Biopsy diagnosis in colitis: Keeping yourself and the patient out of trouble

Robert H. Riddell, MD, FRCP, FRCPd
Mt Sinai Hospital
Prof of Lab Medicine & Pathobiology
University of Toronto
November 14 2015

rriddell@mtsinai.on.ca
Disclosures

- None
Reporting biopsies in IBD

- First colonoscopy (pressure to make a 1\textdegree diagnosis)
  - Does the patient have IBD or any form of colitis that will explain their symptoms?
  - Can it be narrowed down/ a definitive diagnosis made?
  - Does the patient have dysplasia or carcinoma?
- Variations and Traps
- Follow up colonoscopy (no pressure for a 1\textdegree diagnosis)
  - Why is the patient still symptomatic/not responding?
  - Is there active disease/the wrong disease
  - In an asymptomatic patient
    - Any features of increased risk of relapse?
    - Is there dysplasia or carcinoma
Diagnosing IBD on biopsies - needs evidence of

Prior mucosal damage (crypt changes)
- Architecture, atrophy, Paneth cell metaplasia,
  duplicated muscularis mucosae

Chronicity - XS of chronic inflammation, ideally with
  deep plasma cells (Note - N around ICV)

Together = some form of IBD until proven otherwise

Does not distinguish between.....
- Ulcerative colitis and Crohn's disease
- Microscopic colitis - LC, CC,
- Some medications/drugs
- Chronic infections - amebiasis, TB, Syphilis, LGV
Architectural distortion (+ chronic inflammation) = Archetypal IBD
Distal Paneth cell metaplasia
Thickened / duplicated muscularis mucosae - indicates prior ulceration
Note duplicated muscularis mucosae – but the mucosa has returned to normal

An apparently normal biopsy does not exclude UC

SO “There is no evidence of UC in these biopsies”
Basal plasma cells + Eos = IBD  Villanacci V, et al  
When is Architectural Distortion Present?
Ulcerative Colitis is No Fun
Total ulcerative colitis with L-sided activity
Biopsies reflect distribution -demonstrate
M55 2/52 bloody diarrhea
Rectal Bx
Is this IBD?
How to report

1) Description
Arch distortion + Marked chronic inflammation
c. basal plasma cells (=IBD)

2) Interpretation
Rectal biopsy
The features are those of active
inflammatory bowel disease.
The location and diffuseness of the
inflammation favor ulcerative colitis
- ideally after reviewing endo report

NOTE what is NOT in the report
“Chronic active colitis”
“Clinical correlation is recommended”
“This could be IBD, drugs or infection”
How extensive?

In one biopsy – who knows?

Needs set of biopsies to determine
  Extent
  Distribution of disease
But stool was +ive for *C. diff* toxin

Then the patient has a relapse of IBD associated with *C. diff*

*C. Diff* (and other infections) are more common in IBD than in patients without IBD and may precipitate relapses.
Ulcerative colitis - unusual patterns

- Cecal and peri-appendiceal patches
- Return of rectal mucosal architecture to normal
  - Post therapy
  - Gradually over time
- Giant cells & granulomas - mucin (ruptured crypts)
- Rectal sparing of inflammation
  - Diverticular colitis, After therapeutic enemas
  - Immunosuppressives, PSC
- Patchy inflammation - ? Following Rx & “designer” drugs
- Follicular proctitis (Diversion, UC, CD, Chlamydia/LGV)
- Aphthoid ulcers esp fulminant disease - both ends
UC with periappendiceal patch

UC with cecal patch
"Eosinophilic colitis" - ? Extreme TH2 response

Increased eos increase the risk of relapse (but needs Strongyloides search)
Beware all granulomas where crypts should be – levels, CKs, close to MM best for Crohn's
Histological Crohn’s disease

- **Resections** – for complications only – but a good chance to examine the focality of the disease

- **Biopsy diagnosis** is an extension of the changes seen in resections, namely:
  - Marked focal inflammation++ within & between biopsies
  - Erosions/ulcers on a background of minimally inflamed mucosa

- In a patient in an appropriate clinical setting
  NOT fulminant colitis
Typical UC
Typical Crohn's - Cobblestone
Crohn’s Colitis v. Ulcerative Colitis

- Segmental crypt architectural distortion
- Segmental mucin depletion
- Mucin preservation at active sites
- Focal chronic inflammation without crypt atrophy – esp c. EROSIONS/ULCERS

Multiple logistic regression analysis from multiple colonoscopic biopsies
Does the patient have IBD?

? Ulcerative colitis
? Crohn's disease
? Diversion colitis
? Drug effect
? Other

With 4 different biopsies it is impossible to understand the distribution of the disease.
Terminal ileal biopsy – CD or medications (NSAIDs/ASA)
Crohn’s disease - traps

- Other causes of focal active disease:
  - Biopsy of inflammatory polyps
  - Biopsy of granulation tissue at anastomotic lines
  - Cecal or periappendiceal patch
  - Overcalling normal terminal ileal lymphoid aggregates
  - Fulminant colitis of any cause – including UC (aphthoid ulcers, rectal sparing)
Getting the diagnosis from patterns of inflammation
Without a History - What is the diagnosis?

What is it not? (Chr active colitis)

What if Bx only taken from red areas?
One Bx changed
Ulcerative proctitis with Cecal patch

One Bx changed

What’s the trap
Does any other disease produce this combination of changes?
How about this variation?

Diverticular Colitis or CD provided......there are diverticula.
Predom R-sided UC
Think PSC
Crohn’s disease
Is all IBD UC or CD?

- What if it is clearly IBD but does not fit easily into either UC or CD when:
  - Clinical
  - Imaging
  - Endoscopy
  - Histology
  - Serology are all taken into account?

  ....still cannot make a diagnosis

This is one definition of “indeterminate colitis”

OR – IBD-Unclassified (IBD-U)
**IBD-U @ first diagnosis**

- IBD - Usually pancolitis (varying degrees of arch distortion + inflammation with basal plasma cells)

  **BUT**

  Can’t “pull the trigger” on either UC or CD

  e.g. Some degree of rectal sparing

  but Sigmoid inflamed

  Focality but not enough for CD (no erosions on a background of normal mucosa)

  No granulomas

  i.e. Treat as large bowel IBD
Does the patient have IBD?

Architectural distortion + Chronic inflammation c. deep plasma cells = IBD

May or may not be normal endoscopically
(i.e. Diarrhea R/O microscopic colitis)

What if one component only

a) Architectural distortion only

b) Chronic colitis only (normal architecture)
   No XS of IELs
   No thickening of the subepithelial collagen band
Architectural distortion only

- Mild architectural distortion is present without inflammation, and is indicative of prior damage, although the cause of this is unclear.

- It may represent a prior episode of infectious colitis but the possibility of quiescent IBD or medication-associated injury (e.g. NSAIDs) cannot be excluded.

- If the patient's symptoms exacerbate, consideration should be given to repeating the colonoscopy with biopsies to better elucidate the nature of the underlying disease or cause.

- If symptomatic at the time of scoping, these changes cannot explain the symptoms.

IS THERE A PATTERN? Diffuse, increase distally? UC
Ensure not obvious e.g. Post solid organ transplant
Arch normal, diffuse basal plasmacytosis

The diffuse chronic inflammation with basal plasma cells in most biopsies is indicative of a mild but definite chronic colitis.

This may represent mild IBD (although the lack of architectural changes are against this); a variant of microscopic colitis or medication associated injury, especially NSAIDs. There is no excess of intraepithelial lymphocytes or a thickened subepithelial collagen band to suggest either lymphocytic or collagenous colitis. However the changes could represent the healing phase of either of those conditions.

If the patient's symptoms exacerbate, consideration should be given to repeating the colonoscopy with biopsies to better elucidate the nature of the underlying disease.
Diarrhea – Endoscopically Normal but Histologically abnormal

- Microscopic colitides
  - Lymphocytic colitis and variants
    - Giant cell/granulomatous/paucicellular
    - Brainerd type diarrhea (IELs only)
  - Collagenous colitis
- Quiescent IBD
- IBS – most common exit diagnosis (N, WSA)
- Organisms without inflammation
  - Spirochetosis, (Cryptosporidia)
- Melanosis coli, Amyloid
- Iatrogenic – GVHD, CellCept (MPM), NSAIDs/ASA
  - NSAIDs/ASA, Cord colitis syndrome
Diarrhea - Endoscopically Normal but Histologically abnormal

- Microscopic colitides
  - Lymphocytic colitis and variants
    - Giant cell/granulomatous/paucicellular
    - Brainerd type diarrhea (IELs only)
  - Collagenous colitis
- Quiescent IBD
- IBS - most common exit diagnosis (N, WSA)
- Organisms without inflammation
  - Spirochetosis, (Cryptosporididia)
- Melanosis coli, Amyloid
- Iatrogenic - GVHD, CellCept (MPM), NSAIDs/ASA
  NSAIDs/ASA, Cord colitis syndrome
If she hasn't yet, she will soon! . . .
Our job - guiding patient care

What options do our clinical colleagues have?

- **Do nothing** - Reassurance, See you in x years
- **Insufficient data to make a diagnosis**
  
  Repeat the endoscopy, take more Bx - possibly after Rx, then reassess

- **Other tests**

- **Diagnosis made** - most appropriate therapy
Initial colonoscopy:
Biopsies from XX: The features are those of active inflammatory bowel disease. The diffuseness and pattern of the disease favors this being active ulcerative colitis

Follow-up colonoscopy – Previous diagnosis of UC
Biopsies from XX: Features of active ulcerative colitis. There is no evidence of dysplasia.
Drugs associated with an IBD-like picture

CTLA-4 antagonists – MM – Colitis -IBD-like
Yervoy (ipilimumab), Opdivo (nivolumab)

CD20 – Retuximab – Crohn’s-like – usually no plasma cells, apoptosis

Zydelig (idelalisib) P13K\(_d\) – Phosphatidylinositol-3-kinased – activated in B-cell lymphomas (Enterocolitis)

MMF

Cocaine, oral contraceptives, K= resins (kayexylate) can all cause ischemia
Ipilimumab (Yervoy)
Comment

The features are highly suggestive of IBD, especially if the patient is not taking immunosuppressives or receiving monoclonal antibodies such as ipilimumab (Yervoy), nivolumab (Opdivo), rituximab (Rituxan) or Idelalisib (Zydelig). These can cause a colitis that can mimic IBD.
Finally – the great imitator
Rectal lues

- Proctitis only
  - Diff diagnosis of ulcerative proctitis
- No “massive plasmacytosis” – lymphoplasmacytic
- High endothelial venules not overtly obvious

- Think of luetic infection /LGC whenever there is a proctitis that does not readily “fit”, esp if male
Keeping everyone out of trouble

Chronic active colitis

Consistent with

Non-specific colitis

Clinical correlation is required
“Chronic active colitis”

…… is a description, NOT a diagnosis

It needs an interpretation

If WE do not interpret it who does?

…using what criteria? Who saw the slides?

If the patient has IBD it is a lifelong diagnosis

Is it even IBD? Always IBD?
How was this reported?

Chronic active colitis
What would we expect the history to be?
What was it?

F23 proctosigmoiditis
- outside diagnosis - “chronic active colitis”
  (Rx as IBD)

What was the result of the new diagnosis?
Advised to stop taking Chinese herbal enemas - these contain vincristine/vinblastine (from the Madagascan periwinkle in the enema)
Beware of (the epidemic of) “Consistent with”

How should that be interpreted?
    How do we want it interpreted?
        ... Might be
    ... what else is it c/w ?

Usually interpreted as “diagnostic of”
    (now “histologically proven”)
    = permission to treat ..........
        with steroids, biologicals, surgery

It is not a medico-legal escape cause -
    = in all reasonable medical probability

When does it matter? When it directs therapy
“Mild non-specific colitis”,

- in the absence of an endoscopic abnormality = microscopic colitis
  AND it is now “histologically proven” = permission to treat - was that your intent?

- All inflammation is non-specific unless you can see the cause (“bugs”, drugs)

They need an interpretation - what DO they mean?
  Are they really pathological?
  Are they causing the patients symptoms?
  How do YOU want the recipient to interpret it?
  (It is YOUR job - not theirs)
“Clinical correlation is required”

Does this really mean “Clinico-pathology correlation is required”

Who does the “pathology” part of the discussion?

How? Report, E-mail, Ph call
Do’s and Don’t’s

- Do not use descriptions of “colitis” without interpretations
  - You are the one that has seen the slides

- Do not say “C/W IBD, Infection or Drugs”
  - need to say which (they know it is inflamed)

- Do not say C/W Crohn’s in
  - Pouch biopsies
  - Diverted bowel
  - Upper GI biopsies in patients with “hot” colitis