

# This is the End

ERIC SWANSON, M.D.  
DEPARTMENT OF PATHOLOGY  
UNIVERSITY OF UTAH



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## Morphologic and Immunohistochemical Features of Anorectal Tumors

- Review the histologic and immunophenotypic features of malignancies that present in the anorectum
- Update the therapeutic implications of diagnoses in the anorectum
- Explore and understand unexpected findings that may present in routine specimens from the anorectum
  - Implications range from curious to critical



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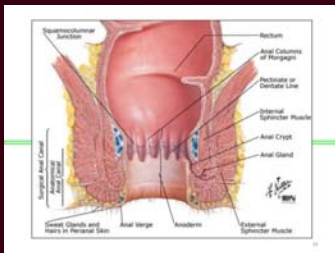
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## Anorectal anatomy



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## Epithelium in anus

- 3 zones
  - Upper third above anal columns is rectal columnar mucosa
  - Anal transition zone
    - Spans distance from anal columns to dentate line
    - Transitional mucosa- multilayered cuboidal cells that are neither columnar or squamous, but have a basal cell layer
    - Occasional goblet cells may be present
  - Distal to dentate line is non-keratinizing stratified squamous epithelium
    - Becomes keratinizing and contains skin adnexal structures at the anal verge

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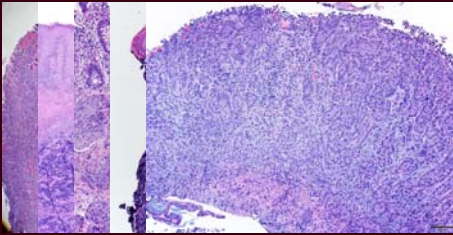
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## Anorectal lesions



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## Anorectal lesions

- Wide variety of primary lesions with vastly different treatment considerations
- Prognosis for each category of lesions is very different
- How to approach anorectal lesions to ensure best diagnosis and treatment for the patient

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### Case 1

- 54 year old woman presents for screening colonoscopy
  - Incidental change in bowel habits noted, with occasional hematochezia
- PMH included history of cervical dysplasia
- Colonoscopy revealed a fungating, partially obstructing large mass in the distal rectum.
  - Located approximately 5-7cm from the anal verge, measuring approximately 4cm in length.

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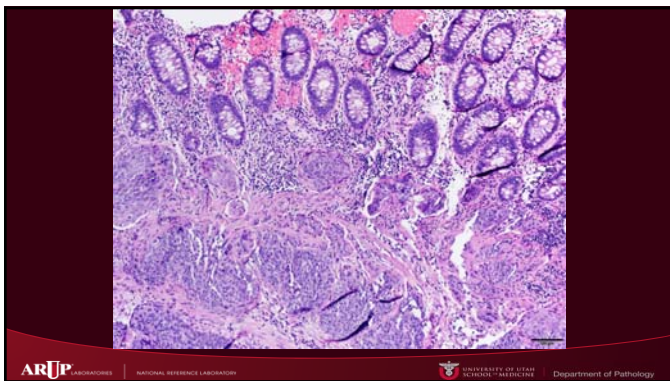
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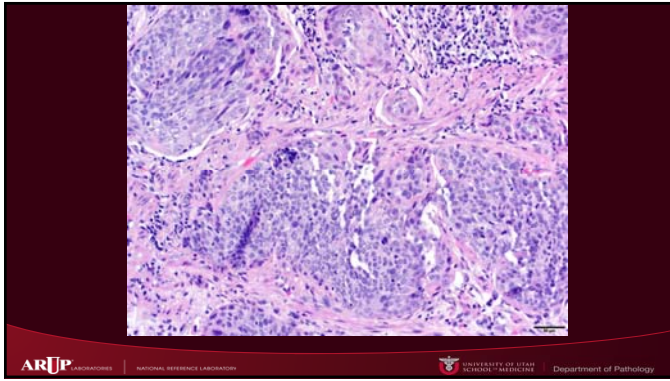
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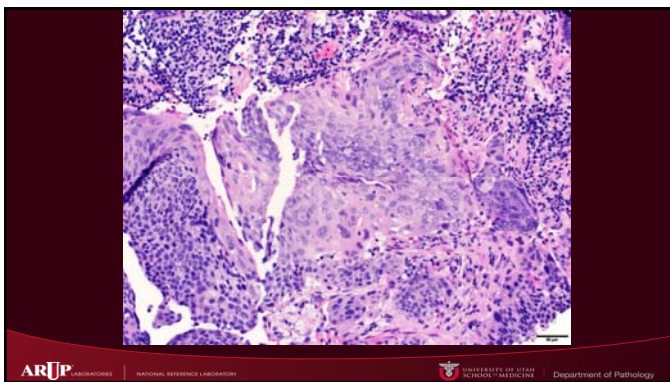
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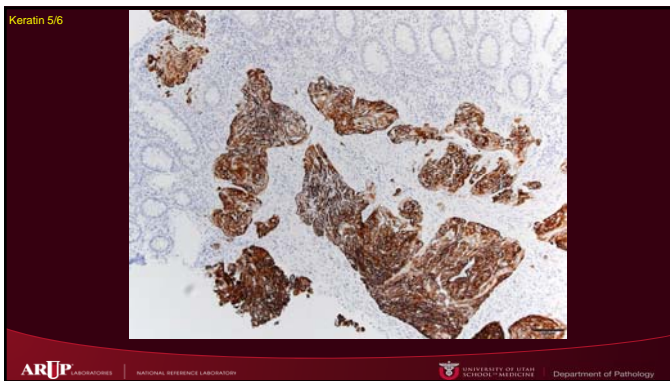
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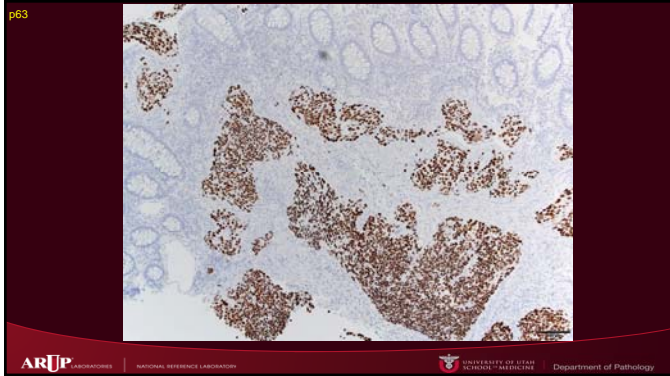
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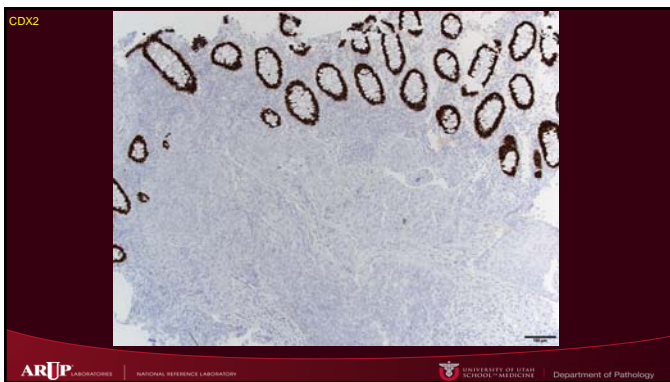
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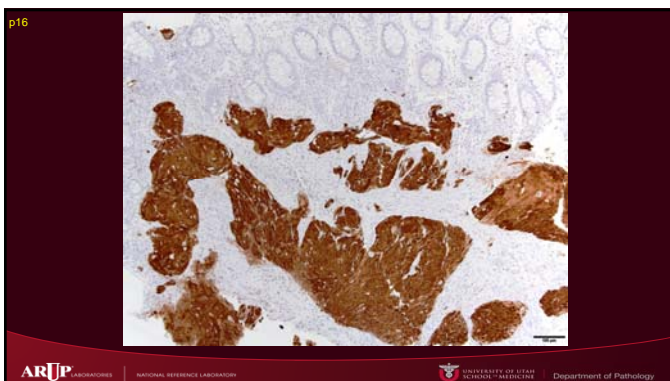
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### Squamous cell carcinoma

- Diagnosis:
  - Histologic clues
    - Keratinization, overlying in situ squamous dysplasia, intercellular bridges
  - Immunostains
    - Positive for keratin 5/6, p63
    - Negative CDX2
  - Exclude the possibility of poorly differentiated adenocarcinoma
  - Diagnostic categories/descriptors such as cloacogenic, transitional, keratinizing, and basaloid no longer used
    - WHO recommends not subtyping histologic variants, and instead can include degree of keratinization, basaloid features, presence of mucinous microcysts, small cell (anaplastic) carcinoma

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### Squamous cell carcinoma

- Predominantly occur in anus, but distal rectal cases do occur
- Treatment
  - In the past, squamous cell carcinoma of the anus treated surgically with APR
  - Now treated with chemotherapy and radiation
    - If good response to treatment, surgery can be avoided
    - APR leads to permanent colostomy

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### Case 2

- 52 year old male with intermittent hematochezia for 5 years
  - Worsening recently
- Colonoscopy revealed fungating tumor in rectum

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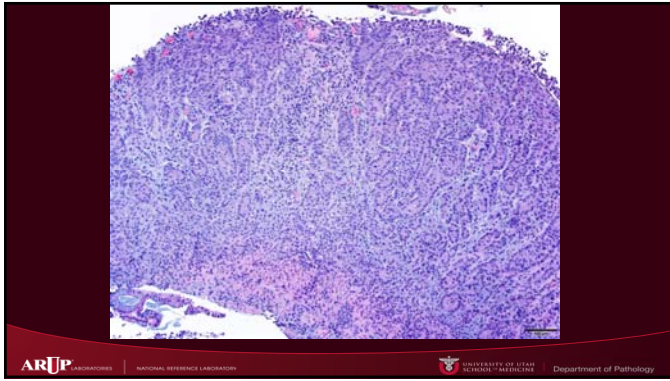
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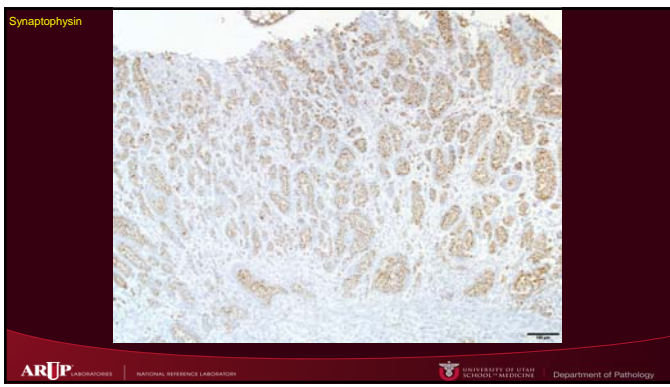
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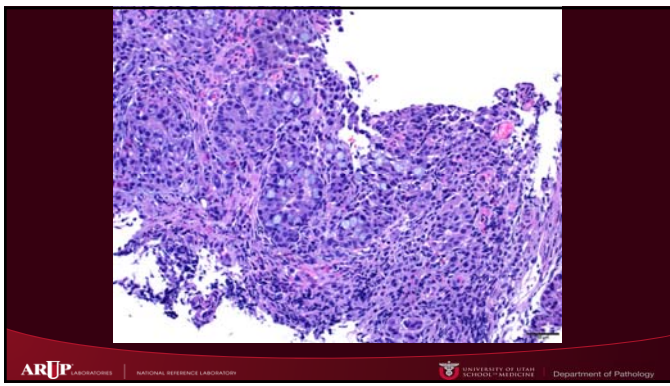
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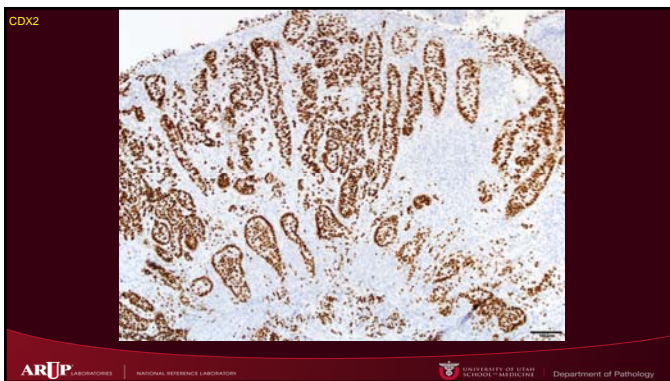
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### Adenocarcinoma, poorly differentiated

- Diagnosis
  - Epithelial dysplasia
  - Mucin production
  - Keratin positivity, CDX2
- Exclude the possibility of neuroendocrine carcinoma
  - Adenocarcinoma can show patchy positive staining for neuroendocrine markers
  - Morphology should be key to diagnosing NE carcinoma

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### Adenocarcinoma

- Treatment (for T3/T4 or node positive tumors)
  - Neoadjuvant chemotherapy and radiation treatment
  - Followed by transabdominal resection

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### Case 3

- 63 year old male with polypoid mass in anterior rectum
- Underwent transanal excision

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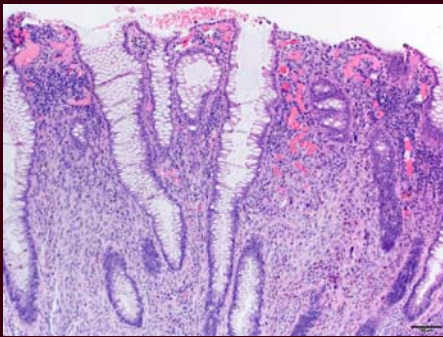
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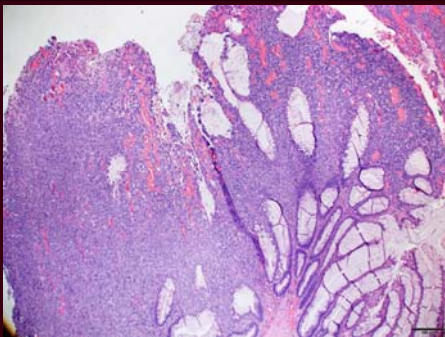
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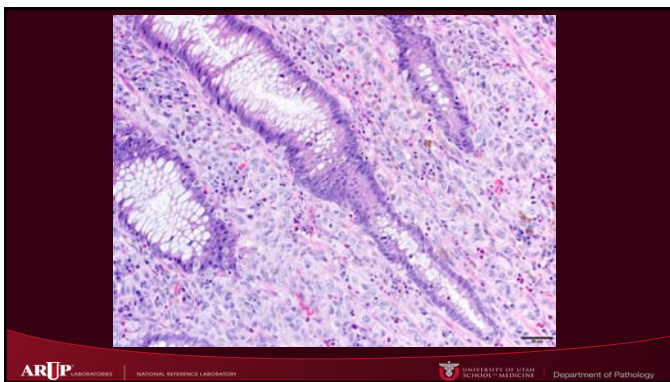
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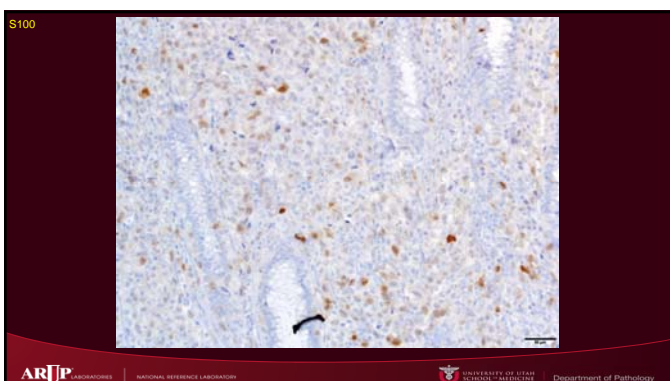
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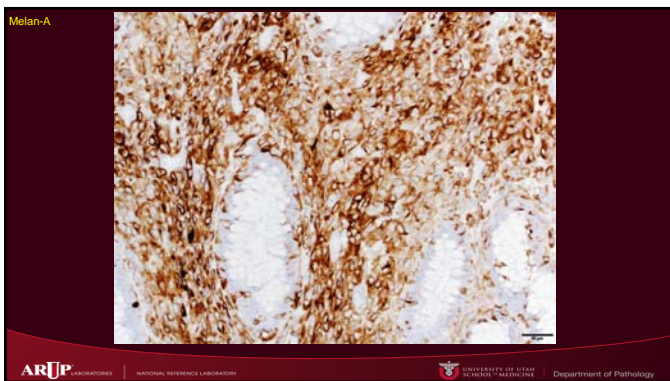
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### Anorectal mucosal melanoma

- Diagnosis
  - In situ precursor lesion
  - Melanin pigment can be clue
  - S100, HMB45, Mel-A, Sox10
  - CD117 (C-kit) can be positive in a significant proportion of melanomas
    - Be careful diagnosing GIST with a limited immunohistochemical work-up

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### Anorectal mucosal melanoma

- Uncommon disease representing approximately 1% of lower gastrointestinal malignancies and 1% of primary melanomas
- Poor prognosis, with 5-year survival of approximately 20%
- Wide local excision is preferred treatment
  - APR reserved for tumors not amenable to resection or with obstructive complications
- Lesions proximal to dentate line present with more advanced disease, likely due to delay in diagnosis
  - Lesions are typically amelanotic, and may be confused with hemorrhoids

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### Case 4

- 47 year old female presents with 2 weeks of a painful hemorrhoid
- Firm mass noted at anal verge extending 6 cm proximally

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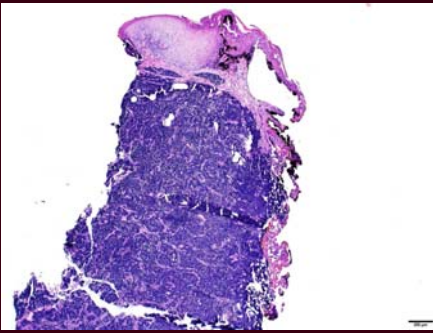
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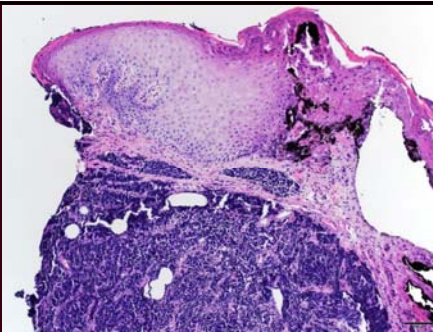
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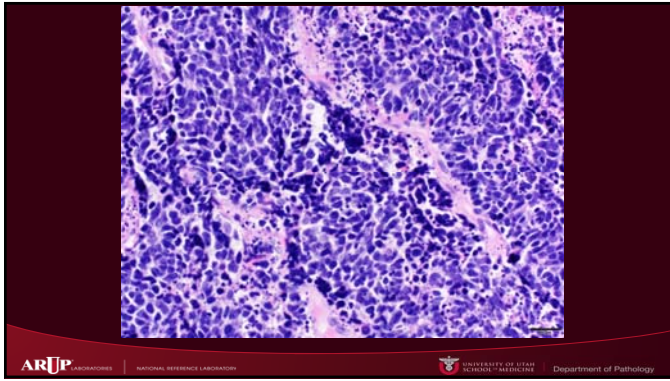
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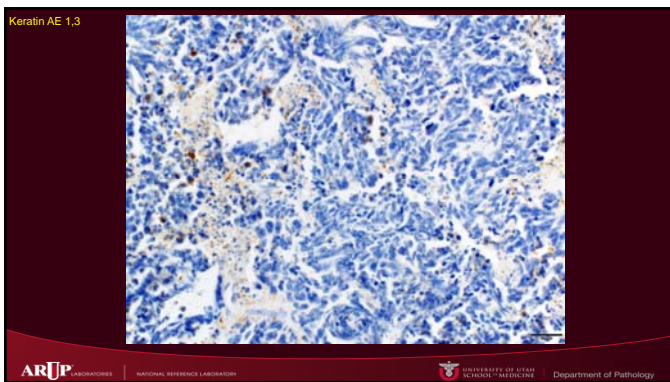
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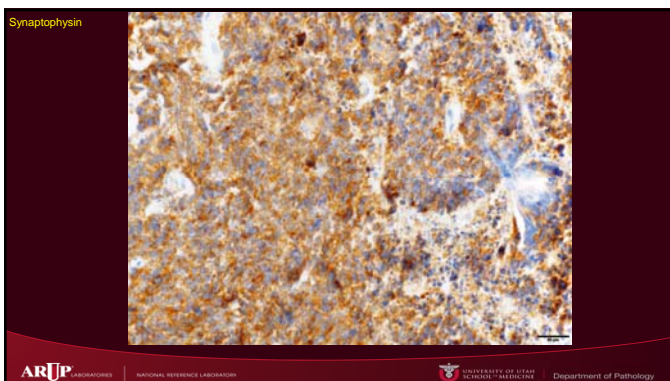
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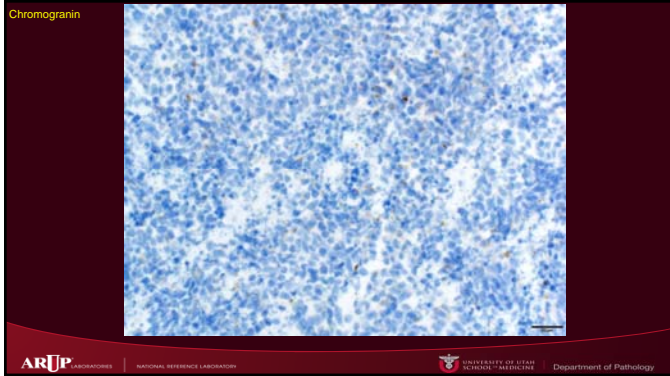
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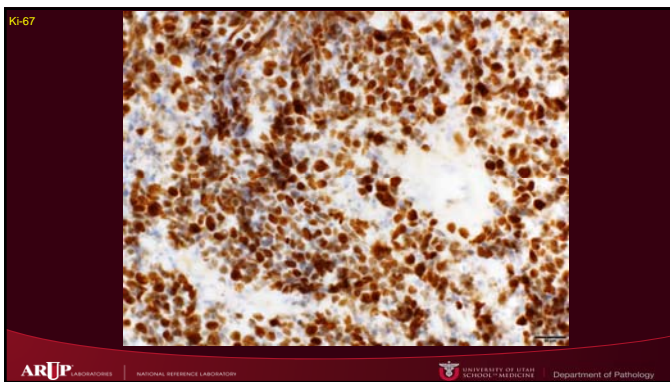
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### Poorly differentiated neuroendocrine carcinoma

- Diagnosis based on morphology and immunophenotype
  - May be confused with poorly differentiated adenocarcinoma or squamous cell carcinoma with basaloid features, melanoma, lymphoma
  - Expression of neuroendocrine markers is common but may be focal
    - Synaptophysin, chromogranin, CD56
  - TTF-1 may be positive
    - Similar to small cell carcinomas of other sites, does not imply pulmonary origin
  - Scattered nests of cells with squamous differentiation can be seen
    - Can stain positive for p63
    - Typically less than 5% of tumor volume

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## Poorly differentiated neuroendocrine carcinoma

- Treatment
  - Resection and chemotherapy
    - Small cell regimen such as cisplatin/etoposide or carboplatin/etoposide
  - Radiation therapy if necessary
- Poor vs. well-differentiated morphology imparts prognosis and treatment considerations
  - Poorly differentiated histology or very high Ki-67 treated with small cell regimen
  - Well-differentiated tumors with intermediate Ki-67 proliferation index may not respond as well to platinum/etoposide
  - Recommend clinical judgement

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## Case 5

- 28 year old male with 3-4 months of rectal pain
- Seen in ED multiple times
  - Presumed to be a rectal abscess
  - Lanced and prescribed antibiotics
- CT scan demonstrated 12 cm perianal mass with extension into pelvic sidewall
- Excisional biopsy performed

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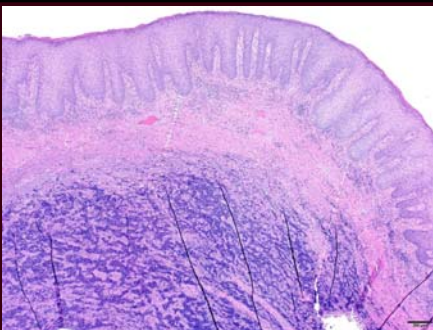
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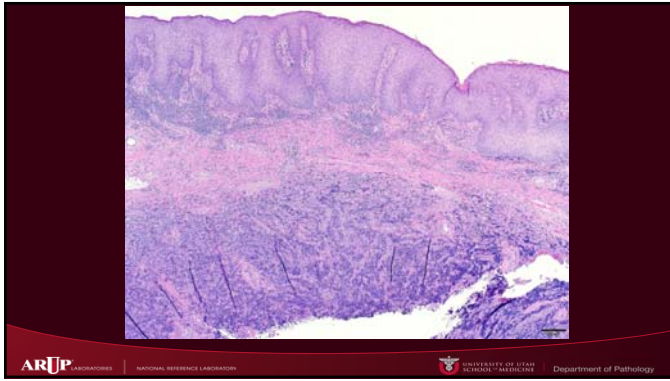
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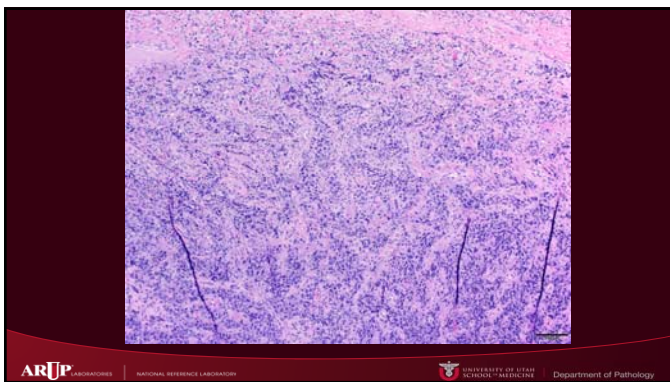
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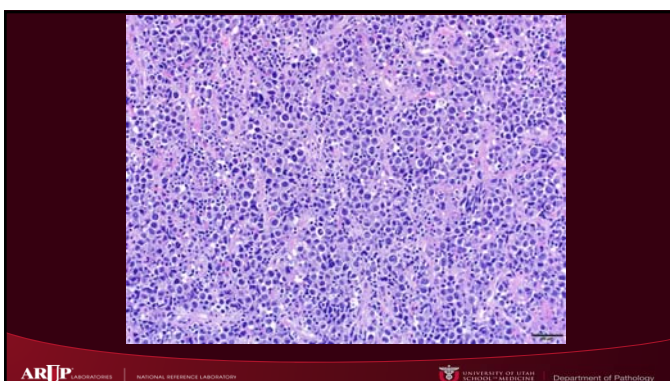
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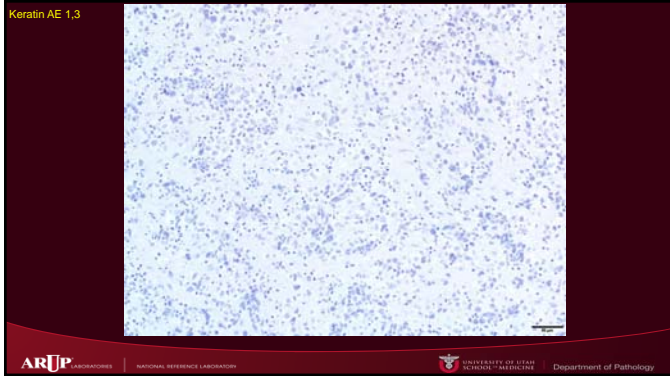
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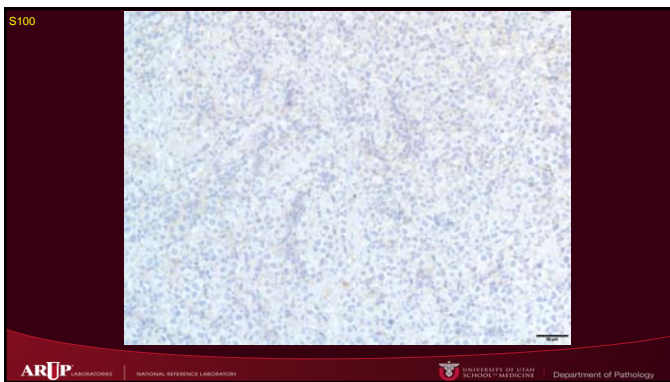
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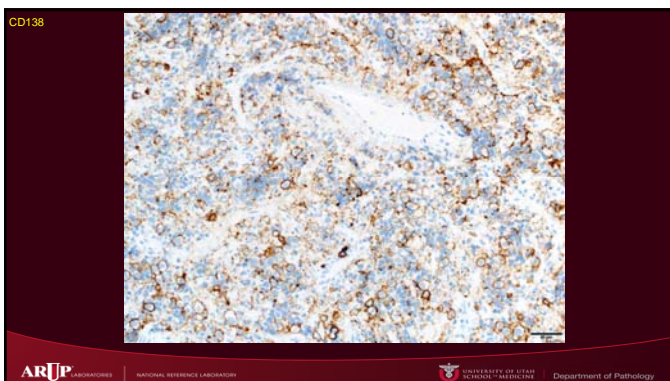
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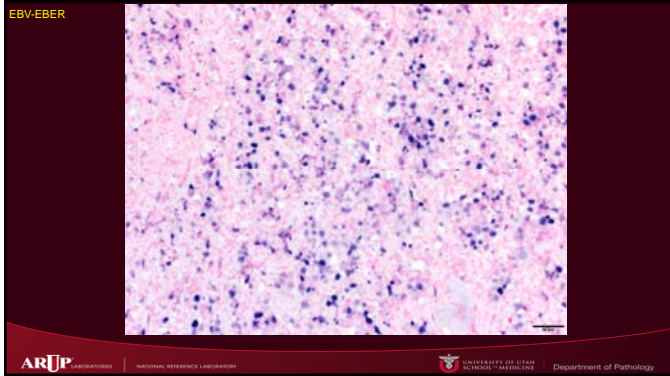
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### Plasmablastic Lymphoma

- Rare neoplasm typically seen in association with immunodeficiency
  - Commonly associated with oral cavity
- Diffuse sheets of large immunoblastic cells with abundant cytoplasm, vesicular chromatin, and prominent nucleoli
- Can be difficult to diagnose with immunostains
  - Tumor lacks expression of CD45 and pan B-cell antigens
  - Carcinomas with plasmacytoid morphology can express CD138
    - Especially plasmacytoid variant of urothelial carcinoma
    - Keratin immunostain would be helpful to differentiate a carcinoma with plasmacytoid features from plasmablastic lymphoma

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### Plasmablastic lymphoma

- Treatment
  - Chemotherapy
    - Treatment used for DLBCL typically thought to be inadequate, and more intensive regimens are used for PBL
    - If they express CD20, Rituximab may be used
  - Prognosis
    - Aggressive neoplasm with a dismal outcome
    - Overall median survival of 8 months

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### Case 6

- 70 year old male who presents with anal pruritus
- Treated for presumed fungal infection without relief
- Colonoscopy showed tubular adenoma in anus, hyperplastic polyps.

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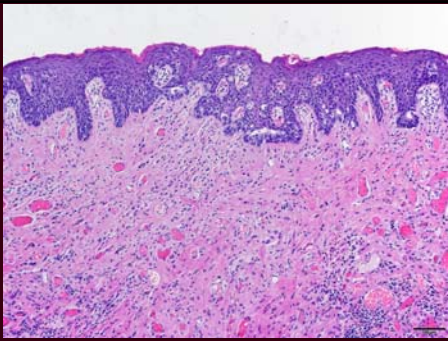
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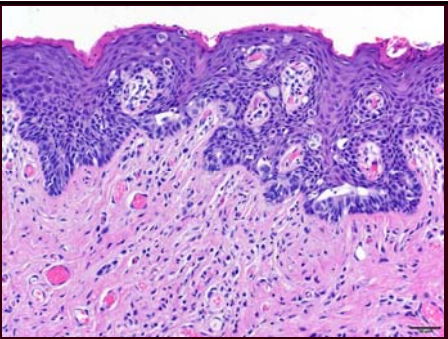
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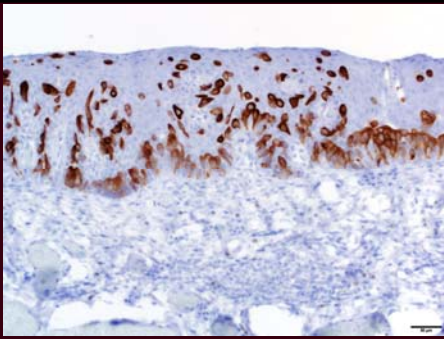
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Keratin 20



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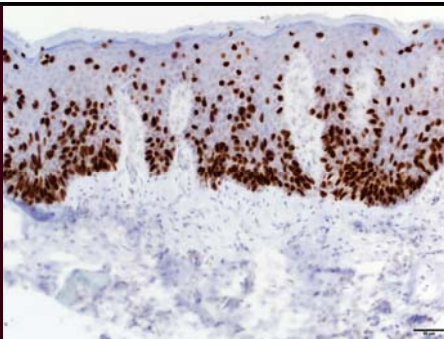
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CDX2



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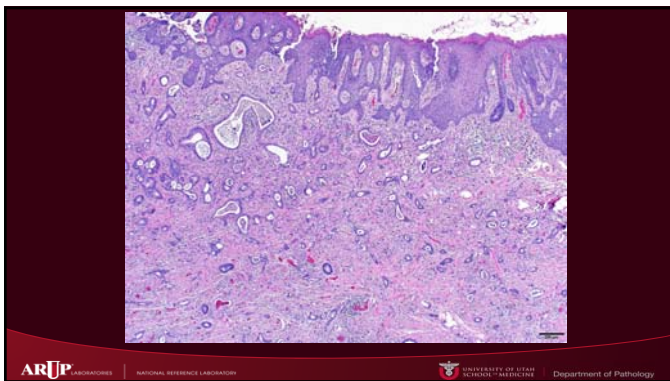
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### Colorectal Adenocarcinoma with Pagetoid Extension

- Epidermal hyperplasia, hyperkeratosis, parakeratosis frequently identified
  - May be helpful at time of frozen section
- Primary Paget's disease is a disease that originates from the epidermis or squamous epithelium
- Secondary Paget's disease
  - Often associated with underlying visceral malignancy
  - Secondary anal Paget's disease most often seen with primary colorectal type adenocarcinoma
    - Others include gynecologic, urologic

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### Colorectal Adenocarcinoma with Pagetoid Extension

- Primary Paget's disease
  - CK7+, CK20-, GCDFP15+
  - Some reports that GATA3 is more sensitive than GCDFP15
- Secondary Paget's
  - Depends on the phenotype of the underlying malignancy
  - Colon CK7+, CK20+, CDX2+, GCDFP15-
- Melanoma
  - HMB45, Melan A
  - S100 may be expressed by Paget cells

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### Colorectal Adenocarcinoma with Pagetoid Extension

- Treated with resection of the primary malignancy and wide local resection of diseased skin
  - Frequent local recurrences
- Chemotherapy dictated by primary lesion as well as aggressiveness of disease

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### Case 7

- 62 year old male with a two year history of mass in the perineal region
  - Started as a small lesion on medial thigh, now involving entire perineum from posterior scrotum to anus (10 x 10 cm)
  - Biopsy show condyloma accuminatum

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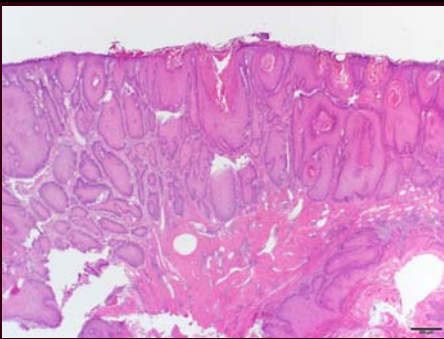
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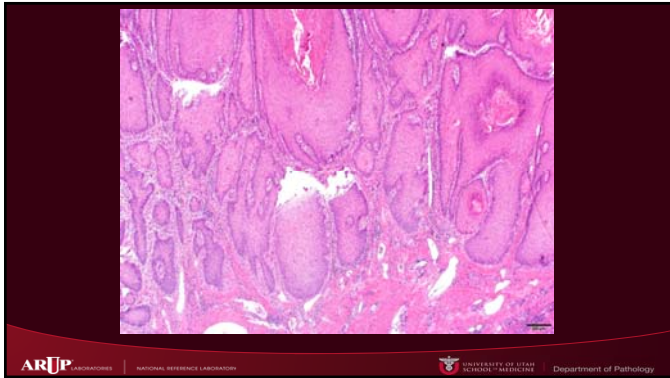
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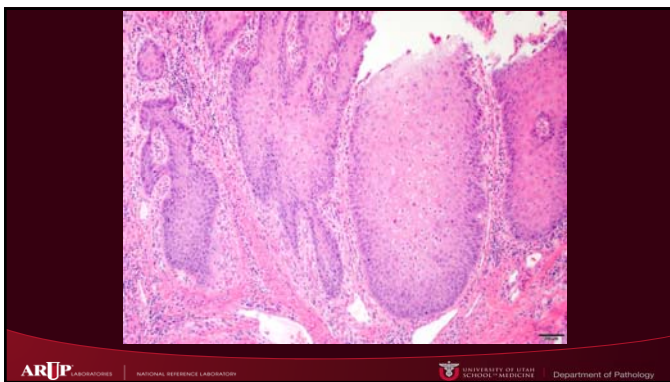
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### Verrucous Carcinoma/Giant Condyloma of Buschke-Lowenstein

- Cauliflower appearance on clinical/gross examination
- Compared with typical condyloma, has a combination of exophytic and endophytic growth
  - Acanthotic epithelium with orderly arrangement of epithelial layers
  - Intact but irregular base with blunt downward projections
  - Some keratin filled cysts may occur
  - Typically show minimal cytologic atypia
    - Mitoses limited to basal areas
- Endophytic growth thought to represent pushing type invasion
- If evidence of severe cytologic atypia or convincing infiltrative/jagged invasion, consider a diagnosis of squamous cell carcinoma
  - Need extensive sampling to rule out conventional SCC
  - Can occur in up to 40% of cases

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## Verrucous Carcinoma/Giant Condyloma of Buschke-Lowenstein

- Thought to be HPV 6/11 related
  - Some recent reports debate whether these lesions are HPV related
- Intermediate clinical behavior between condyloma and squamous cell carcinoma
- Local destructive invasion and recurrence without metastasis
- Treatment
  - Local resection
  - Chemotherapy, radiation therapy for SCC and for refractory cases

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## Case 8

- 45 year old female with long history of hemorrhoids
- Increased prolapse and bleeding recently

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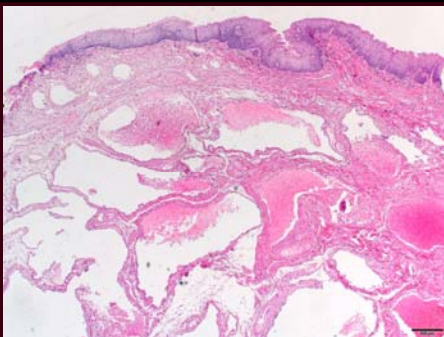
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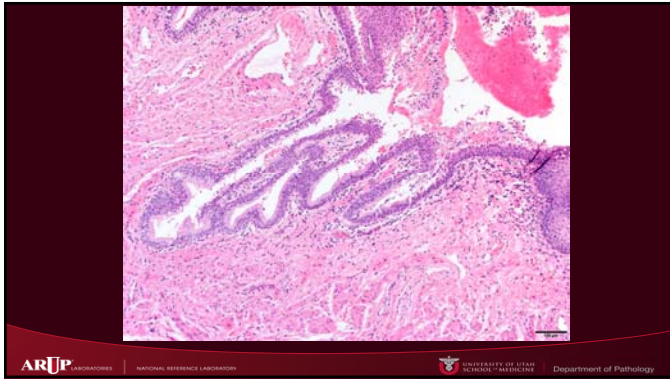
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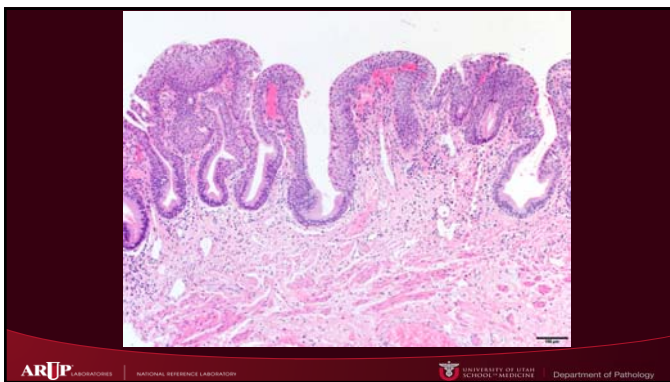
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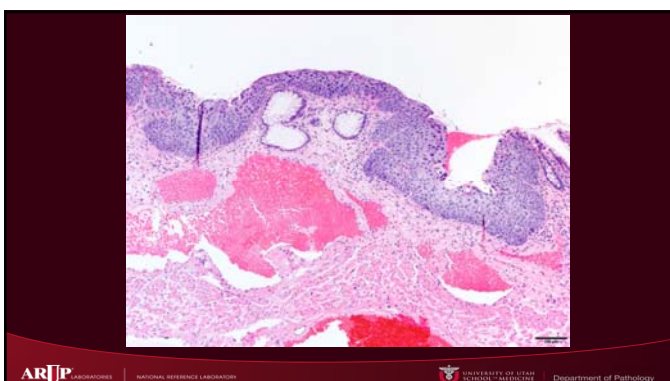
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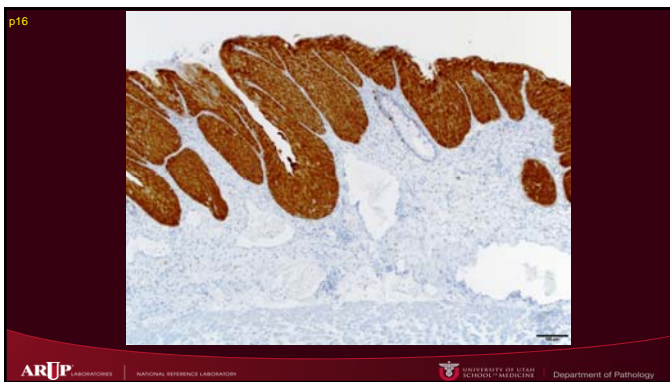
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## High Grade Squamous Intraepithelial Lesion

- Encompasses anal intraepithelial neoplasia 2-3 (AIN II-III)
- High risk HPV related (HPV 16/18)
- Diagnosis
  - Lack of orderly maturation of squamous cells towards surface of epithelium
  - Increased nuclear to cytoplasmic ratios
  - Mitotic figures in upper 2/3 of epithelium
  - p16 immunohistochemistry
    - Helps to distinguish high grade dysplasia from hyperplasia and reactive atypia
    - Requires strong diffuse staining, full thickness
      - Nucleus and cytoplasm typically stain positive

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## High Grade Squamous Intraepithelial Lesion

- Treatment
  - Topical therapy
    - Trichloroacetic acid
  - Topical immunomodulators
    - Imiquimod
  - Local infrared coagulation
  - Electrocautery ablation
  - Observation

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## Case 9

- 74 year old female with recent diarrhea and hematochezia
- Possible hemorrhoid seen and removed by surgeon

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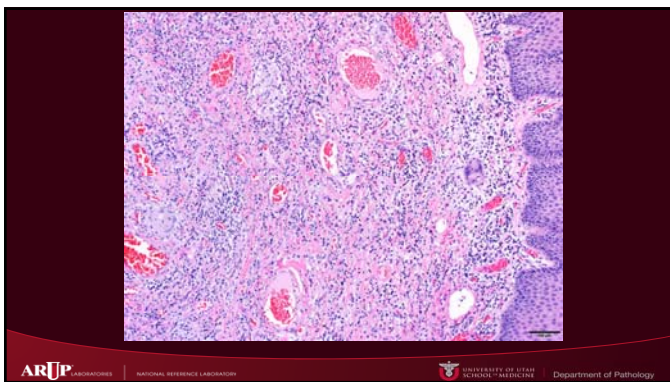
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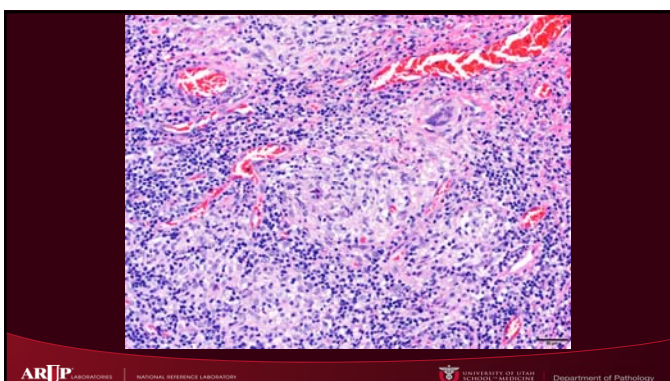
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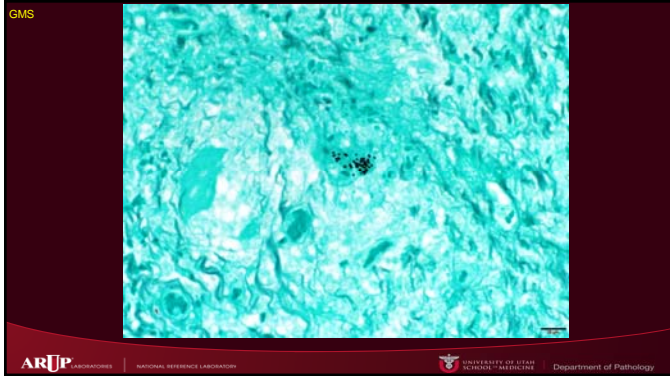
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### Histoplasmosis

- Patient had a distant history of a positive skin test
- Imaging showed spleen with multiple calcified nodules consistent with granulomatous disease
- Lymphohistiocytic infiltrates with granulomas
  - Intracellular yeast forms within histiocytes (2-5 microns)
- Important to use special stains when background warrants
- 5% of immunocompetent persons may be infected with histoplasmosis
- Disseminated disease treated with Amphotericin B

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### Case 10

- 33 year old who recently noted a mass protruding from anus
- Anoscopy demonstrated a 4.0 x 3.0 cm pedunculated polyp near the anal verge
- Patient recently emigrated from Sudan
- Also noted incidental abdominal pain

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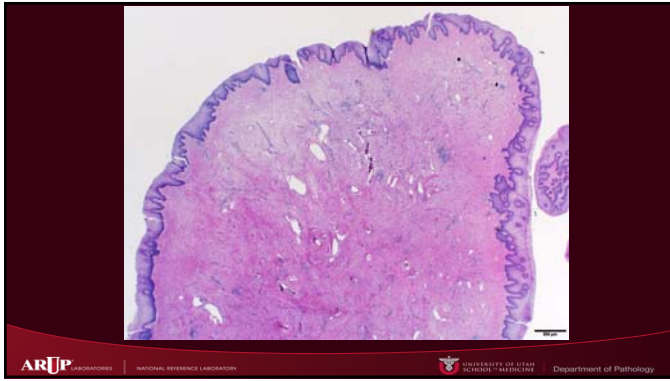
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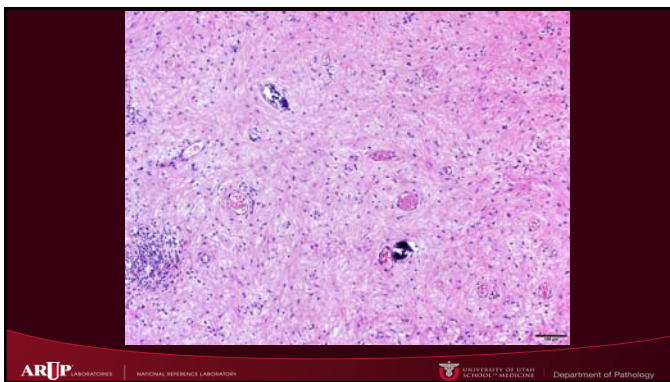
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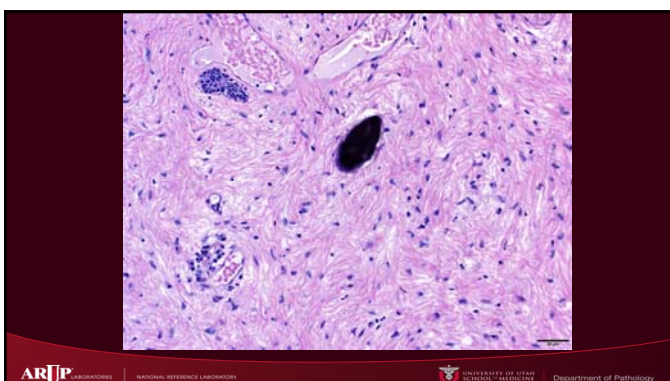
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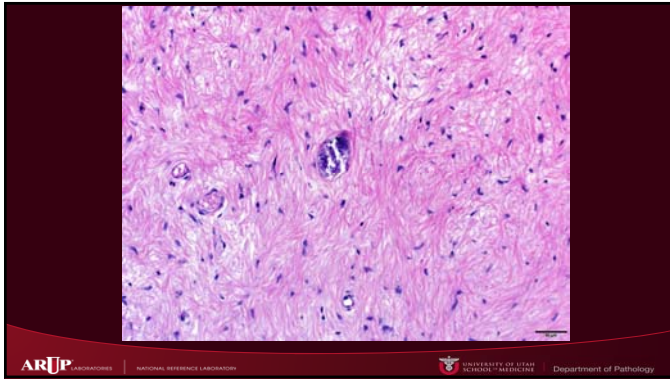
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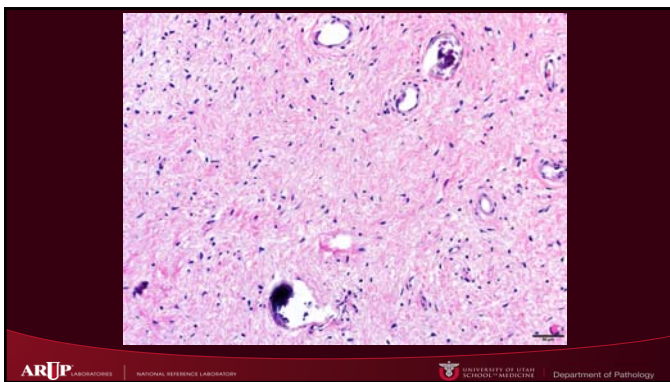
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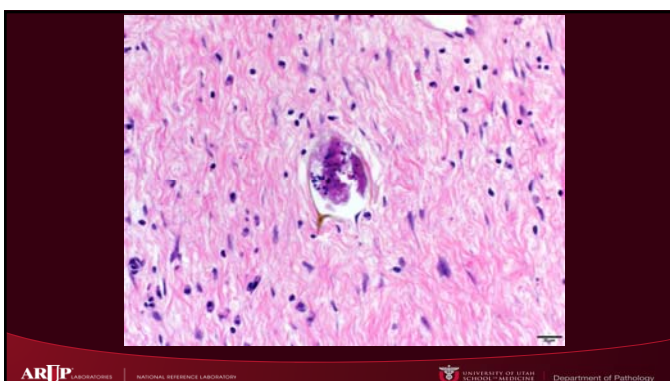
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## Schistosomiasis

- Intestinal schistosomiasis can be caused by multiple species
  - *S. mansoni*, *S. japonicum*, *S. mekongi*, *S. intercalatum*, *S. guineensis*
  - Cause abdominal pain, diarrhea, hematochezia
  - Adult worms live in blood vessels, females lay eggs
  - Has been reported in colon and anal polyps
- Travel through intestines retrograde through portal veins into mesenteric venules
  - May also involve liver with associated portal hypertension
- *S. hematobium* causes urogenital schistosomiasis
  - Blood in urine

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## Schistosomiasis

- Typically diagnosed by eggs in stool (ova and parasite examination)
- Treatment
  - Praziquantel
    - Inexpensive and effective

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## Case 11

- 59 year old with rectal polyp

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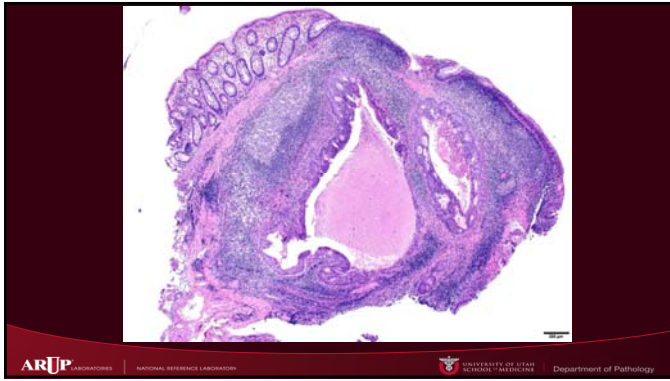
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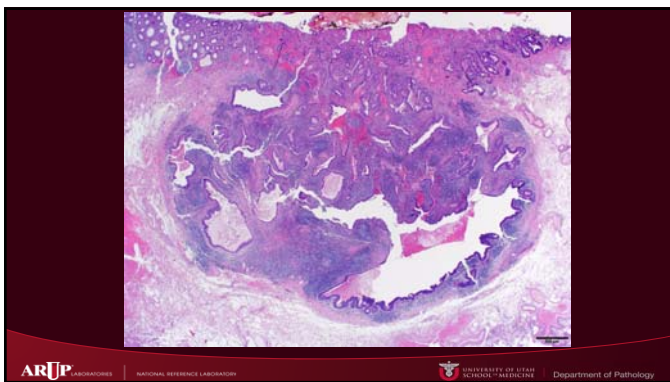
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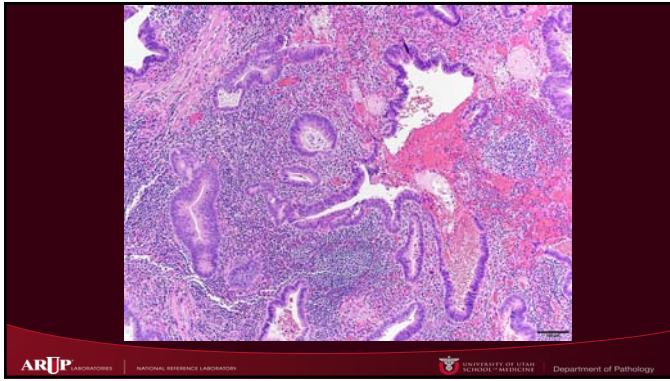
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Dysplasia in rectal tonsil

- Rectal tonsil
  - Localize lymphoid hyperplasia in rectum
- Dysplastic epithelium herniates into submucosa
  - Epithelium surrounded by lamina propria
  - No desmoplastic stromal response to indicate submucosal invasion
- Transanal excision margins negative

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Case 12

- 54 year old woman with screening colonoscopy
- Endoscopist noted 2 cm lesion in anus
  - Told patient that she had anal cancer, referred to U of U to see colorectal surgeon
- Transanal excision of lesion was performed

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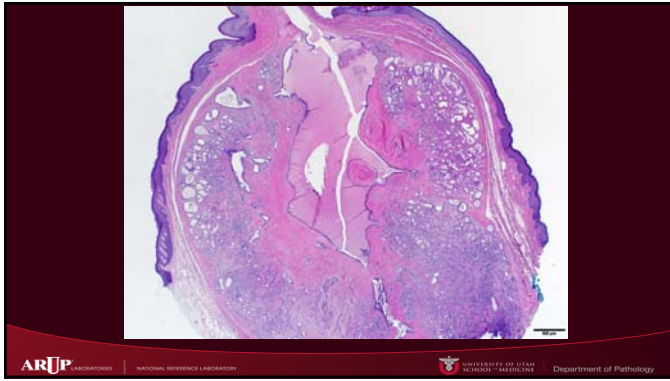
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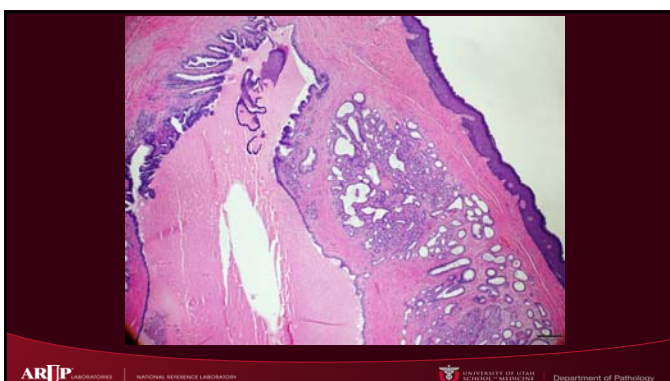
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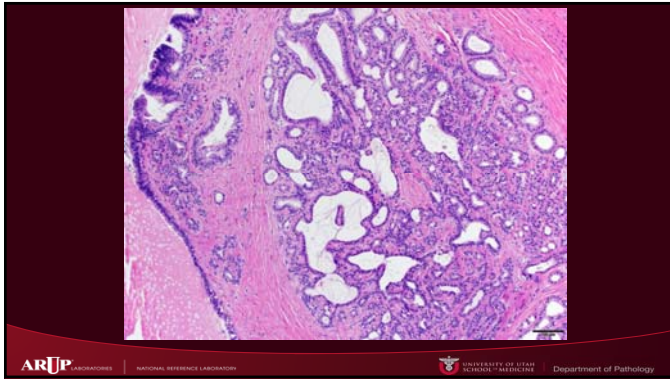
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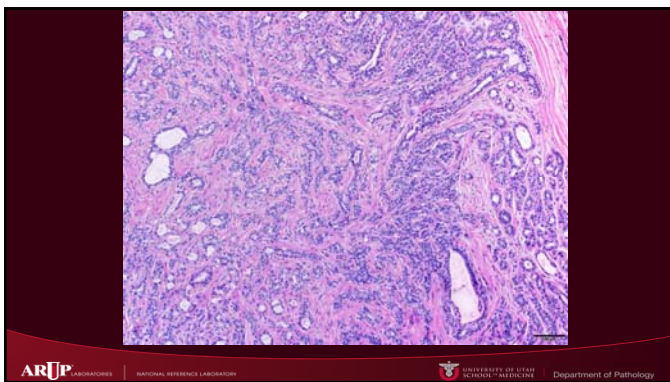
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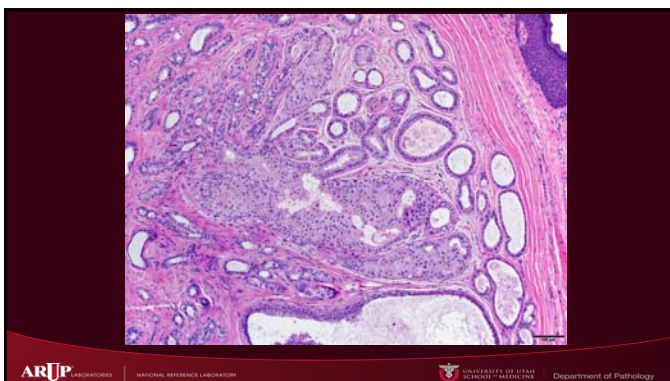
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## Anogenital Mammary-Like Glands

- Originally considered to represent ectopic breast tissue, milk line remnant
- Now thought to be a normal constituent of the anogenital area
- Lesions bear a striking resemblance to breast tissue
- Hidradenoma papilliferum is thought to belong to this group of lesions, and is the most common presentation
- Any type of breast lesion (benign or malignant) may be recapitulated in the MLGs
  - Sclerosing lesions, ductal carcinoma, fibroepithelial lesions, etc.

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