Anal Pathology – Nonneoplastic and some key neoplasms – With A Bit of Backwash into the Rectum

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Disclosure Statement

Dr. Montgomery reports no relevant financial relationships with commercial interests.

Anal Pathology is best categorized as...

- Diseases related to embryologic development
  - i.e. pediatric
- Non-neoplastic/Inflammatory diseases
- Neoplasms

Embryology/ Normal Anatomy

The anal canal forms during the fourth to seventh week of gestation

The superior two thirds of the primitive anal canal is derived from the endoderm

The inferior one third of the anal canal develops from the ectoderm

Embryology and Normal Anatomy

Where these two epithelial derivatives fuse (endoderm and ectoderm) is indicated by the irregular dentate line

The dentate line also indicates the approximate former site of the anal membrane that ruptures in the eighth week of gestation
Anatomy of the Anal Canal

Histology and Endoscopic Appearance

Superior to Dentate Line
Inferior to Dentate Line

Colorectal type mucosa
Prominent Vasculature
Stratified squamous mucosa
No skin appendages

Anal columns (Columns of Morgagni)
Anal sinuses (Sinuses of Morgagni)
Dentate Line and Anal Valves

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Anal Transitional Mucosa

IHC and ultrastructurally different from bladder

Direct transition from colorectal type to squamous type mucosa

Anal Gland

The perianal stroma normally has an extensive lymphatic drainage

Non-Neoplastic and Inflammatory Lesions of the Anal Canal

Anal Fissures and Tears
Hemorrhoids
Fibroepithelial Polyps
Inflammatory Cloacogenic Polyps
Inflammatory Bowel Disease
Suppurative Disease
Hemorrhoids

Traditional view: varicosities of the submucosal veins

Current view: “sagging” or “slippage” of the normal cushions of hemorrhoidal fibrovascular tissue found in the anal canal that serves a protective role during defecation

Slippage exacerbated by strain of defecation and/or increased pelvic pressure

Hemorrhoids-Clinical Features

Wide age range (middle age and older)
No gender differences
Frequent in pregnancy
Most common presentation is painless bleeding or minor pain during defecation
Acute exacerbation of pain may indicate thrombosis or infarction

Organizing Thrombus
-may mimic angiosarcoma or Kaposi’s sarcoma

Hemorrhoids and papillary endothelial hyperplasia
Anal Tags (Fibroepithelial Polyps)

Projections of anal mucosa with associated submucosal tissue that enlarge in response to:
- congestion
- irritation
- infection
- injury

“Sentinel Tag” refers to fibroepithelial polyp at proximal end of an anal fissure or ulcer.

Anal Tags (Fibroepithelial Polyps)

Often submitted to pathologist as hemorrhoid.

Do not contain microscopic evidence of:
- dilated or thick walled vessels
- recent or remote hemorrhage
- organizing thrombi

Identical to acrochordons (fibroepithelial polyp) of the skin.

Pitfall alert – “pagetoid dyskeratosis” (reactive change) on surface of anal tags.
Inflammatory Cloacogenic Polyps

Manifestation of mucosal prolapse syndrome in the anal canal
Mucosal prolapse → local trauma and ischemic injury → inflammation, repair and regenerative changes
Slight female predominance
Occurs at any age; but 80% under 50 years.
Less common in cultures with high dietary fiber content
Typical presentation rectal bleeding of long duration

Typically sessile
May be single or multiple
Usual size 1-2 cm
May mimic tubular adenomas

At low power villiform architecture may resemble villous adenoma

Most common location is anterior wall of anorectal junction
Chronic disorder, requiring conservative approach to manage patient discomfort
Medical therapy includes increase in dietary fiber or topical treatment with human fibrin sealant
Frequently recurs after therapy

Inflammatory Bowel Disease

In *ulcerative colitis*, involvement of the anus is typically of a nonspecific nature and indistinguishable from patients’ without colitis
Histology shows superficial nonspecific inflammation

The anal canal is involved in ~25% of patients with small intestinal disease and 50-80% of those with colonic disease
May be initial presentation of Crohn’s disease in one third of patients
Crohn's Disease of Anus

Reactive squamous epithelium overlying non-caseating granulomatous inflammation with giant cells

Differential Diagnosis of Granulomatous-Like Inflammation of the Anal Canal

Crohns Disease
Tuberculosis (AFB stain)
Syphilis
Sarcoid
Other infections

Clinical Features of Crohn's Disease of the Anal Canal
Induration of the anal skin, multiplicity of lesions, and skin discoloration
Anal fissures, fistulas, ulcers, abscesses, tags and strictures
Fistulas may be in atypical locations and quite far from the anal canal (clue to etiology)

Management of Crohn's Disease of the Anal Canal
Anal lesions poorly responsive to usual medical therapy for intestinal Crohn disease, such as steroids and aminosalicylates
Antibiotics, immunomodulators (Cyclosporin A, azothioprine, etc) useful in managing fistulae
Surgical: drainage of abscesses, fistulotomy, flap or graft repair of fistulae, resection of intestinal disease, proctectomy

Idiopathic Suppurative Disease of the Anal Canal
Anal abscesses and fistulas represent a continuum of anorectal suppurative disease
Believed to result following infection of an anal duct
Acute phase of infection results in abscess
Chronic phase of infection results in fistula
- Anal duct provides the framework for the formation of a fistula from the perianal soft tissues to the anal canal.

Differential Diagnosis of Anal Suppurative Disease

Idiopathic/infectious Causes (most common)
- Foreign body type giant cells to fecal matter may be seen
Crohns Disease
- Look for granulomatous inflammation
Hydradenitis Suppurativa
- Associations are obesity and diabetes
Malignancy

Hydradenitis Suppurativa
Problem: Syphilis

- Rising incidence of primary and secondary syphilis cases in the United States.
- Disproportionally affect men who have sex with men (MSM) population.
  - For example in U.S.A, in 2006, 64% of the reported P&S syphilis cases were among men who have sex with men (MSM).
  - Increases in syphilis in MSM population reported in Chicago, Seattle, San Francisco, Southern California, Miami, New York City
  - Outbreaks are associated with a high rate of HIV co-infection (20-70%)

http://www.cdc.gov/std/syphilis/STDFact-MSM-Syphilis.htm

Problem: Chlamydia

- Proctitis outbreaks reported in parts of U.S.A, Europe (United Kingdom, Sweden, Denmark, Norway, Finland and the Netherlands, Canada, and Australia.
- Mainly associated with lymphogranuloma venereum (LGV) serovar L2 but reports of non-LGV associated serovars (G, D, J) are documented.
- Five European countries reported a total of 503 confirmed LGV cases in 2010. From those with known information on mode of transmission, 98% were diagnosed in MSM.
- In 2010, the United Kingdom reported 2.8 times as many cases as in 2009 (428 and 155 cases, respectively).
Syphilis and Chlamydia Proctitis: Patient Presentation is diverse
• Rectal bleeding
• Anal pain
• Tenesmus
• Anal discharge
• Fever, chills, nausea, vomiting, weight loss
• Pruritus
• Rarely asymptomatic
• Perianal ulceration
• Imaging studies may show a “rectal mass”

Endoscopic findings
• Ulcers (may be large)
• Mass lesion
• Abscess
• Fissures, anal fistulae

Case 1
• 34 y/o HIV + male who presents to ER with rectal pain exacerbated by BMs that started 3 weeks prior to presentation. Pain started w a “burning sensation” and then progressed to the formation of a “mass”. +30 pound weight loss. No rectal bleeding, abdominal pain, pain with urination, or fever. +nausea and vomiting
• Marked tenderness on rectal exam. Rapid HIV test +.
• CT impression sigmoid colitis.

Case 1
• Flex sigmoidoscopy showed mucosal friability and ulceration in the rectum.
Normal rectum

Case 1

Low power appearance: too "blue" for

Crypts may be shortened but overall still look like "test tubes in a rack"

Case 1

RPR on this admission 1:128, FTA-ABS 4+.
Infectious disease physician doubtful of the possibility of "syphilis in the colon". Requested a silver stain.
Case 1

- Patient’s symptoms improved after antibiotic therapy.

Case 2

- 45 year old white female presents with rectal bleeding and anal pain.
- Previously diagnosed with hemorrhoids and then ulcerative colitis (UC).
- Symptoms did not respond to UC treatments.
- Re-presented with worsening bleeding and pain.

Case 2: DDx

- Malignant neoplasm
- Diversion/diverticular associated colitis
- Inflammatory bowel disease
- Infection
  - Submitted CMV, AFB, GMS, and PAS nonreactive
  - “Syphilis unlikely based on a paucity of plasma cells”

Case 2

- Clinical demographics did not quite match demographics of this process.
- After discussing the unusual histologic features with the clinician...
  - Patient was an HIV+ male to female transgender/MSM with several high-risk factors for STI proctocolitis
Case 2: Clinical course

RPR 1:1024
FTA-Ab- reactive
T. pallidum IHC noncontributory on GI biopsy.
Patient was treated for syphilis and all symptoms and endoscopic abnormalities resolved.

Case 3

- 33 y/o HIV+ male presents to the ED with rectal pain for 2-3 days. Not relieved by sitz baths. Associated with urgency and yellow discharge. No fever, no nausea and vomiting. No penetration or trauma to the rectum in the last few months.
- CT of abdomen/pelvis showed:
  - A rectal mass that appears to be extending through the wall and along the pelvic sidewall, and is abutting the prostate.
  - No lymphadenopathy.
  - Indeterminate hypodensities in the liver of uncertain etiology but could represent metastatic deposits.

Case 3

Colonoscopy showed erythema, edema, friability, and loss of vascular pattern in the rectum to approximately 12 cm. No mass identified.
Remainder of the colon normal.
Case 3

- Pt initially denied MSM behavior but GI fellow was persistent and pt finally provided that history.
- RPR Negative
- Urine + for chlamydia.
- Rectal culture + for chlamydia.
- Patient treated with antibiotics as an in-patient. Has not followed up in clinic.

Case 4

- 45 y/o HIV+ male presented to GI clinic with rectal bleeding and change in bowel habits.
- Colonoscopy showed nodular, ulcerated mucosa in the rectum that extended from the anal verge to 15 cm from the dentate line. Remainder of the colon normal.

Ancillary Studies: Generally not helpful

<table>
<thead>
<tr>
<th>Submucosal fibrosis</th>
<th>All Patients</th>
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</thead>
<tbody>
<tr>
<td>Silver stain (result)</td>
<td>3 (negative)</td>
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</table>
Most important differential is with IBD

Pseudoepitheliomatous hyperplasia

Uncharted territory: Gonorrhea proctitis

Percentage of Urethral Neisseria gonorrhoeae Isolates Obtained from MSM* Attending STD Clinics, Gonococcal Isolate Surveillance Project (GISP), 1990–2011

*MSM = men who have sex with men


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Case 5

- Transgender male who was admitted to ER with acute proctitis.
- Concerns existed as to whether this was primarily a traumatic proctitis versus an infectious proctitis.
- Given ceftriaxone (NG) and Doxycycline (CT) in ER.

Case 5

- Patient improved after initiation of antibiotics. Doxycycline d/c after chlamydia tests came back negative.
Gonorrhea proctitis

• There is limited literature regarding the microscopic appearance of gonorrheal proctitis.
  • Compared to patients with syphilis, biopsies from patients with rectal gonorrhea are more often normal.
  • McMillan et al. report normal biopsies in 10/18 (55%) with rectal gonorrhea vs. 3/10 (30%) with rectal syphilis.
  • A subsequent study by some of the same authors similarly reports normal biopsies in 33 out of 57 (57.9%) biopsies in patients with rectal gonorrhea.
  • Endoscopic appearance may be normal.

Abnormal biopsies in the setting of rectal gonorrhea show less striking inflammation than in cases of syphilis.

• Mild to moderate increase in lamina propria lymphocytes and plasma cells.
• +/- neutrophils within the crypts and the intestinal lumen.
• In approximately 5% of the cases, the inflammatory infiltrate within the lamina propria is predominantly neutrophilic and superficial.
• Similar to syphilis and chlamydia infection, architectural distortion is not a feature of gonorrheal proctitis.

Common Benign Neoplasms of the Anal Canal

Hydradenoma Papilliferum
Granular Cell Tumors
Condyloma Acuminatum (common genital warts)

Clinical Features of Hidradenoma Papilliferum

Females in 4th to 6th decade
Typically seen as small (2-3 mm) dermal nodule covered by unremarkable skin
Lesion unencapsulated, but well circumscribed
Asymptomatic
Resection is curative

Hidradenoma papilliferum - lobulated
Hidradenoma papilliferum - lobulated
Condyloma Acuminatum

Condyloma acuminatum (common genital warts) is a sexually transmitted disease caused by members of the human papillomavirus family (HPV).

- Most common neoplasm of the anal canal
- Perianal skin most common location
- May occur with other sexually transmitted diseases

Clinical Features of Condyloma Acuminatum

- Most common in sexually active adults (both genders)
- More frequently seen in male homosexual population
- Increased incidence also seen in:
  - HIV+ individuals
  - Organ transplant recipients
  - Smokers
  - Alcohol abuse
  - Cervical intraepithelial neoplasia

Pathologic Features of Condyloma Acuminatum

- White/tan-colored lobulated masses
- Wide size range (millimeters to centimeters)
- The term “Condyloma” essentially synonymous with Anal intraepithelial neoplasia grade I
- Low propensity for progression to malignancy
- Most often caused by HPV-6 and HPV-11 serotypes

- Papillomatous architecture
- Marked acanthosis
- Surface parakeratosis
- Orderly maturation

Koilocytes
Condyloma – these conglomerates of vessel clusters are a diagnostic clue in "burned out" lesions.

ISH – HPV 6,11

Condyloma Acuminatum with High Grade Dysplasia

Clinically banal condylomata may harbor areas of high grade dysplasia/anal intraepithelial neoplasia, particularly in high risk populations. Due to infection by HPV-16 and HPV-18 instead or other viral serotypes, high grade dysplasia arising within a condyloma should be reported as for squamous dysplasia/anal intraepithelial neoplasia nomenclature system.
Condyloma with HPV 16/18

Carcinomas of the Anal Canal
1% of all large bowel cancers

Squamous Cell Carcinoma (most common)
- keratinizing, non-keratinizing, verrucous and cloacogenic types

Adenocarcinoma
- rectal type, or arising within anal glands or fissures

Small Cell Carcinoma

Undifferentiated Carcinoma

Squamous Dysplasia of the Perianal Skin and Anal Canal

Variously termed
- anal intraepithelial neoplasia (AIN)
- anal canal intraepithelial neoplasia (ACIN)
- anal squamous intraepithelial neoplasia (ASIL)
- Bowen's disease

Precursor of invasive squamous cell carcinoma

Epidemiologic, clinical, and pathologic similarities to cervical and vulvar intraepithelial neoplasia

Bowen's disease refers to squamous dysplasia of the perianal skin or anal margin

Anal Intraepithelial Neoplasia (AIN) refers to squamous dysplasia of the anal canal.

Bowen’s Disease

Middle aged and older individuals
Females > Males
More common in Caucasians
Prevalence 2-3 per 1000 individuals
May reach >4% in MSM population

Bowen’s Disease
Perianal itching most common presentation
Erythematous, scaly plaques
Found in tissues removed for variety of unrelated, benign reasons
- Hemorrhoids, anal tags, etc.
Frequently associated with cervical intraepithelial neoplasia

Bowen's Disease
Disorganization of Epithelium
Loss of Polarity
Abundant Mitoses
Acanthosis and Parakeratosis
Anal Intraepithelial Neoplasia (AIN)

Occurs in the transitional epithelium above the dentate line.

Three grades
- Mild (AIN I)-low grade
- Moderate (AIN II)-high grade
- Severe (AIN III)-high grade

Very strong association with human papilloma virus infection, particularly HPV types 16 and 18.

High grade AIN most common in HIV-positive MSM.
- 5 to 30% of cases occur in HIV-negative MSM.
- High grade AIN is rare in heterosexual men.

High grade AIN is increased in women who are HIV-positive.

Other associations:
- anal intercourse
- concomitant abnormal cervical cytology
- Immunosuppression in solid organ transplant patients

Using P16 and Ki-67

Ki-67, is a sensitive and specific marker for dysplasia in mature squamous epithelium and is therefore helpful for confirmation of AIN1 and condyloma.

A Ki-67 positive result can be defined as the presence of a cluster of at least two strongly stained epithelial nuclei in the upper two-thirds of the epithelial thickness.

This labeling pattern does NOT separate low- and high-grade intra-epithelial neoplasia.

Additionally, it does not separate low-risk from high-risk HPV type lesions.

It should also be noted that reactive lymphocytes express Ki-67 and should not be interpreted as epithelial cells.

Lastly, it does not distinguish reparative changes from intra-epithelial neoplasia.
Using P16 and Ki-67

Based on the limitations of Ki-67 labeling, it is useful to combine it with p16 immunolabeling, which is evaluated using a two tier system:
1. Absent or discontinuous, patchy nuclear and cytoplasmic staining pattern is considered as a negative result.
2. A positive result consists of diffuse and strong staining of cells of the basal and parabasal layers of the squamous epithelium, with or without superficial staining.

High grade anal intraepithelial neoplasia. This lesion is very subtle on hematoxylin and eosin but several atypical mitoses are a clue that this is a high grade lesion.

Ki-67 immunolabeling in high grade anal intraepithelial neoplasia. There is labeling throughout the thickness of the squamous epithelium in this case depicted. A positive result can be defined as the presence of a cluster of at least two strongly stained epithelial nuclei in the upper two-thirds of the epithelial thickness. The key point of this labeling pattern is that it is not useful for separating low- and high-grade intra-epithelial neoplasia.

P16 immunolabeling in high grade anal intraepithelial neoplasia. This preparation is from the area just depicted. In cases such as this, finding strong p16 immunolabeling is good evidence for high grade anal intraepithelial neoplasia.

P16 immunolabeling in high grade anal intraepithelial neoplasia. There is strong diffuse immunolabeling.
Prognosis and Therapy of Bowen’s Disease/AIN

The rate of progression of Bowen’s disease/AIN is approximately 2 to 5%.
The treatment of choice is wide local excision/ablation.
Therapeutic modalities include cryotherapy, CO2 laser ablation, topical 5-fluorouracil, argon laser therapy, and photodynamic therapy.
Patients at risk may benefit from anal swab cytology (anal Pap smear) as part of clinical monitoring.

This is a biopsy of an anal mass from an adult male patient.
Diagnosis – Anal duct/anal gland carcinoma
Anal Duct/Gland Carcinoma

Rare - Armed Forces Institute of Pathology (AFIP) reported only 7 convincing cases. 5 cases in our series.

Tubules originating from ducts that open onto the mucosal surface.

Intramural, without a luminal in situ component.

May exhibit pagetoid spread.

Variable overlying surface ulceration.

CK7+ and CK20-, CDX2- akin to the anal glands and ducts.

DDX - prostate cancer (which is often CK7-, CK20-) and gynecologic carcinomas.

Many have behaved aggressively.

Paget’s Disease of the Anal Canal

The most common site of extramammary Paget’s disease is the vulva and contiguous perineal skin.

Disease primary to the perianal skin may also occur, albeit rarely.

Most commonly associated with an underlying carcinoma of the rectum OR adjoining Paget’s of the perineum.

Clinical Features

No clear gender predilection (once cases associated with vulvar disease are excluded).

Most cases occur from the sixth through the ninth decades.

Erythematous, scaly patches.

Paget’s Disease

Large, cytologically malignant cells

Pale granular cytoplasm

Scattered throughout epidermis.

PAS stain
Differential Diagnosis of Paget's Disease of the Anus

Anal Intraepithelial Neoplasia
- **PAS negative**

Spread of colorectal carcinoma in a pagetoid fashion

Melanoma In Situ
- **PAS negative, S100/HMB45/Melan A positive**

The presence or absence of melanin alone does not help make the diagnosis
- Paget's cells can contain melanin
- 20% of melanomas are amelanotic
- Melanin can be found in neoplastic keratinocytes within Bowen's disease
Thank you