Differential Diagnosis of IBD and Microscopic Colitis

Mark T. Osterman, MD MSCE
Assistant Professor of Medicine
University of Pennsylvania

Question: Which of the following is/are seen in CD but not UC?
1. Rectal sparing
2. Skip lesions
3. Noncaseating granulomas
4. Gastritis and duodenitis
5. All of the above

ABCs of IBD and Microscopic Colitis

UC Overview
- Confined to colon
- Begins in rectum, extends proximally in continuous fashion
- Confined to mucosa and submucosa
- Cryptitis/crypt abscesses
- Lamina propria expansion with acute and chronic inflammatory cells
- Crypt architectural distortion

UC Pathology

UC Endoscopy
**CD Overview**

- Any segment of GI tract, mouth-anus
- Rectal sparing
- Discontinuous (“skip lesions”)  
  - Perianal: skin tags, fissures, fistulae
- Transmural inflammation, complications:
  - Stricture, perforation, fistula, abscess
- Non-caseating granulomas
- Chronic inflammatory infiltrate
- Crypt architectural distortion

**CD Pathology: Granuloma**

---

**CD Endoscopy**

---

**Microscopic Colitis Overview**

- Collagenous and lymphocytic colitis
- Confined to colon
- Transverse/proximal colon affected most
- Epithelial injury: flat, mucin depletion
- Increased intraepithelial lymphocytes
- Lamina propria expansion with plasma cells/lymphocytes ± eosinophils (CC)
- Subepithelial collagen band >10 µm (CC)
- Relative crypt architectural preservation

---

**Microscopic Colitis Pathology**

---

**Defining UC and CD: Things We See …**

**But Don’t Always Know What to do with**
**Does Discontinuous Disease = CD?**

- Rectal sparing (relative, absolute)
- General patchiness
- Periappendiceal / cecal patch

**Rectal Sparing Can Occur in Untreated UC**

- **Pediatrics**
  - Histo: relative 30% vs. 3% (adults), absolute 3% vs. 0%¹
- **PSC-UC**
  - Endo: 13% initial, 30% any time (peds)²
  - Endo or histo: any time, 52% vs. 6% (UC)³
  - Histo: any time, 28% vs. 25% (UC)⁴

¹Glickman JN et al, Am J Surg Pathol 2004
²Lofus EV Jr et al, Gut 2010
³Fauzi WN et al, J Pediatr Gastroenterol Nutr 2001

**Rectal Sparing Can Occur in Untreated UC**

- Fulminant colitis
  - Relative >> absolute rectal sparing (dominant proximal colon ulceration)¹ ²
- Adults
  - Histo: 12% of biopsies normal after treatment with placebo enemas³

¹Odze RD, J Clin Gastroenterol 2004
²Geboes K et al, Inflamm Bowel Dis 2008

**General Patchiness Can Occur in Untreated UC**

- **Pediatrics**
  - Histo: 42% (5/12) with either mild patchy inflammation or normal

**Treated UC**

<table>
<thead>
<tr>
<th>Author Yr</th>
<th>N</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odze '93¹</td>
<td>11</td>
<td>Rectal sparing: histo 36%</td>
</tr>
<tr>
<td>Bernstein '94²</td>
<td>39</td>
<td>Rectal sparing: endo 13%, histo 15% (absolute 5%) Patchiness: endo 44%, histo 33%, both 23%</td>
</tr>
<tr>
<td>Levine '96¹</td>
<td>24</td>
<td>Rectal sparing: histo 46% (absolute 8%)</td>
</tr>
<tr>
<td>Kleer '98⁴</td>
<td>41</td>
<td>Rectal sparing: histo 34% Patchiness: endo 59%, histo 54%</td>
</tr>
<tr>
<td>Kim '99⁵</td>
<td>32</td>
<td>Rectal sparing: endo 47%, histo 31%, both 6% Patchiness: endo 19%, histo 31%, both 13%</td>
</tr>
<tr>
<td>Joo '05⁶</td>
<td>56</td>
<td>Rectal sparing: endo 32%, histo 30% (absolute 5%) Patchiness: endo 30%, histo 25% (absolute 4%)</td>
</tr>
</tbody>
</table>

¹Odze RD et al, Am J Surg Pathol 1993
⁴Ladefoged K et al, Scand J Gastroenterol 2005
⁵Kim B et al, Am J Gastroenterol 1999

**Periappendiceal / Cecal Patch**

- 0-86% of UC colectomy specimens¹
- Prospective endoscopic studies

**Conflicting prognostic data**

<table>
<thead>
<tr>
<th>Author Yr</th>
<th>% PAP</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Haens ’97²</td>
<td>75 (15/20)</td>
<td></td>
</tr>
<tr>
<td>Yang ’99³</td>
<td>26 (24/94)</td>
<td>23% in treated, 32% in untreated</td>
</tr>
<tr>
<td>Matsumoto ’02⁴</td>
<td>58 (23/40)</td>
<td>Higher histo grade in ascending in PAP+</td>
</tr>
<tr>
<td>Ladeoglu ’05⁵</td>
<td>27 (20/75)</td>
<td>20% of these had histo grade = 0</td>
</tr>
<tr>
<td>Byeon ’05⁶</td>
<td>52 (48/94)</td>
<td>∆PAP status: 43% in PAP+, 29% in PAP-</td>
</tr>
</tbody>
</table>

¹Rubin DT et al, Dig Dis Sci 2010
²D’Haens G et al, Am J Gastroenterol 1997
³Yang S-K et al, Gastrointest Endosc 1999
⁴Matsumoto T et al, Gastrointest Endosc 2002
⁵Ladeoglu K et al, Scand J Gastroenterol 2005
⁶Byeon J-S et al, Inflamm Bowel Dis 2005
Does Backwash Ileitis = CD?

- Backwash or 1° ileal involvement?\(^1\)
- 5-10 cm of ileal involvement
- Erythema/edema ± superficial ulceration
- ICV without ulceration/stenosis
- Mild patchy neutrophilic inflam in lamina propria, focal cryptitis/crypt abscesses\(^2\)
- No granulomas, transmural lymphoid aggregates, fissuring ulcers\(^2\)
- Smooth/tubular appearance on radiology

\(^1\)Riddell RH, in: Kirsner J (ed), Inflammatory Bowel Disease 2000
\(^2\)Haskell H et al, Am J Surg Pathol 2005

Do Granulomas = CD?

- Granulomas in UC\(^1\)
  - Associated with ruptured crypts or extravasated mucin
  - Neutrophils, lymphocytes, multinucleated giant cells, foamy macrophages
- Granulomas in CD\(^1,2\)
  - 15-82\% of surgical, 3-68\% of endoscopic
  - Non-caseating, epithelioid
  - Not associated with ruptured crypts

\(^1\)Yantiss RK et al, Histopathology 2006
\(^2\)Hamosh D et al, Gastroenterol Clin Biol 1999

Does Transmural Inflammation = CD?

- Fulminant UC
  - Often involves >50\% mucosal surface, leading to extensive fissuring ulcers\(^1\)
  - Transmural lymphoid aggregates under areas of severe ulceration\(^2,3\)
  - Toxic megacolon: serosal inflammation\(^4\)
- CD: transmural lymphoid aggregates under intact mucosa

\(^1\)Yantiss RK et al, Am J Surg Pathol 2006
\(^2\)Gamlich T et al, Colorectal Dis 2003
\(^3\)Price AB, J Clin Pathol 1978
\(^4\)Yantiss RK et al, Histopathology 2006

Does Superficial Inflammation = UC?

- CD colitis
  - Transmural lymphoid aggregates more common in ileum than colon\(^1\)
  - Less transmural complications than CD in other areas\(^1\)
  - Can be superficial/continuous like UC\(^2\)
  - Nongranumatous milder course than granulomatous CD colitis\(^3\)

\(^1\)Yantiss RK et al, Histopathology 2006
\(^2\)Haarpaz N et al, Mod Pathol 2001
\(^3\)Morpurgo E et al, Dis Colon Rectum 2003

Do Aphthous Ulcers = CD?

- Common in CD, especially in terminal ileum and proximal colon\(^1\)
- Can be found in 17\% (11/65) of UC colectomy specimens\(^2\)

\(^1\)Tacla M, Arq Gastroenterol 1990
\(^2\)Yantiss RK et al, Histopathology 2006
Does Gastritis = CD?

- EGD/biopsy for work-up of pediatric IBD
  - UGI granulomas in 12-28% of IBD pts
- H. pylori
  - More common in non-IBD (41% vs. 27%)³
  - Gastritis rare in general population⁴
- Endoscopic changes⁵-⁸
  - UC 33-66%, CD 51-78%
  - Erythema, edema, erosions, aphthous ulcers, nodularity, polyps seen in both

¹IBD Working Group of ESPGHAN, J Pediatr Gastroenterol Nutr 2005
²IBD Working Group of NASPGHAN, J Pediatr Gastroenterol Nutr 2007
³Luther J et al, Inflamm Bowel Dis 2010
⁴Genta RM et al, Gastroenterology 2008
⁵Ruuska T et al, J Pediatr Gastroenterol Nutr 1994
⁶Abdullah BA et al, J Pediatr Gastroenterol Nutr 2002
⁷Hori K et al, J Gastroenterol 2008
⁸Kovacs M et al, J Crohns Colitis 2012

Does Gastritis = CD?

- Histological changes¹-⁷
  - UC 19-82%, CD 33-92%
  - Acute + chronic, diffuse + focal, crypt abscesses, lymphoid aggregates, ulceration seen in both

¹Tobin JM et al, J Pediatr Gastroenterol Nutr 2001
²Sharif F et al, Am J Gastroenterol 2002
³Abdullah BA et al, J Pediatr Gastroenterol Nutr 2002
⁴Hori K et al, J Gastroenterol 2008
⁵Sonnenberg A et al, Inflamm Bowel Dis 2011
⁶Hummel TZ et al, J Pediatr Gastroenterol Nutr 2002
⁷Kovacs M et al, J Crohns Colitis 2012

Focally Enhanced Gastritis

- Microscopic lesion
- >1 foveolum/gland surrounded/infiltrated by lymphocytes/monocytes/plasma cells + neutrophils in background of normal

<table>
<thead>
<tr>
<th>Author Yr</th>
<th>N</th>
<th>CD</th>
<th>UC</th>
<th>Con</th>
<th>Spec, PPV for CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parente '00²</td>
<td>361</td>
<td>43%</td>
<td>12%</td>
<td>19%</td>
<td>Spec 84%, PPV 71%</td>
</tr>
<tr>
<td>Sharif '02³</td>
<td>238</td>
<td>65%</td>
<td>21%</td>
<td>2%</td>
<td>Spec 87%, PPV 79%</td>
</tr>
<tr>
<td>Hummel '12⁴</td>
<td>172</td>
<td>69%</td>
<td>24%</td>
<td>7%</td>
<td>Spec 87%, PPV 79%</td>
</tr>
</tbody>
</table>

¹Oberhuber G et al, Gastroenterology 1997
²Parente F et al, Am J Gastroenterol 2000
³Sharif F et al, Am J Gastroenterol 2002
⁴Hummel TZ et al, J Pediatr Gastroenterol Nutr 2012

CE in Suspected CD

- Yield in meta-analysis¹
  - vs. SBR (N=8): 52% vs. 16% (p<0.0001)
  - vs. CTE (N=3): 68% vs. 21% (p<0.00001)
  - vs. MRE (N=3): 55% vs. 45% (p=NS)
  - But in many, “erosions” = CD
- Using consensus gold standard CD Dx²
  - Sens: CE 83%, SBFT 50% (p=NS), CTE 67% (p=NS)

¹Oberhuber G et al, Gastroenterology 1997
²Parente F et al, Am J Gastroenterol 2000
³Goldstein JL et al, Clin Gastroenterol Hepatol 2005
⁴Goldstein NS, Am J Clin Pathol 2006
⁵Maiden L et al, Gastroenterology 2005
⁶Sidhu R et al, Clin Gastroenterol Hepatol 2010

Does Duodenitis = CD?

- Endoscopic changes¹-⁴
  - UC 13-23%, CD 27-41%
  - Erythema, edema, erosions, ulcers (also aphthous), granular, friable seen in both
- Histological changes¹-⁷
  - UC 3-29%, CD 26-48%
  - Acute + chronic, villous atrophy, increased IELs, ulceration seen in both

¹Ruuska T et al, J Pediatr Gastroenterol Nutr 1994
²Abdullah BA et al, J Pediatr Gastroenterol Nutr 2002
³Hori K et al, J Gastroenterol 2008
⁴Kovacs M et al, J Crohns Colitis 2012
⁵Sonnenberg A et al, Inflamm Bowel Dis 2011
⁶Hummel TZ et al, J Pediatr Gastroenterol Nutr 2012
⁷Kovacs M et al, J Crohns Colitis 2012

But, Yield ≠ Diagnosis

- Spec: CE 53%, SBFT 100%, CTE 100%¹
  - 14% healthy abnl CE (mucosal breaks)²
  - Isolated ileitis on ileoscopy
    • Endo/histo similar to CD (chronic)³,⁴
    • ASx: 0% (0/14) CD after med 5.3y³
    • Min Sx: 29% (8/28) CD after mean 3.6y⁴
    • NSAID use: 55-68% abnl CE after 2wk²,⁵
      - Undisclosed NSAID use⁶

¹Solem CA et al, Gastrointest Endosc 2008
²Goldstein JL et al, Clin Gastroenterol Hepatol 2005
³Goldstein NS, Am J Clin Pathol 2006
⁵Maiden L et al, Gastroenterology 2005
⁶Sidhu R et al, Clin Gastroenterol Hepatol 2010
CE in Suspected CD
- Problems with low spec (high false pos)
  - Unnecessary immunosuppressives
  - Undesirable psychological effects
- Can we improve spec for suspected CD?
  - Need for standardized grading scale
  - >3 ulcers: sens = 77%, spec = 89%, PPV = 50%, NPV = 96%
  - Stop NSAIDs prior to CE
- CE used only selectively in suspected CD

CE in IBD-U
- Small studies show potential promise
  - High NPV: negative result reassuring for lack of SB disease

Does Diffuse Enteritis = CD?
- Diffuse enteritis, often after UC colectomy
  - 42 cases: 16 in US/Europe, 26 in Japan
  - Duodenum + jejunum/ileum/stomach
  - Most after colectomy, some within 1mo
  - 81% pancolitis, M:F 2:1, age 3-61y (µ 31)
  - Diffuse ulceration, patchy white exudate
  - Diffuse superficial acute/chronic inflam, crypt distortion, no skipping/granuloma
  - Rx: steroids + 5-ASA/AZA/CsA, ?relapse

Do Anal Fissures = CD?
- Paucity of data in UC
- General population
  - Midline, single, painful
- CD
  - Eccentric (9-20%),1 multiple (14-33%),1 painless unless ulcer/fistula/abscess
  - Prevalence: 21-35% (referral-based),1 11% (population-based)2
  - Often associated with skin tags

Do Perianal Skin Tags = CD?
- UC: up to 25% may have Type 2 skin tags
- CD
  - Type 1: large edematous hard cyanotic, pain as arise from healed fissure/ulcer
  - Type 2 ("elephant ear"): soft, flat, broad/narrow, various size, smooth, painless
  - Prevalence: 24-47% (referral-based),1,3,4 20% (population-based)5
  - Distribution (Type 2): 47% in colitis, 16% in ileocolitis, 37% in ileitis

Clinical Findings of IBD-U
- Absolute rectal sparing (endo & histo)
- Backwash ileitis: >10 cm, aphthous ulcers
- Microscopic ileitis in L-sided UC
- Severe focal gastritis
- Anal fissures / skin tags
- Large oral aphthous ulcers
- Growth failure
- Term “IC” only for colectomy specimen

*Tukey M et al, Am J Gastroenterol 2009
1Tukey M et al, Inflamm Bowel Dis 2009
2Mehdizadeh S et al, Endoscopy 2008
3Lopes S et al, Inflamm Bowel Dis 2010
4Tukey M et al, Am J Gastroenterol 2009
1Maunoury V et al, Inflamm Bowel Dis 2007
1Tukey M et al, Inflamm Bowel Dis 2007
2Mehdizadeh S et al, Endoscopy 2008
3Lopes S et al, Inflamm Bowel Dis 2010
1Maunoury V et al, Inflamm Bowel Dis 2007
2Mehdizadeh S et al, Endoscopy 2008
3Lopes S et al, Inflamm Bowel Dis 2010
1Maunoury V et al, Inflamm Bowel Dis 2007
2Mehdizadeh S et al, Endoscopy 2008
3Lopes S et al, Inflamm Bowel Dis 2010
1Maunoury V et al, Inflamm Bowel Dis 2007
2Mehdizadeh S et al, Endoscopy 2008
3Lopes S et al, Inflamm Bowel Dis 2010
1Maunoury V et al, Inflamm Bowel Dis 2007
2Mehdizadeh S et al, Endoscopy 2008
3Lopes S et al, Inflamm Bowel Dis 2010
Any Other Ways to Define UC and CD?

Predicting Dx Change: UC to CD

- 21 cases, 52 UC and 56 CD controls
- Med time to change in Dx = 4y
- Cases had greater disease extent at initial colonoscopy than UC controls
  - Pancolitis: 48% vs. 17% (p=0.008)
- Multivariable predictors at presentation
  - Non-bloody diarrhea (OR 11 [2.0-83])
  - Wt loss (OR 6.3 [1.7-25])
- Serologies did not add to prediction

Prideaux L et al, Inflamm Bowel Dis 2012

Serologies: Prevalence

<table>
<thead>
<tr>
<th>Antibody</th>
<th>CD</th>
<th>UC</th>
<th>Other GI</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA</td>
<td>6-38</td>
<td>41-73</td>
<td>8</td>
<td>0-8</td>
</tr>
<tr>
<td>ASCA</td>
<td>29-69</td>
<td>0-29</td>
<td>0-23</td>
<td>0-16</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>24-55</td>
<td>2-24</td>
<td>5</td>
<td>5-20</td>
</tr>
<tr>
<td>Anti-CBir1</td>
<td>50-56</td>
<td>6</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Anti-I2</td>
<td>38-60</td>
<td>42</td>
<td>NR</td>
<td>15</td>
</tr>
<tr>
<td>ACCA</td>
<td>8-25</td>
<td>5-7</td>
<td>3-20</td>
<td>0.5-12</td>
</tr>
<tr>
<td>ALCA</td>
<td>19-27</td>
<td>3-8</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>AMCA</td>
<td>12-28</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Anti-C</td>
<td>10-25</td>
<td>2-11</td>
<td>11</td>
<td>2-12</td>
</tr>
<tr>
<td>Anti-L</td>
<td>18-26</td>
<td>3-7</td>
<td>23</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Serologies: IBD vs. Healthy

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA</td>
<td>17</td>
<td>98</td>
<td>98</td>
<td>16</td>
</tr>
<tr>
<td>ASCA</td>
<td>31-45</td>
<td>90-100</td>
<td>97-100</td>
<td>14-23</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>27</td>
<td>94</td>
<td>96</td>
<td>17</td>
</tr>
<tr>
<td>ACCA</td>
<td>6-19</td>
<td>86-97</td>
<td>89-95</td>
<td>11-15</td>
</tr>
<tr>
<td>ALCA</td>
<td>15</td>
<td>94-99</td>
<td>96-98</td>
<td>11-16</td>
</tr>
<tr>
<td>AMCA</td>
<td>9-26</td>
<td>92-97</td>
<td>95-96</td>
<td>11-17</td>
</tr>
<tr>
<td>Anti-C</td>
<td>7</td>
<td>98</td>
<td>97</td>
<td>11</td>
</tr>
<tr>
<td>Anti-L</td>
<td>12</td>
<td>99</td>
<td>99</td>
<td>11</td>
</tr>
</tbody>
</table>

Serologies: IBD vs. Other GI

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA</td>
<td>41-45</td>
<td>91-98</td>
<td>95-100</td>
<td>14-29</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>27</td>
<td>75</td>
<td>92</td>
<td>9</td>
</tr>
<tr>
<td>ACCA</td>
<td>19-40</td>
<td>84-89</td>
<td>93</td>
<td>9-28</td>
</tr>
<tr>
<td>ALCA</td>
<td>15-20</td>
<td>93-99</td>
<td>92-100</td>
<td>8-24</td>
</tr>
<tr>
<td>AMCA</td>
<td>26</td>
<td>93</td>
<td>98</td>
<td>10</td>
</tr>
</tbody>
</table>
Serologies: All CD vs. UC

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA-</td>
<td>52</td>
<td>91</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>ASCA+</td>
<td>37-72</td>
<td>82-100</td>
<td>87-95</td>
<td>38-68</td>
</tr>
<tr>
<td>ASCA+/pANCA-</td>
<td>52-64</td>
<td>92-94</td>
<td>86-95</td>
<td>62-66</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>29</td>
<td>81</td>
<td>83</td>
<td>25</td>
</tr>
<tr>
<td>ACCA</td>
<td>9-21</td>
<td>84-97</td>
<td>78-87</td>
<td>24-52</td>
</tr>
<tr>
<td>ALCA</td>
<td>15-26</td>
<td>92-96</td>
<td>78-90</td>
<td>25-53</td>
</tr>
<tr>
<td>AMCA</td>
<td>12-28</td>
<td>82-97</td>
<td>65-92</td>
<td>25-52</td>
</tr>
<tr>
<td>Anti-C</td>
<td>10-25</td>
<td>90-98</td>
<td>87-88</td>
<td>29-39</td>
</tr>
<tr>
<td>Anti-L</td>
<td>18-26</td>
<td>93-97</td>
<td>90-91</td>
<td>30-40</td>
</tr>
</tbody>
</table>

Prideaux L et al, Inflamm Bowel Dis 2012

Serologies: Colonic CD vs. UC

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA+</td>
<td>25-44</td>
<td>86-95</td>
<td>76-83</td>
<td>56-61</td>
</tr>
<tr>
<td>ASCA+/pANCA-</td>
<td>30-38</td>
<td>91-92</td>
<td>77-82</td>
<td>56-60</td>
</tr>
</tbody>
</table>

Prideaux L et al, Inflamm Bowel Dis 2012

Serologies: IBD-U

- ASCA / pANCA
  - 31/97 (32%) IBD-U patients reclassified after mean 6y: 17 CD, 14 UC
  - ASCA+/pANCA- predicted CD in 80%
  - ASCA-/pANCA+ predicted UC in 64%
  - 48% of patients were ASCA-/pANCA-

Joosens S et al, Gastroenterology 2002

Genetics

- 110/163 IBD loci a/w both CD and UC
- 43 of the other 53 show same direction of effect in the non-associated disease
- Suggests that most biological mechanisms involved in 1 disease have a role in other
- 113/163 (69%) shared with other diseases
- IBD loci markedly enriched in psoriasis and ankylosing spondylitis
- Overlap with 1° immunodeficiencies and mycobacterial infections

Jostins L et al, Nature 2012

Question: Which of the following is/are seen in CD but not UC?

1. Rectal sparing
2. Skip lesions
3. Noncaseating granulomas
4. Gastritis and duodenitis
5. All of the above