study


GASTROENTEROLOGY 2013;144:74-80

Adenomas - Complete resection 93% SSA/P - 67%

Options – go back quickly Follow Surgical removal - TPC

SCENIC Guidelines

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5. Colectomy if not resectable endoscopically + IPAA (? Role of segmental excision)
Only focal mucosal lesions that could be clearly distinguished from the surrounding mucosa were classified by pit pattern.

Role of random biopsies

**IF you are good at chromoendoscopy in detecting dysplastic lesions -? Necessary**

Are random biopsies still useful for the detection of neoplasia in patients with IBD undergoing surveillance colonoscopy with chromoendoscopy?

Drille Moussa,1 Matthieu Allea2 Dominique Cazado-Ratier,1 Xavier Trottier,1

On-line Gut Jan 23 2017 – GETAID group

Roughly equal detection in random and targeted biopsies (24/114 pts in target group, vs 18/107 in random group)

Watanabe T et al Gastroenterology 2016;151:1122-1130

**Significance of Invisible dysplasia (SCENIC study)**

- **Synchronous Ca** -
  - Invisible low grade - 22% of patients (18/81) had CRC on colectomy (20 studies)
  - Videoend + before - but why were they resected??
  - Invisible high grade dysplasia - 42-67% have CRC on resection

- **Metachronous Ca** (no pan proctocolectomy)
  - CRC developed in 7/122 (6%, range 3-9%)
  - Mean follow-up of 15 to 50 months:
    - 4 studies from the video-endoscopic - c. 1.5% pa = 15% in 10y
  - Role of multifocality is unclear
  - So should you do panproctocolectomy anyway?

**GETAID study**

1000 colonoscopies in 1000 patients

Used chromo + 4 random/10cms

5 “expert pathologists” reviewed all

Rate of detection of dysplasia in random biopsies

0.2% (1/500). 1.2% of all colonoscopies

Useful in patients with tubular colons, PSC, previous history of neoplasia

In c 15% of patients dysplasia is ONLY found in random biopsies (85% visible)

BUT what is the implication of finding dysplasia in random biopsies?

**High Rates of Metachronous Colon Cancer or Dysplasia After Segmental Resection or Subtotal Colectomy in Crohn’s Colitis**

Batra A, Maurer, MD, FACC,1 David B. Sobey, MD,1 Danielle Kroes, BA, Reem Harb, MA, MD, FACC,1 Thomas O’Brien, MD, FACC,1 and Joel J. Baca, MD, FACC,1 (Inflamm Bowel Dis 2013;19:1827–1832)

64 pts with Crohn’s and CRC

47 Segmental resection 17 Subtotal colectomy

19 New cancers (40%) 6 New cancers (35%)

21 of these 25 pts undergoing surveillance

Mean time to 2nd cancer 6.8y

- Dysplasia only (43% new dysplasia 50% New dysplasia)

(In UC, 1/3 - >50% of cancers are interval cancers)
Why is targeting lesions so important?

Pitfalls in Surveillance

Length 100 cm  Circumference 10cm  Area 1000cm²

needs 1000/3.14 equally spaced biopsies  -  c. 320 biopsies

….and then you want to what?

So multifocality...........?

Where does this leave the Local gastroenterologists
What should they do?

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Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study
E Mooiweer et al  Am J Gastroenterol 2015; 110: 1014-1021

Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview

Editorial: Miles to Go on the SCENIC Route: Should Chromoendoscopy Become the Standard of Care in IBD Surveillance?
Peter D R Higgins  Am J Gastroenterol 2015: 110: 1035-1037

Paradigm Shift in the Surveillance and Management of Dysplasia in Inflammatory Bowel Disease (West)
Digestive Endoscopy 2016, 28: 265-271
Roy Soetilno, Tanya Kaltenbach, Kenneth R McQuaid, Venkataraman Subramanian, Rahul Kumar, Alex R Bartunek and Louis Laime

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  – Inflammation and repair
  – Dysplasia with inflammation
• Are we winning the battle?
• Can the same sort of logic be applied to dysplasia / carcinoma in IBD?

Novel Classification of Dysplasia in IBD
Noam Harpaz, John Goldblum, Neil Shepherd, Robert Riddell, Carlos Rubio, Michael Vieth, Robert Odze

Conventional dysplasia - top down

LGD  HGD

Criteria for HGD – nuclei to cell lumen, loss of polarity, architecture

Conventional but bottom-up (crypt) dysplasia (Villous)
Beware villous dysplasia
Can mature up and
Invade down

Hypermucinous change/dysplasia

?PGA-like
Small bowel pattern
Dysplasia with terminal differentiation
Bx F 36
F36 – what would you suggest?

Inflammatory polyp-like DALM/Ca
Dysplasia/Ca with terminal differentiation

P53 crypt

Dysplasia/Ca with terminal differentiation
Loss of goblet cells/mucin depleted/basal dysplasia

What are the non-goblet cells?
- Mature absorptive
  - Colonic, small intestinal, serrated
- Crypt cells that are not maturing
- The mucin-depleted parts of various dysplasia pathways
Serrated changes in IBD

- Diffuse superficial serrations (IBD + non-IBD)
- Superficially in inflammatory polyps
- Conventional types of hyperplastic polyps
- SSA / SSA-like
- TSA / TSA-like
- Unclassified (often combinations)

In IBD any of the previous can have dysplasia

Further along
Superficially serrated
No architectural complexity
? Nuclear grade (low)
Hybrids serrated/GC depleted
Remember the poorly diff Ca
Hp – goblet cell variant

SSA-like (1.2–10% esp CE) + dysplasia
F 53 Crohn’s
TSA-Like M55 UC Polyp TC
Sigmoid polyp
Pan-UC
Summary – serrated lesions in IBD
Superficial serrated changes common - IBD + non IBD
Serrations occur in inflamm (Ps) polyps beneath erosions
Can become dysplastic
Ensure completely excised locally
All variants of hyperplastic polyp can be found in IBD
-some may have LGD
SSA (-like) lesions occur
TSA (-like) lesions occur
Unclassified serrated dysplastic lesions
If dysplastic can invade
Need to rethink and recognize the subtle variants

Indefinite for dysplasia (IND / IFD)

Is it unequivocally dysplastic?
Is it unequivocally negative?
If the answer to both questions is NO
This is indefinite for dysplasia (IFD)
But what does it mean?
Inter (intra)observer variability
(With apologies to Abraham Lincoln)

All will agree with me some of the time
Therefore – all will likely disagree with me…some of the time
(who have I not offended)
Some will be glad they don’t ever have to look at this stuff
We all think (?know) we are right all of the time

Reproducibility
IND always has terrible kappas
Published examples – ?best examples
I have already shown examples of IFD (or less)
giving rise directly to invasive carcinomas

PROGRESSION OF IND TO LGD or worse

Aneuploidy increases the risk of progression
Won-Tak Cho…… Maria Westerhoff
Human Pathology (2015) 46, 939-947
PS3 IHC increases the risk of progression
Bela Horvath et al
Gastroenterology Report, 3(4), 2015, 344-349

Interpreting Indefinite for Dysplasia IFD/IND
Using Barrett’s as a paradigm

• Most mutations are already present in the adjacent non-dysplastic mucosa
  - In EAC Tp53 and SMAD4 are also found

Whole-genome sequencing provides new Insights into the clonal architecture of Barrett’s esophagus and esophageal AdCa

• # Single nucleotide variants (SNVs) present in the EAC samples was 18,786 (median)
  - interquartile range (IQR) 15,007-32,034
•  12,714 for the adjacent Barrett’s esophagus samples.
  - (IQR 6,604–21,559)
• Controls –esophageal squames or PBLs
• Copy Numbers especially increased in EAC.
**Indefinite for Dysplasia**

UC is likely already highly mutated in Bxs Neg for dysplasia

- Mutations /pathways affected increases with age, length of history, activity
- IFD likely already highly mutated

IFD in New colitics /kids have fewer mutations so can repair normally

i.e., Same morphology (IFD) - different outcomes depending on intactness (or not) of (critical) repair mechanisms/pathways

Mutations - transcription - proteins / function (IHC)

Inevitably synchronous / metachronous dysplasia

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**Inflammation & repair vs crypt dysplasia**

- **Beware**
  - Restituting epithelium (crypt or surface)
  - Surface maturation,
  - Active inflammation
  - Crypts within 3 crypts can show reactive changes
  - If unsure, back off to IFD

- **But**
  - Dysplasia can be diagnosed in the presence of marked inflammation (ulcerated adenoma) - just be sure or 2nd opinion (even if downgraded)
Why do we still fail to detect dysplasia and carcinoma in IBD??

- Lesions are missed endoscopically - possibly because of the failure to use optimal techniques - all studies have patients who developed invasive lesions while under surveillance.
- Different pathways may have different criteria for IFD, LGD, HGD - decreasing kappas but making the diagnoses of dysplasia difficult.
- Minimally dysplastic lesions may be missed on biopsy
- Lesions are not adequately removed (Pohl)
- CRCs arise rapidly
- We choose to follow dysplastic lesion - esp LGD
- Patients fail to return for colonoscopy
- Patients refuse surgery

Do we still see patients under surveillance developing AdCa?

- YES
  a) Incidentally in resections
  b) In patients who had had previous unremarkable surveillance Endo+Bx
    ? 30-40%

Summary - Pathways to dysplasia

- Identification of morphological pathways
  - Conventional, Hypermucinous, Terminally differentiated, goblet cell loss
  - Serrated - SSA-like, TSA-like, Unclassifiable
  - Combinations
  - Crypt dysplasia common - don't over-diagnose if restitution, acute inflammation with, maturation back-off/send off and villous
  - Villous changes usually bad - ? crypt bases OK
- SCENIC consensus - implications
- IFD and implications - why pts still get Ca's
- DALMs - RIP

Preventing cancer in IBD

- Background, Terminology & Definitions
- Problems with colitic cancers
- Dysplasia
  - Endoscopic detection & Rx
  - Histological subtypes
    - Conventional, Hypermucinous,
    - Terminally differentiated, Goblet cell depleted
  - Serrated lesions - HPs, SSA-like, TSA-like
  - Indefinite for dysplasia - background mutated++
  - Crypt dysplasia/mutation, Villous, Overlap
  - Inflammation and repair - back off if matures
  - Dysplasia with inflammation
- Are we winning the battle? Pts still get Ca

Thanks

Mt Sinai, Toronto
- Mai Iwaya Yoko Tateishi
- Jay Conner

Biopsy project - Amigos - Group of seven
- Noam Harpaz, John Goldblum, Neil Shepherd, Carlos Rubio, Michael Vieth, Robert Odze