Colonoscopic Findings

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Objectives

• Differentiate colonoscopic findings and their implications for morbidity & mortality
• Review genetics & epidemiology of colon polyps, and their syndromes
• Discuss Inflammatory Bowel Disease; morbidity, mortality, colon cancer risk
• Recognize implications of ischemic colitis
• Recognize miscellaneous colonoscopic finding implications
Agenda

- Ulcerative colitis, case and discussion
- Crohn’s Disease: case and discussion
- Treatment of IBD
- CRC surveillance: case and discussion
- Ischemic colitis: case and discussion
- Miscellaneous conditions

Case #1: Ulcerative Colitis

- 45F, applying for $1M life coverage
- UC since age 25
- Disease involving L side colon
  1-2 exacerbations/year
  current Rx: Asacol (mesalamine)
- well controlled for past 2 years
- screening c/scope every 2 years: N
- No other medical problems
- BP, build N
- Labs: CBC, SMAC N, urine N
UC Long Term Health Concerns

- Flares of Ulcerative Colitis
- Complications of Medications
- Colon Cancer Risk
- Complications of Surgery

Ulcerative Colitis Disease Extent

- Proctitis: 28%
- Left-sided Colitis: 25%
- Extensive Colitis: 47%
- Backwash ileitis: 7%

Left Sided vs Pan Colitis

- Progression to Pan-colitis in 25 yrs: 50%
- Progression to Colectomy at 25 yrs: 40% vs 15%

Copenhagen County: 1979-1996
Langholz, Scan J Gastro 1996
UC Colorectal Cancer Risk

<table>
<thead>
<tr>
<th>Location/Dates</th>
<th>UC cohort</th>
<th># CRC</th>
<th>Annual Crude incidence</th>
<th>Cumulative Risk at 30 yrs</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Florence, ’78-'92</td>
<td>689</td>
<td>10</td>
<td>0.12%</td>
<td>NR</td>
<td>1.79(0.9-3.3)</td>
</tr>
<tr>
<td>Manitoba, ’84-'97</td>
<td>5344</td>
<td>36</td>
<td>0.16</td>
<td>NR</td>
<td>2.75(1.9-4.0)</td>
</tr>
<tr>
<td>Copenhagen, ’62-’87</td>
<td>1160</td>
<td>13</td>
<td>0.06%</td>
<td>2.1%</td>
<td>1.9(1.0-3.4)</td>
</tr>
<tr>
<td>Veszprem, ’74-'04</td>
<td>723</td>
<td>13</td>
<td>0.15%</td>
<td>7.5%</td>
<td>NR</td>
</tr>
<tr>
<td>Olmsted, MN, ’40-’01</td>
<td>378</td>
<td>378</td>
<td>0.1%</td>
<td>2.0%</td>
<td>1.1(0.4-2.4)</td>
</tr>
<tr>
<td>Kaiser-CA, ’98-’10</td>
<td>10,895</td>
<td>55</td>
<td>76/100,000</td>
<td>NR</td>
<td>1.3-2</td>
</tr>
<tr>
<td>Denmark, ’79-’08</td>
<td>32,911</td>
<td>268</td>
<td></td>
<td></td>
<td>1.07(0.95-1.21)</td>
</tr>
</tbody>
</table>

CRC Risk Modification: Risks

- Duration of IBD
- Extent of IBD
- Primary Sclerosing Cholangitis
- Family Hx of Colorectal Cancer
- **Severity of Chronic Bowel Inflammation**
  - Any data for Mesalamine chemoprevention?
- Age at UC Diagnosis
UC Surveillance: Adequate? Is most invisible?

- Rutter, GIE 2004:
  - 23% (25/110) neoplastic lesions invisible
- Rubin, GIE 2007:
  - 39% (29/75) lesions invisible, 30% ALM, 29% irregular mucosa
- Velayos, ACG 2009:
  - 26% (16/61) LGD invisible, 26% DALM
- Marion, AJG 2008: 25% (3/12) lesions invisible, chromoendoscopy: 17 additional dysplastic lesions

Probability of Finding Cancer

If Colectomy Done Immediately

Bernstein, Lancet 1994
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Case #2: Crohn’s Disease

- 30F, applying for $500,000 life coverage
- Crohn’s colitis diagnosed at age 28
- Hospitalised for acute exacerbation 1 year ago
- Patchy involvement of colon; rectum not involved
- Presently asymptomatic
- Current Rx 5-ASA, prednisone 5mg/d
- No other medical problems
- BP N; build N
- CBC, Blood chemistry profile N
Crohn’s Disease Mortality:

- Small absolute increased risk
- Hazard Ratio 1.52, in a 2007 meta-analysis

Canavan, 2007; Meta-analysis

Effect of Therapy Depends Structural Damage & Progression

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Cumulative Probability of Surgery for Crohn’s Disease

Years
Probability (%)

0
20
40
60
80
100
0 2 5 8 11 14 17 20 ±2 SD

• Approximately 30% have >2 surgeries at 30 yrs


UC vs Crohn’s Colitis: a Difference?

• Diagnosis: patchy vs continuous
  – 10% of the time: Indeterminate Colitis

• Treatment:
  – Mesalazine Differences?

• Outcome:
  – Colorectal Cancer risk? Operative Options?
Crohn’s Colitis
Indeterminate Colitis: Ileal Pouch Anal Anastomosis

<table>
<thead>
<tr>
<th></th>
<th>Pt</th>
<th>IC</th>
<th>Follow-up Yr</th>
<th>IC Failed</th>
<th>UC Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al Mayo Clinic Rochester 2000</td>
<td>1519</td>
<td>82</td>
<td>10</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>1519</td>
<td>82</td>
<td>10</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td>Pishori et al Cleveland Clinic Florida 2004</td>
<td>303</td>
<td>4.3%</td>
<td>4</td>
<td>0%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Koltun et al Lahey Clinic 1991</td>
<td>253</td>
<td>18</td>
<td>28%</td>
<td>0.4%</td>
<td></td>
</tr>
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- 30F, applying for $500,000 life coverage
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- BP N; build N
- CBC, Blood chemistry profile N
Current treatments UC and CD

Therapy Options

– Mesalamine/5-aminosalicylates
– Azathioprime/6MP, Methotrexate
– Biologics
– Clinical Trial
– Surgery
Therapy: Overview

- Ulcerative colitis
  - Active disease
    - mesalamine
  - Maintenance
- Crohn’s disease
  - Active disease:
    - “step-up” vs early combination therapy
  - Maintenance

UC: Historic Outcomes of Initial Steroids

@1 month:
- Complete Response: 54%
- Partial response: 32%
- No Response: 14%

@1 year:
- Prolonged Response: 46%
- Steroid Dependent or Surgery: 54%

Faubion, Gastroenterology 2001
Therapy: Overview

• Ulcerative colitis
  – Active disease
    • Mesalamine (topical and/or oral) (50%)
    • Steroids
    • Biologics and/or immunosuppressant
  – Maintenance
    • Mesalamine
    • Immunosuppressants, Biologics

SUCCESS
Clinical Remission Without Corticosteroids at Week 16 in CUC

Primary Endpoint

Proportion of Patients (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>24% (18/76)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>22% (17/77)</td>
<td>p=0.009</td>
</tr>
<tr>
<td>IFX + AZA</td>
<td>40% (31/78)</td>
<td>p=0.022</td>
</tr>
</tbody>
</table>

Panaccione R, DDW 2011.
Therapy: Overview

- Crohn’s disease
  - Active disease
    - Steroids (prednisone, budesonide)
    - Biologics and/or immunosuppressant
  - Maintenance
    - Immunosuppressants, Biologics

Early Combined Infliximab + Azathioprine Versus Conventional Therapy in Active Early Crohn’s Disease

D’Haens, Lancet 2008
SONIC
Clinical Remission Without Corticosteroids at Week 26 in CD

Primary Endpoint

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>52/170 (30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>75/169 (45)</td>
<td>0.009</td>
</tr>
<tr>
<td>IFX+ AZA</td>
<td>96/169 (57)</td>
<td>0.022</td>
</tr>
</tbody>
</table>


SONIC
Mucosal Healing at Week 26 in CD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Patients (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + placebo</td>
<td>18/109 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFX + placebo</td>
<td>28/93 (30)</td>
<td>0.023</td>
</tr>
<tr>
<td>IFX+ AZA</td>
<td>47/107 (44)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

Side-effects of anti-TNF Therapy

- Headache, nausea
- Eczema/Psoriasis
- Infection
- Hypersensitivity
- Infusion/Injection Reactions
- Malignancy
- Hepatotoxicity
- Demyelinating Disorders
- Autoimmunity

Meta-Analysis of Mortality in 5356 Patients with Crohn’s Disease in 21 Studies of Anti-TNF Therapy

Peyrin-Biroulet L. Clin Gastroenterol Hepatol 2008
Meta-Analysis of Malignancy in 5356 Patients with Crohn’s Disease in 21 Studies of Anti-TNF Therapy

Peyrin-Biroulet L. Clin Gastroenterol Hepatol 2008

Meta-Analysis of Serious Infection in 5356 Patients with Crohn’s Disease in 21 Studies of Anti-TNF Therapy

Peyrin-Biroulet L. Clin Gastroenterol Hepatol 2008
Natalizumab: Progressive Multifocal Leukoencephalopathy

- 3 cases of PML
- 2 years of combined natalizumab/beta-interferon therapy – one fatality
- FDA review: voluntary suspension of the program 2/05
- Reinstated for MS '06
- Approved for Crohn's '08

Van Assche G et al. NEJM 2005; Langer-Gould A et al. NEJM 2005
Kleinschmidt-DeMasters and Tyler NEJM 2005

Main Side Effects of Azathioprine

- Pancreatitis
- Drug Fever
- Liver Inflammation
- Bone Marrow Suppression
- Serious infections
- Lymphoma
Prednisone

Acne
Facial Swelling
Osteoporosis
Diabetes
Glaucoma
Infection
Anxiety/Agitation

Highest Risk of Serious Infections

Corticosteroids
Narcotics

TREAT registry
Lymphoma Incidence by Age:
- 20-24: 2.4/100,000
- 35-39: 7.3/100,000
- 40-44: 10.5/100,000 = 1/10,000
- 65-70: 64/100,000

SEER, 2000-08

• Meta-analysis of 6 studies examining risk of lymphoma among IBD patients:
  - RR for lymphoma of 4.18
    • 3891 patients: 11 lymphomas (2 HD)
    • Duration of Rx: 12.5m - 4.4 yrs.
    • NNT associated with 1 additional lymphoma per year:
      - 4357 (for 20-29 year olds) to 355 (for 70-79 year olds)

Adjusted Hazard Ratios for Lymphoma

• Thiopurines***
  – Continuing: 6.86*
  – Discontinued 1.44 (NS)
  – Never (NS)
• Thiopurine vs all other pts: 5.26**

* p< .0001, **p< .0002
***compared to general pop

Risks of Combination Therapy

- Opportunistic Infections on Steroids
- SONIC data at week 54:
  - Similar Risk mono vs combination
- Retrospective Series:
  - Rare Hepatosplenic T cell lymphoma
Surgery for UC: Long Term risks?

- Pouch Failure (8%)
- Chronic Pouchitis (up to 50%)
- Crohn’s Disease: (6%)
- Overall, well tolerated procedure

Pouchitis: Long Term Risks

- Chronic Pouchitis (50%)
- Dysplasia or Cancer of Rectal Cuff (Rare)
- Differential Diagnosis of Crohn’s Disease
  - Fistulas
  - Pre-Pouch ileitis
  - Pouch Failure
Case #3: CRC Screening

- M 51 years applying for $750,000 life coverage
- FH:
  - Father: CRC at age 65, alive age 80
  - Brother: CRC age 48
  - Sister: cancer of endometrium age 52
- Mild hypertension x 10 years, Rx ACE inhibitor
- Otherwise in good health
- BP, build are N
- screening colonoscopy at age 50 was N

Screening Colonoscopy Guidelines
Lifetime Risk of Colon Cancer

- General: 5%
- Personal History of Dysplastic Polyp: 15%
- HNPCC mutation: 70-80%
- Familial Polyposis Syndrome: >95%

Etiology of Hereditary CRC

- Sporadic (65%-85%)
- Familial (10%-20%)
- Hereditary nonpolyposis colorectal cancer (HNPCC) (5%)
- Familial adenomatous polyposis (1%)
- Rare CRC syndromes (<0.1%)

Modified from Burt RW et al. Prevention and Early Detection of CRC, 1996
When to Suspect Familial Syndrome?

Classic Features of FAP

- Estimated penetrance for cancer and adenomas is greater than 90%
- Risk of extracolonic tumors (ampullary, desmoid, osteoma, thyroid, brain, other)
- Majority due to germline APC mutations
- Treatment: Colectomy, with follow-up upper gut surveillance
HNPCC (Lynch Syndrome)

- Tumor in proximal colon predominates
- Often Early age at CRC diagnosis (~45 years)
- Multiple primary cancers
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, sebaceous skin tumors, small bowel, bile ducts
- Results from failure in Mis-Match Repair Genes
  - MSH2, MLH1 are most common mutations
  - Leads to Microsatellite Instability

Amsterdam Criteria

1. 3 or more relatives with CRC
2. One a first-degree relative of the other two
3. Two or more generations
4. One CRC by age 50
5. FAP excluded

Revised Bethesda Guidelines

- Colorectal cancer at age < 50 yrs
- Synchronous or metachronous colorectal or HNPCC-associated tumor
- CRC with 1 or more FDR with CRC or other HNPCC tumor, 1 less than age 50 yrs
- CRC with 3 or more relatives with CRC or other HNPCC tumor at any age

Umar et al JNCI 2004 96:261

Case #3: CRC Screening

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- Mild hypertension x 10 years, Rx ACE inhibitor
- Otherwise in good health
- BP, build are N
- screening colonoscopy at age 50 was N
Case #4: Ischemic Colitis

66F applying for $1M life coverage
DM2 for 15 years, Rx: metformin and HS insulin
HBP for 8 years, uncomplicated, Rx ACEi
2009: Hospital admission x3d re abdominal pain, hematochezia, spontaneous resolution
colonoscopy: ‘focal areas of ischemic colitis’ in sigmoid
BMI 31, BP 140/88, PX is N
Labs: A/C glucose 7, A1C 7.1, MA+, remainder N

Ischemic Colitis

• Predominantly > age 65
• Abdominal pain; BRBPR
• 15% develop gangrene
• 85% develop transient ischemia
  – resolves without sequelae
  – minority develop chronic colitis, +/- stricture
Ischemic ulcer

Necrosis of Colonic Wall

Edematous Folds

Ischemic Ulcer

Arterial circulation to the large bowel

10%

25%

60%

SMA: Superior mesenteric artery, SMA: Superior mesenteric artery
Mechanism of colonic injury

- Sudden temporary reduction in blood flow
- Anatomic changes in mesenteric vessels
  - Microvascular disease
  - Vasospasm
- In majority cases no occluding lesion is seen on angiography
- Microvascular plexus of colon relatively poorly developed; wall of colon is relatively thick

Ischemic Colitis: settings

- Major vascular surgery
- Myocardial infarction
- Hypertension, hypercholesterolemia, DM, CAD
- Drugs
- Unusual causes
  - Long distance running
  - Spontaneous (young adults)
  - Long airplane flight
  - Infection (CMV, E Coli 0157:H7)
Ischemic colitis: mortality

- 313 hospitalised cases, f/up 4 months
- R colonic disease has worse outcome
- Surgery predicted mortality
- L colonic disease better outcome

Bradnt; AM J Gastroen, 2010

Angiodysplasia

- >60
- Acquired, sporadic, 0.8% all c/scopes
- Chance finding on endoscopy
- Commoner with ESRD and VWD
- Associated with aortic stenosis
- Dilated, thin-walled submucosal veins
  - ? Due to venous obstruction
- Colon: R side predominates
- No Rx if found on screening colonoscopy
  - Risk of bleeding is unclear
**Diverticular Colitis**

- >50
- Segmental, distal colon, in area of diverticular disease
- Spares rectum
- Pathogenesis unknown
- Mild erythema to frank UC-type colitis
- Involves inter-diverticular area
- Rx: antibiotics, mesalamine, prednisone
  - Resolution/relapse
  - May suggest more complicated DD
  - May evolve into IBD

**Microscopic Colitis**

- Collagenous colitis
- Lymphocytic colitis
**Microscopic colitis**

- Watery diarrhea, abdo pain
- Onset in middle-age
- Uncommon- 5/100,000
- Cause unknown
- N colonoscopy or mild erythma, edema
- Diagnosed on biopsy
  - Inflammatory infiltrate
- Rx: anti-diarrheals, budesonide, sulfasalazine

**Collagenous colitis**

- Band of sub-epithelial collagen
- ? Underlying disorder of collagen
- NSAIDS?
- Other drugs: statins, omerozole
Lymphocytic Colitis

Mononuclear infiltrate in epithelium and in lamina propria

Microscopic colitis: Natural History

• Cessation of diarrhea in 70%; 30% relapse
• Lymphocytic colitis more favourable course
• Surgery rarely required
• No increased risk of CRC
• Normal mortality
Questions?