

MECHANISMS OF HUMAN DISEASE: LABORATORY SESSION
GASTROINTESTINAL (GI) PATHOLOGY LAB #2
Wednesday, January 11, 2012

Faculty Copy

GOAL:

1. Describe the basis morphologic and pathophysiologic changes in various diseases of the gastrointestinal tract.
2. Define (Describe) and correlate symptoms and signs of a disease with the structural changes of the diseased organs.

OBJECTIVE:

1. Review the normal gross and histologic anatomy of the gastrointestinal tract.
2. Describe the morphologic characteristics of pseudomembranous colitis.
3. Describe the morphologic characteristics of idiopathic inflammatory bowel disease.
4. Describe the morphologic characteristics of neoplastic colon polyps.
5. Describe the morphologic characteristics of colonic adenocarcinoma.

CASE 1

CHIEF COMPLAINT: Diarrhea.

HISTORY: A 47-year-old woman undergoes an elective hysterectomy for menorrhagia and leiomyomata. She receives several doses of cefazolin for surgical prophylaxis. Two days after surgery she develops profuse, green-tinged diarrhea.

PHYSICAL EXAMINATION:

Vitals: BP 135/90, HR 95/min, RR 18/min, T 99°F

Patient is alert and oriented. Her abdomen is soft and non-tender with a surgical incision that has no associated erythema or discharge. She has hyperactive bowel sounds.

1. What is the main clinical problem?

Diarrhea, post-surgery

2. What is your differential diagnosis of clinical problem?

Pseudomembranous colitis (antibiotic associated colitis), other acute infectious diarrhea, antibiotic side effect

3. What lab test(s) should be ordered?

Stool for C. difficile toxin

ELISA-based assays for C. difficile are often based only upon detection of toxin A, the enterotoxin. The LUMC lab ELISA detects both toxins A and B

4. Identify organ, describe pathologic changes in the virtual microscopy slide.

Colon, sections reveal inflammation of the mucosa. A pseudo-membrane of fibrin, mucous, neutrophils and cellular debris forms a “cap” on the surface of the mucosa. The colonic glands are intact but dilated being filled with mucous which streams through the mouth of the gland to the surface. There is a patchy infiltrate of neutrophils in the submucosa beneath the muscularis mucosa. The mucosa is not ulcerated.

5. What is your diagnosis?

Antibiotic-associated colitis/ Pseudomembranous colitis

6. What is the etiology of this disease?

- **Acute colitis characterized by formation of an adherent exudate (inflammatory pseudomembrane) overlying sites of mucosal injury**
- **Caused by Clostridium difficile**
 - **Rare normal flora**
 - **Colonizes intestinal tract after normal gut flora has been altered by antibiotic therapy**
 - **Major hospital acquired pathogen (spores acquired in hospital)**
- **C. difficile releases two protein exotoxins (toxin A and toxin B) that bind to receptors on intestinal epithelial cells, leading to massive secretion of fluid (diarrhea) and an acute inflammatory infiltrate**

7. What is the therapy for this disease?

- **Stop antibiotics if possible**
- **Metronidazole (oral preferred)**
- **Vancomycin (oral preferred)**

CASE 2

CHIEF COMPLAINT: “I have blood in my stool.”

HISTORY: 33 year-old male has noticed blood in his stool recently. He has crampy left lower abdominal pain associated with frequent bowel movements and tenesmus (ineffective urge to defecate)

PHYSICAL EXAMINATION:

Vital signs: BP 140/85, HR 83, RR 18, T 98°F

Alert and oriented healthy appearing male with left lower quadrant tenderness on palpation of the abdomen. No masses or organomegaly are detected and there is no evidence of external hemorrhoids.

1. What is the main clinical problem?

Bloody diarrhea

2. What is your differential diagnosis of this clinical problem?

Ulcerative colitis

Infectious/bacterial colitis

Crohn disease

Malignancy

3. What laboratory/diagnostic tests are indicated?

Stool culture

– **Result - no bacterial growth**

Colonoscopy

4. Identify the organ/describe pathologic findings in the virtual microscopy slide.

Colon – significant “gross” findings include mucosal friability, mucosal erosions/ulceration (often along long axis of colon), islands of regenerating mucosa “pseudopolyps”, serosal surface normal, wall not thickened

The section of colon reveals chronic inflammation and mucosal ulceration. The lamina propria contains an infiltrate of mononuclear inflammatory cells, many of which are plasma cells. The lamina propria is edematous and contains many congested blood vessels. The normal glandular architecture is distorted by the inflammation and crypt abscesses (collections of neutrophils) are noted. The submucosa is inflamed while the muscularis propria and serosa are not. No pseudomembrane is evident. Chronic changes may occur– architectural disorder, submucosal fibrosis, and gland atrophy.

5. What is your diagnosis?

Ulcerative colitis

6. What are the complications of this disease?

- **Toxic megacolon**
- **10 % patients “backwash ileitis”; appendix may be involved**
- **Dysplasia with possible progression to carcinoma (risk 20 to 30 fold increased if pancolitis present > 10 yrs.)**
- **Fever due to multiple microabscesses and/or endotoxemia may occur secondary to transmural bacteremia.**

- **Extraintestinal manifestations → ankylosing spondylitis, uveitis, migratory polyarthritis, skin lesions (pyoderma gangrenosum), sclerosing cholangitis/pericholangitis; HLA-B27 occurs with increased frequency in patients with IBD and ankylosing spondylitis, HLA-DR2 increased with UC.**

CASE 3

CHIEF COMPLAINT: “I’m having a lot of diarrhea and I feel nauseous and sick to my stomach.”

HISTORY: 19-year-old female college student presents with non-bloody diarrhea, nausea, vomiting and crampy abdominal pain. She has lost 15-20 lbs recently, and has a history of a “touchy stomach” with diarrhea in the past.

PHYSICAL EXAMINATION:

Vitals: BP 130/80, HR 92/min, RR 18/min, T 98°F.

Extremely thin, anxious female with right lower quadrant abdominal pain on palpation. She has no palpable masses or organomegaly.

1. What is the main clinical problem?

Crampy abdominal pain, non-bloody diarrhea

2. What is the differential diagnosis of this clinical problem?

Ulcerative colitis, Crohn Disease, acute bacterial colitis, malignancy

3. Describe the organ/pathologic changes in the virtual microscopy slide.

Small intestine. Sections show chronic inflammation of all layers from mucosa to serosa. There is a large ulcer and fissure which extends to the muscularis propria. The bed of the fissure is composed of granulation tissue. The lamina propria contains a mononuclear inflammatory infiltrate. The submucosa, muscularis propria, and serosa contain aggregates of lymphocytes and epithelioid histiocytes and giant cells (non-caseating granulomas).

4. What is your diagnosis?

Crohn disease

5. What are the complications of this disorder?

- **Fistula/fissure**
- **Fibrosing strictures**
- **Obstruction**
- **Malabsorption**
- **Potential for transformation to cancer (much lower than in UC, 5 to 6 fold increase in long standing cases).**
- **Extraintestinal manifestations: migratory polyarthritis, sacroiliitis, ankylosing spondylitis, erythema nodosum, clubbing of the fingertips; cholangitis may occur but not as strong association as with UC**

- **HLA DR1-/DQw5 associated with 27% patients with Crohn dz.**

COMPARE/CONTRAST

U.C.

- **Bloody diarrhea**
- **Continuous colonic/ rectum**
- **Mucosal inflammation
ulcers**
- **Inflammatory pseudopolyps**
- **↑ Risk carcinoma**

CROHN DZ

- **Non-bloody diarrhea**
- **All of GI Tract but spares rectum, skip lesions**
- **Transmural inflammation, linear serpentine**
- **Granulomas**

CASE 4

CHIEF COMPLAINT: “I’m so tired all the time.”

HISTORY: 60-year-old woman with a history of hypertension presents with easy fatigability. She occasionally baby-sits her grandchildren and notes she never had a problem taking care of them in the past, but lately she is completely “worn out” at the end of the day.

PHYSICAL EXAMINATION: Slightly obese female in no apparent distress, who has a soft protuberant abdomen, without masses or organomegaly.

LAB TESTS: WBC 7,200/mm³; Hgb 10.2gm/dl; Hct 30 %; MCV 74; Plt 164,000/mm³

1. What additional tests are indicated?

Evaluation of microcytic anemia

– Results:

- **Iron low, TIBC elevated, % saturation low**
- **Ferritin low**

2. Initial Diagnosis?

Iron deficiency anemia

3. Identify organ and describe pathologic changes.

Colon. The section of tissue is polypoid. Under microscopic examination, the section of colon reveals a polyp arising from the normal colonic mucosa. The polyp is composed of multiple glands, varying in size, shape and orientation. Although some glands are cystically dilated, most are tubular (>75%). The glands are lined by goblet cells and epithelium with elongated cells containing hyperchromatic nuclei that are pseudostratified within the cytoplasm (atypical or “dysplastic” epithelium). There is no invasion of the lamina propria or submucosa. (Compare normal colonic mucosa to adenomatous epithelium).

4. What is your diagnosis?

Tubular adenoma.

CASE 5

CHIEF COMPLAINT: None

HISTORY: 50 year-old businessman is referred for flexible sigmoidoscopy after a physician discovered occult blood in stool during routine screening physical. The remainder of the screening tests are normal.

PHYSICAL EXAMINATION: Alert and oriented male patient. Abdominal exam reveals a scaphoid abdomen, soft and non-tender with no masses or organomegaly.

LAB TESTS: occult blood present in stool, Hgb 14 g/dl

1. What is the main clinical problem?

Unexplained blood in stool

2. What is your differential diagnosis?

Esophageal or peptic ulcer, colonic lesion (polyp), colonic adenocarcinoma

3. Identify organ/describe pathology.

Colon - The lesion is polypoid. A section of the colon reveals a broad based polyp which for the most part forms villi (>50%). In one area, the neoplasm forms tubular glands. Villi are lined by an epithelium which is dysplastic, with cells containing enlarged, hyperchromatic and pseudostratified epithelium.

4. What is your diagnosis?

Villous adenoma

6. What are potential complications of this diagnosis?

Malignant transformation greater than in tubular adenomas; tend to occur in older individuals, often in the rectum or rectosigmoid, but may be located anywhere. They are generally sessile, up to 10 cm in diameter, or cauliflower like. When invasion occurs, there is no stalk or buffer zone as in most tubular adenomas, so that the tumor extends directly into the bowel wall.

Clinico-pathologic Correlation: Colonoscopy Screening Intervals after Colonic Polypectomy:

- **Hyperplastic polyps: 10 years**
 - **Exception: hyperplastic polyposis syndrome**
- **1-2 small (<1cm) tubular adenomas with only low grade dysplasia: 5-10 years**
- **3-10 adenomas, any adenoma >1cm, villous features, high grade dysplasia: 3 years, then 5 years**
- **>10 adenomas: 3 years, consider familial syndrome**
- **Sessile adenomas removed piecemeal: 2-6 months follow-up to verify complete removal. Follow-up after that individualized**
- **Consider more intensive surveillance in patients with possible HNPCC**

CASE 6

CHIEF COMPLAINT: “I’ve been feeling tired lately.”

HISTORY: 60-year-old obese male with ischemic heart disease, has easy fatigability and “palpitations” recently. He does not smoke and drinks alcohol only occasionally.

PHYSICAL EXAMINATION: Alert and oriented male with soft protuberant abdomen which is soft and non-tender. No masses or organomegaly are detected.

LAB TESTS: Hgb 11.9 g/dl Hct 35%, MCV 79

1. What is the main clinical problem?

**Fatigue, palpitations
Microcytic anemia**

2. What is your differential diagnosis?

Fe-deficiency anemia from GI lesion (ulcer, polyp, carcinoma), unstable angina (may be primary problem or secondary to anemia/blood loss), other heart disease (valvular problems).

3. Identify organ/describe pathologic changes in the virtual microscopy slide.

Colon; Sections of the colon show a moderately differentiated adenocarcinoma. The neoplasm forms glands and filiform structures. The carcinoma infiltrates the submucosa but not the deeper layers in this section.

4. What is your diagnosis?

Adenocarcinoma of the colon

5. What are potential complications?

Bleeding, obstruction, metastasis, paraneoplastic syndromes

7. What genes may be involved in this disease process?

Loss of one normal copy of the cancer “suppressor” gate-keeper gene APC and/or loss of DNA caretaker genes (MSH2) occurs early in the adenoma-carcinoma sequence. Mutations of K-ras seem to occur next. Additional mutations or losses of heterozygosity inactivate the tumor suppressor gene p53, losses on chromosome 18q, leading finally to the emergence of carcinoma, in which additional mutations occur (Robbins figure 17-49).