DEC 2020 DIAGNOSIS LIST

20-1201: syphilitic colitis [large bowel; GI path+ID path]
20-1202: metastatic leiomyosarcoma [lung; GYN pathology]
20-1203: large B-cell lymphoma with IRF4 translocation [LN; hematopath]
20-1204: extranodal NK/T cell lymphoma [testis; hematopath]
20-1205: extranodal marginal zone lymphoma [uterus; hematopath]
20-1206: synovial-like metaplasia [uterus; GYN pathology]
20-1207: Russell body cervicitis [uterus; GYN pathology]

Disclosures December 7, 2020

Dr. Ankur Sangoi has disclosed a financial relationship with Google (consultant). South Bay Pathology Society has determined that this relationship is not relevant to the planning of the activity or the clinical cases being presented. The following planners and faculty had no financial relationships with commercial interests to disclose:

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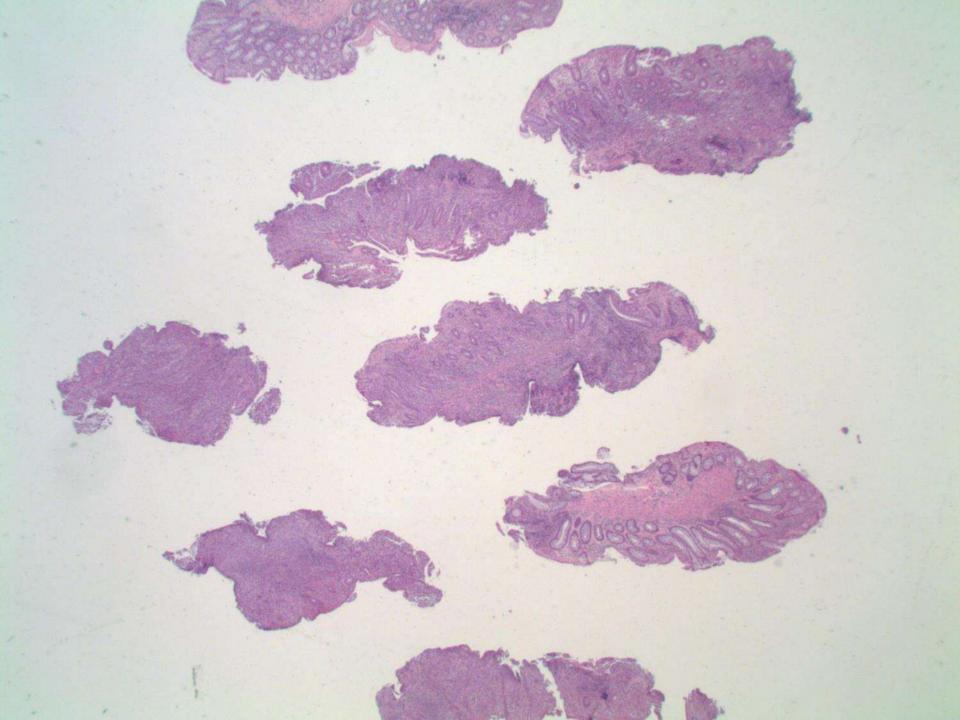
Activity Planners/Moderator:

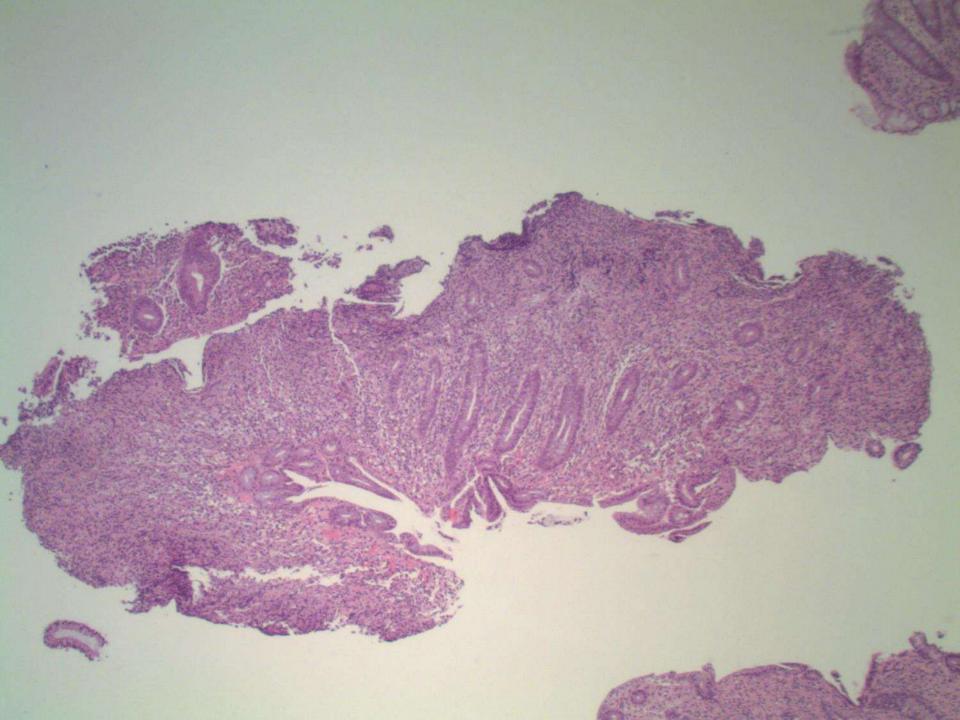
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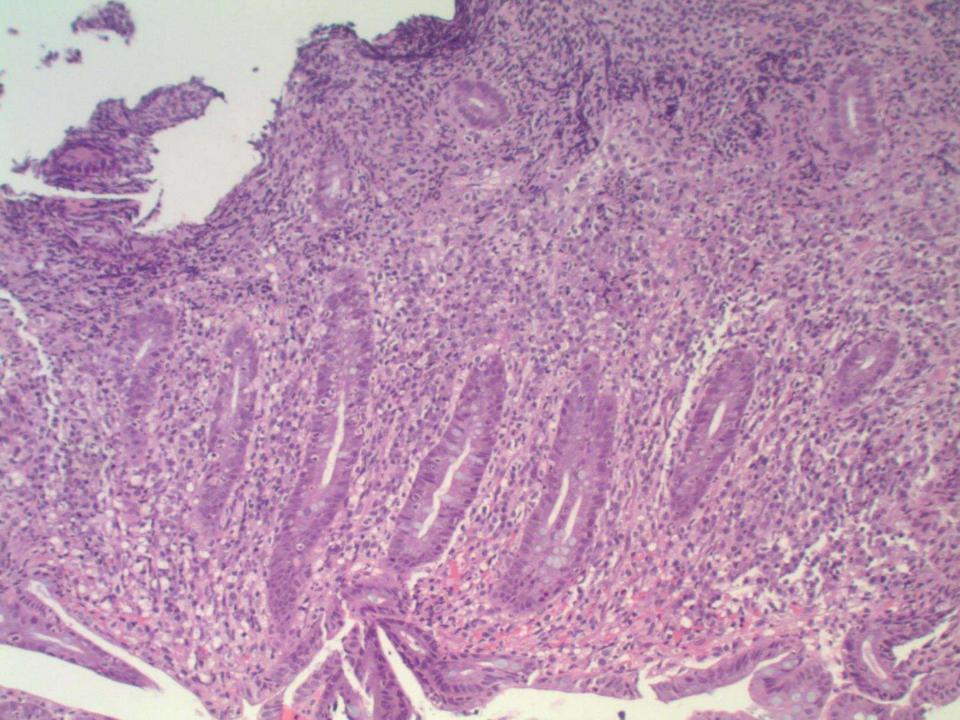
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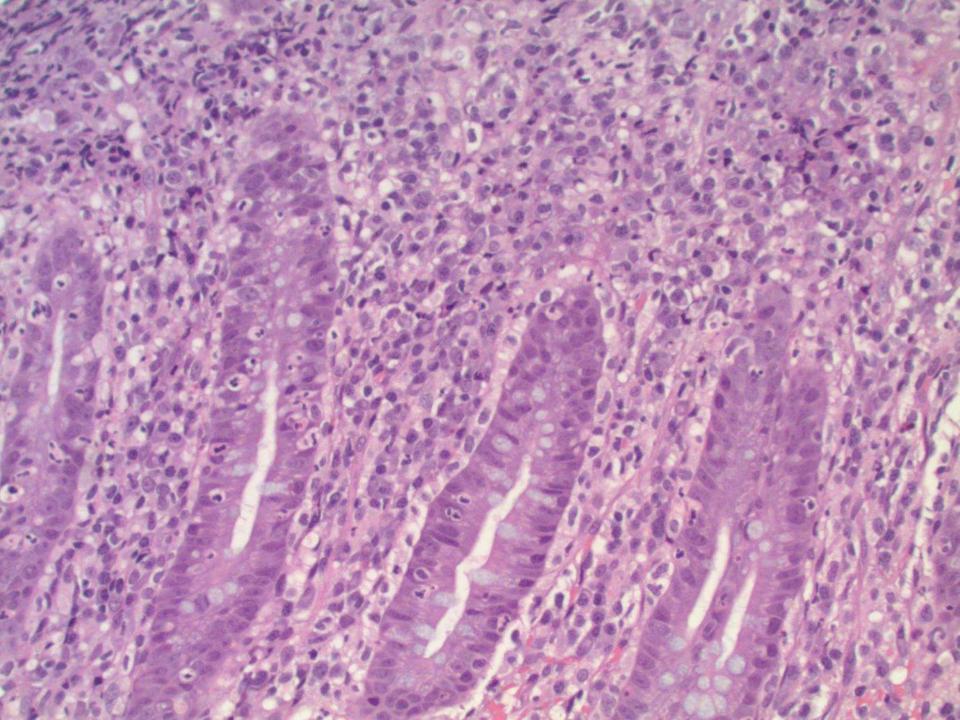
Natalie Patel; El Camino Hospital

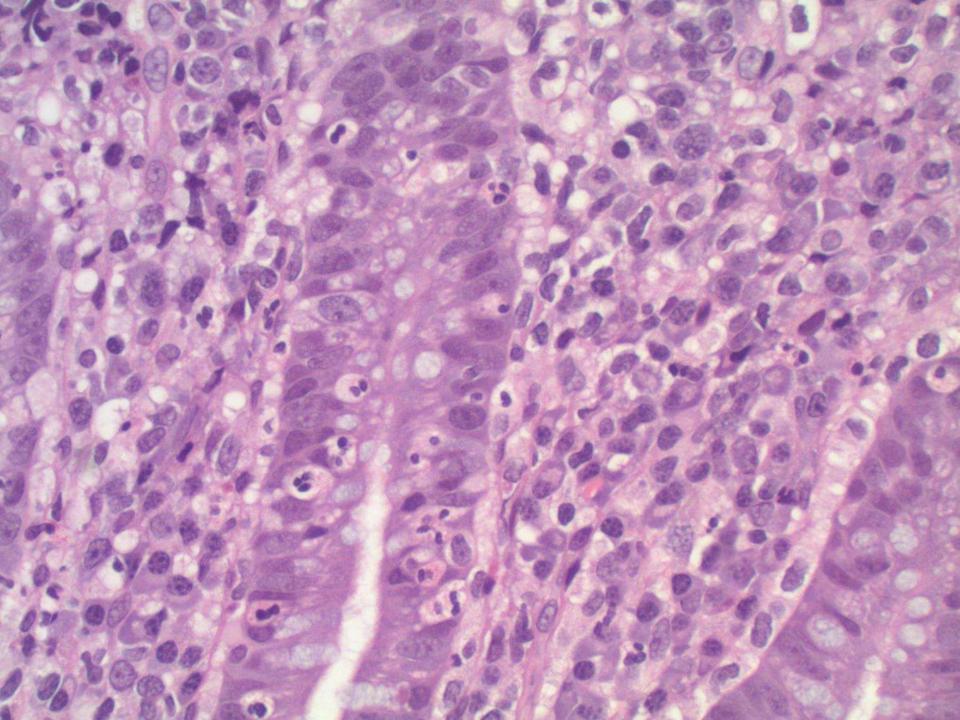
58-year-old M, reported h/o IBD/UC. Recently presented with rectal bleeding, stool cultures negative for C.diff. Patient put back on mesalamine and bleeding improved, however continued to have discomfort. Left colon/rectal biopsy performed, rule out CMV.

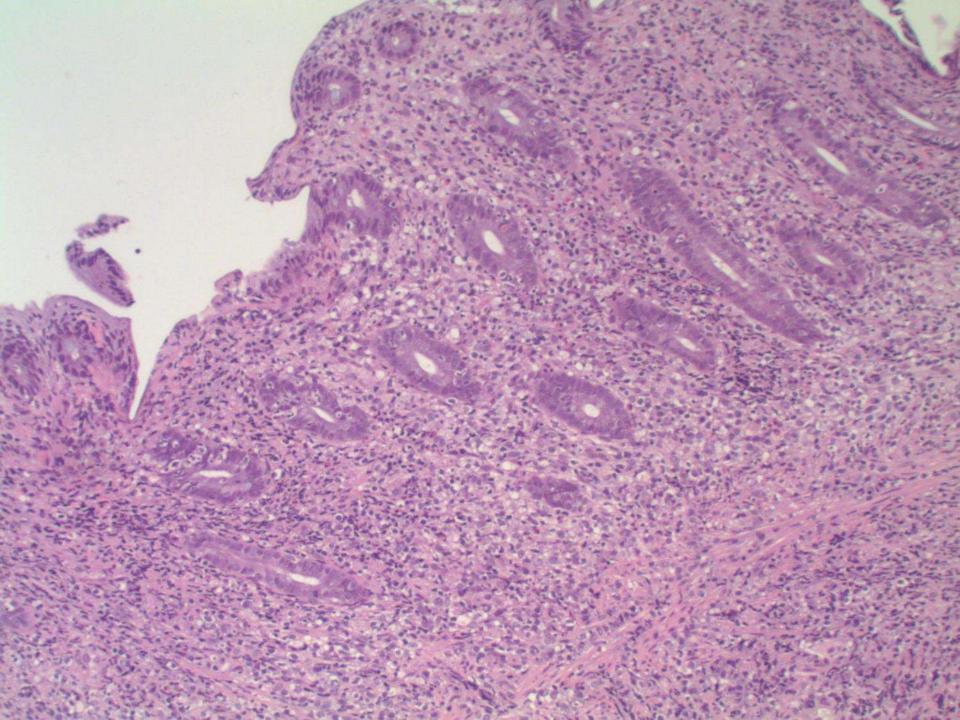


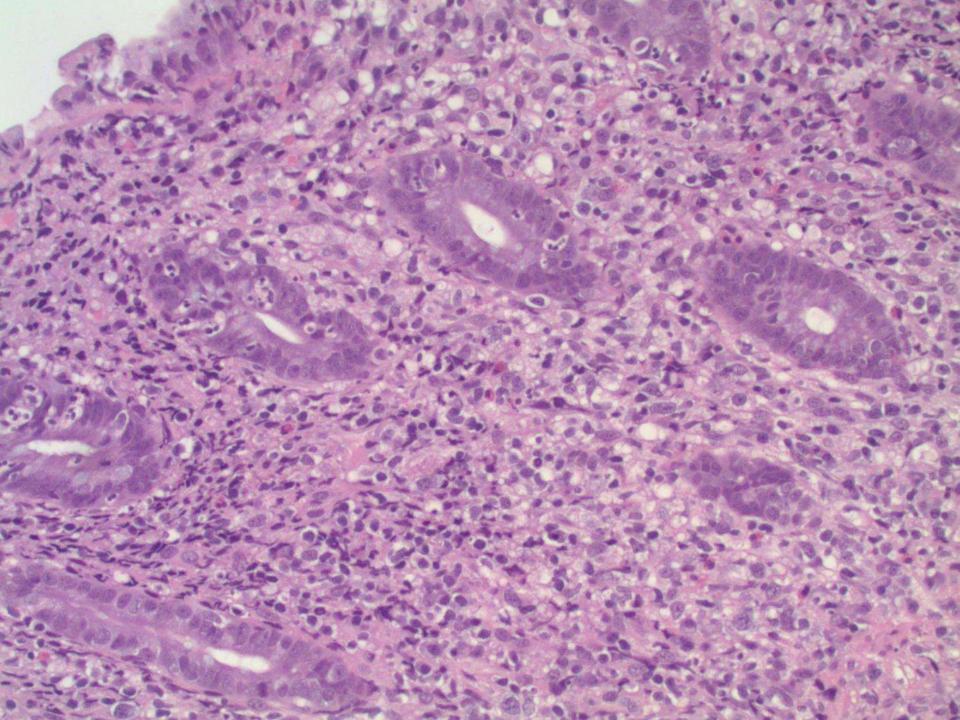


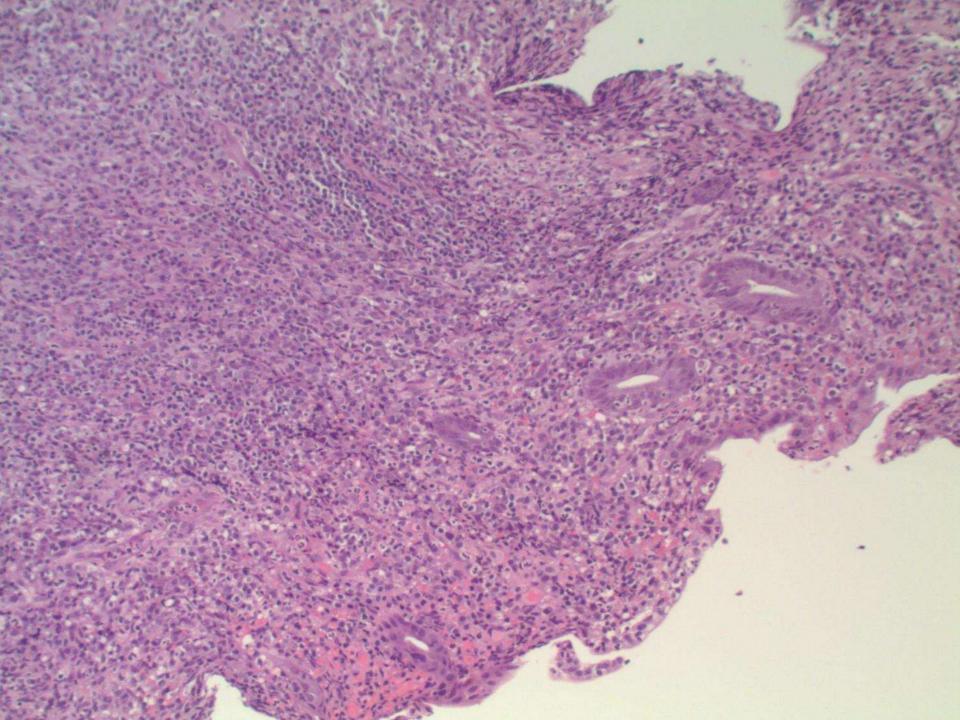


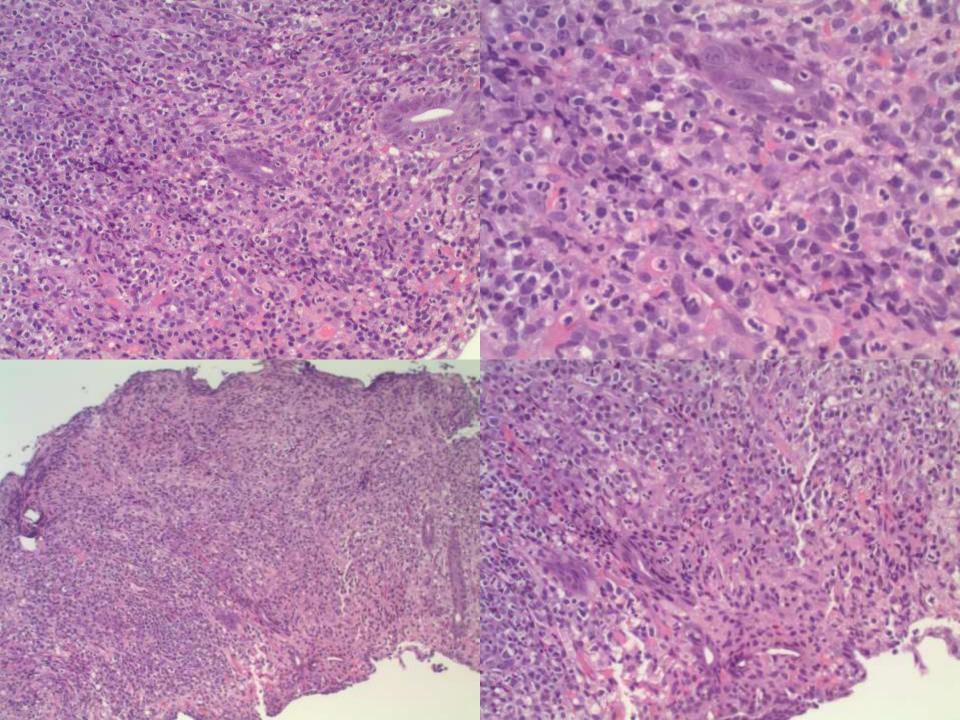








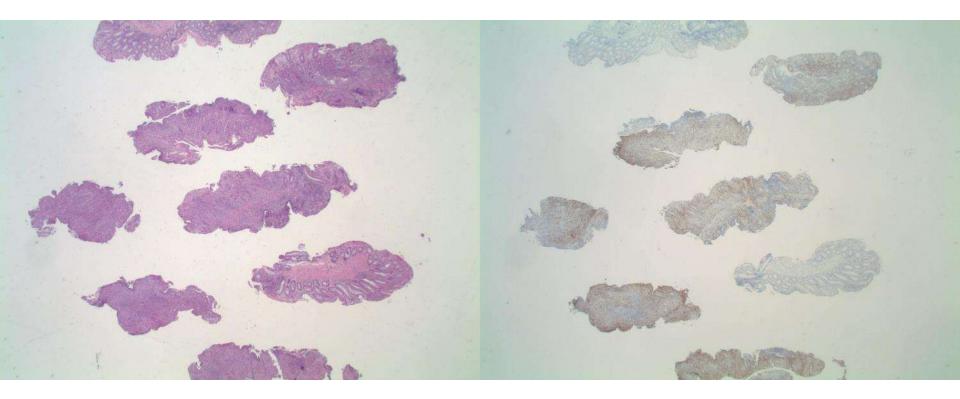


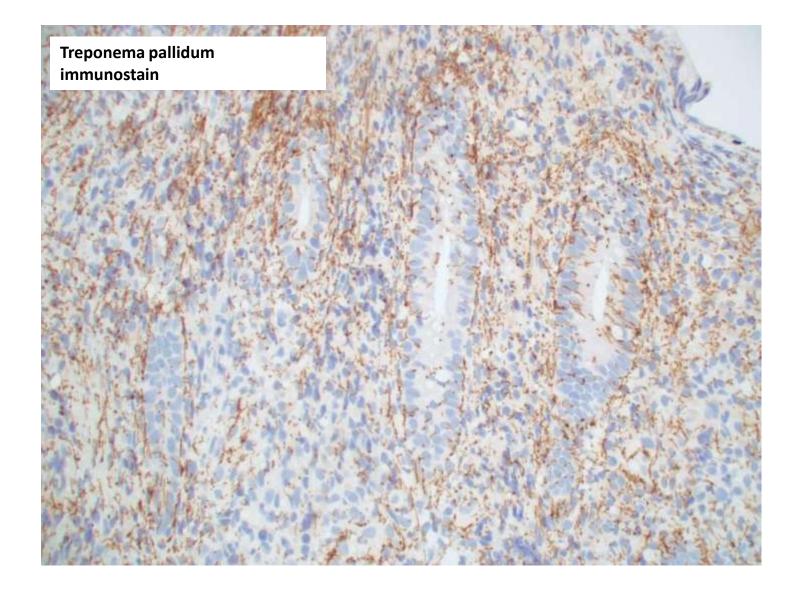


IHCs

- Warthin starry: Negative
- CMV: Negative
- Treponema pallidum: Positive

Treponema pallidum IHC



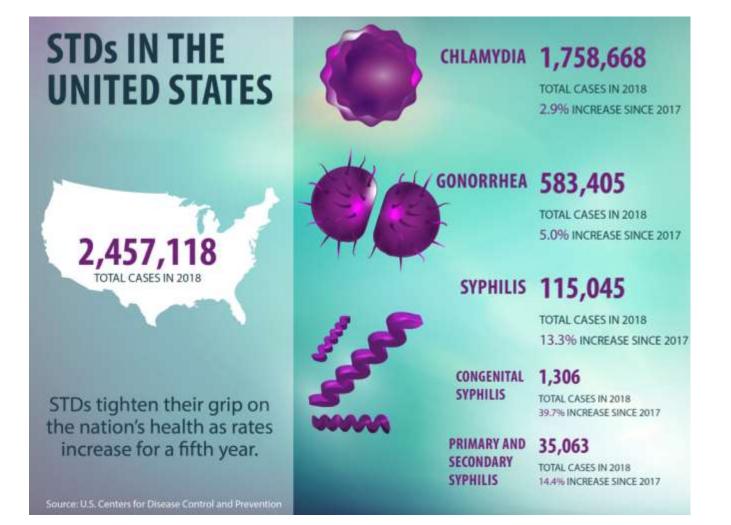


Findings

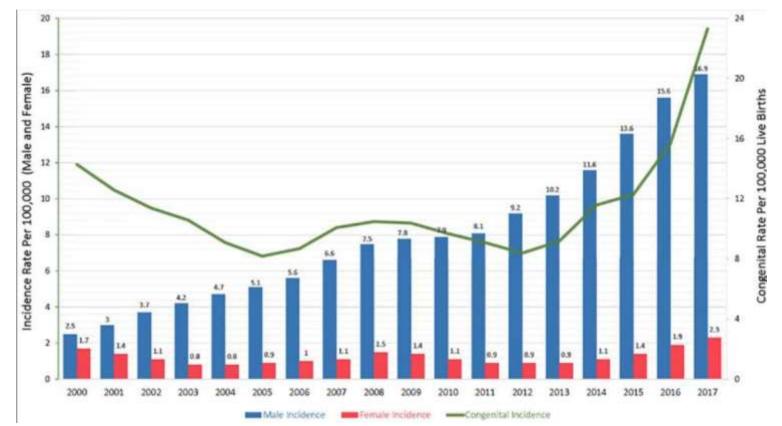
- Colonoscopy: Rectal ulceration
- History of colitis for 3 years diagnosis of ulcerative colitis on mesalamine
- History of unprotected sex with men 4 months prior
- Tests:
 - 1. HIV/Hep B/Tb/Gonorrhea/chlamydia: negative
 - 2. RPR: Reactive (titer: 1:256)
 - 3. FTA antibody: Positive

Syphilis (Treponema pallidum)

- STD dating back to 15th century
- Steady increase in cases since 2001
- > 35,000 primary and/or secondary cases in 2019 (highest since 1991)
 - >85% in men
- Reportable disease to federal and state level
- Fun fact: Venereal disease –reference to Venus the goddess of love



Incidence of primary, secondary, and congenital syphilis rates 2000-2017

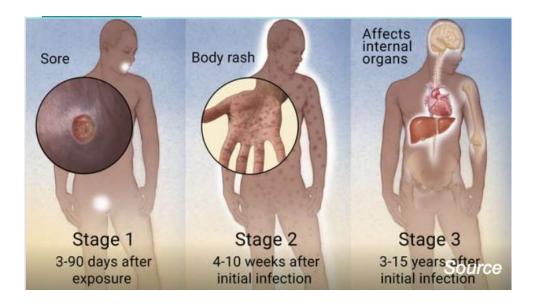


Demographics

- Men (MSM)
- African Americans
- HIV infection
- Increasing rates attributed to:
 - Unsafe sexual behavior practices
 - Diminished funding for prevention of STI

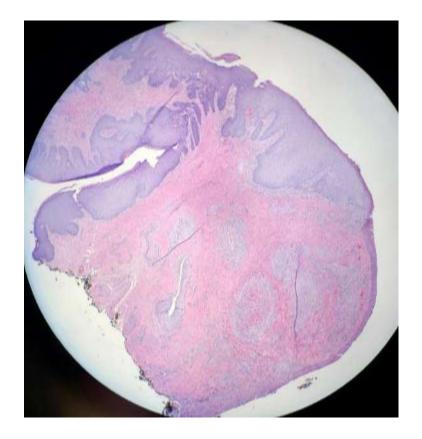
Syphilis

- Spiral gram (-) bacteria
- Affects skin, organs and aerodigestive tract depending on phase
- Diagnosis based primarily on clinical and lab findings
- Anorectal region:
 - Abscess
 - Anal fissure/fistula
 - Mass lesion
 - Ulceration



"The greater imitator"

- Be on high alert, especially @ the anorectal location
- Histologic findings may vary:
 - 1. Plasma cell rich/lymphoid aggregates
 - 2. Lymphohistiocytic with or without granulomas
 - 3. Lymphoma-like
- Other clues:
 - Inflammation is out of proportion for degree of crypt distortion
 - Perineural plasma cells
 - Obliterative endarteritis





Key points

- Syphilis is on the rise!
- Always consider infection if the biopsy just doesn't fit IBD (DDX: syphilis/LGV)
- Seeing a paucity of plasma cells does not exclude syphilis
- A negative spirochete/treponema pallidum immunostain does not exclude the diagnosis
 - Spirochete stain may stain other spirochetes (e.g. Brachyspira)
 - Correlate with serologic tests (RPR/FTA)
- Alert clinician to test for other co-infections (gonorrhea/chlamydia trachomatis/HIV)

References

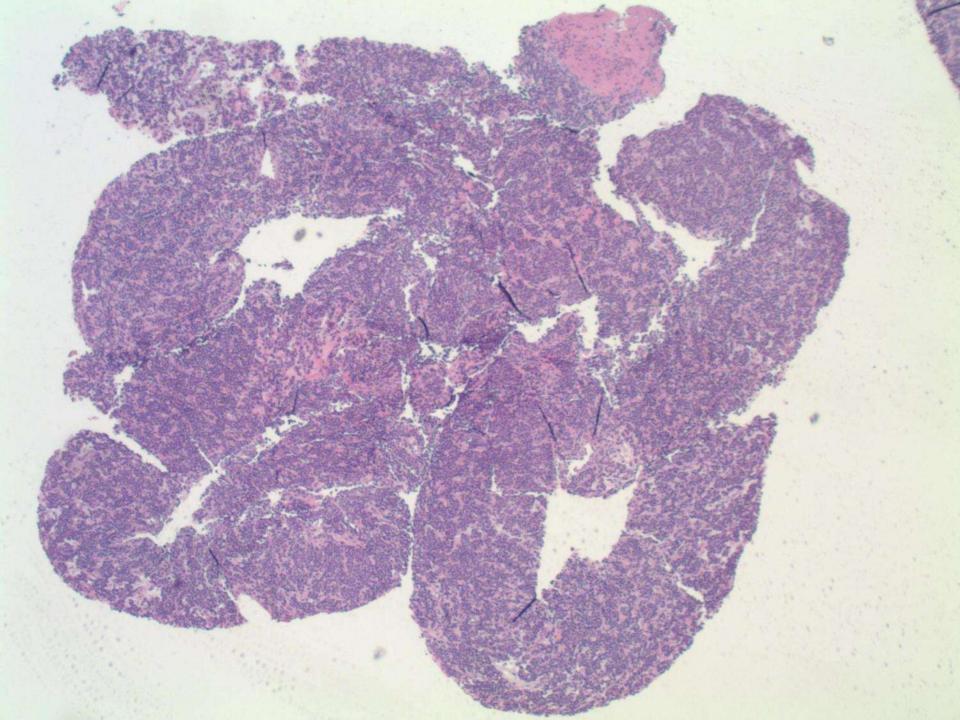
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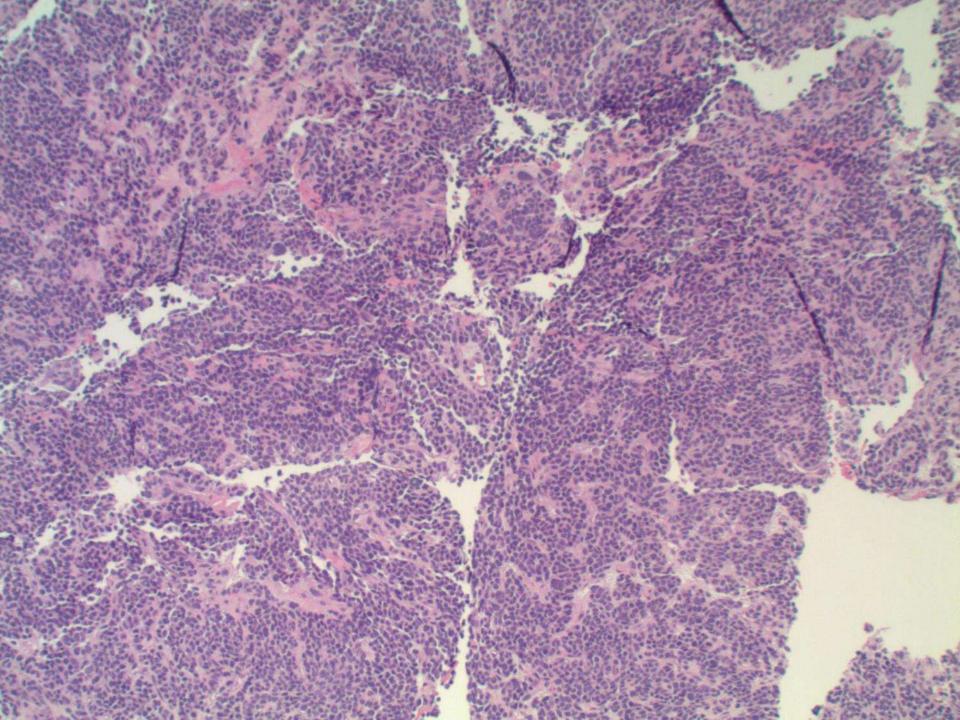
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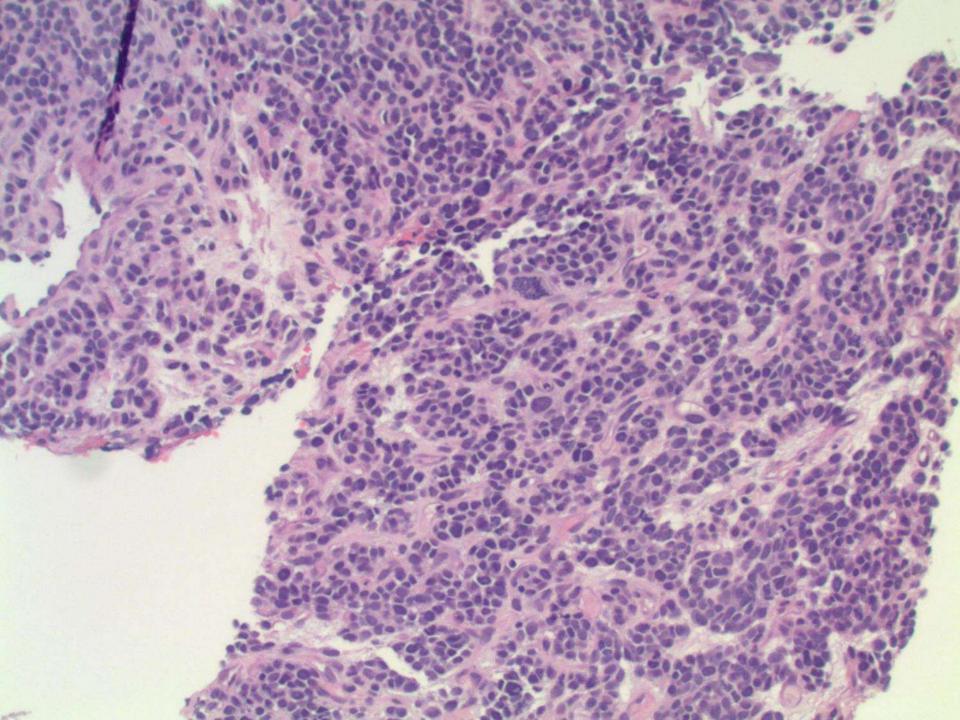
Mahendra Ranchod; Good Samaritan Hospital

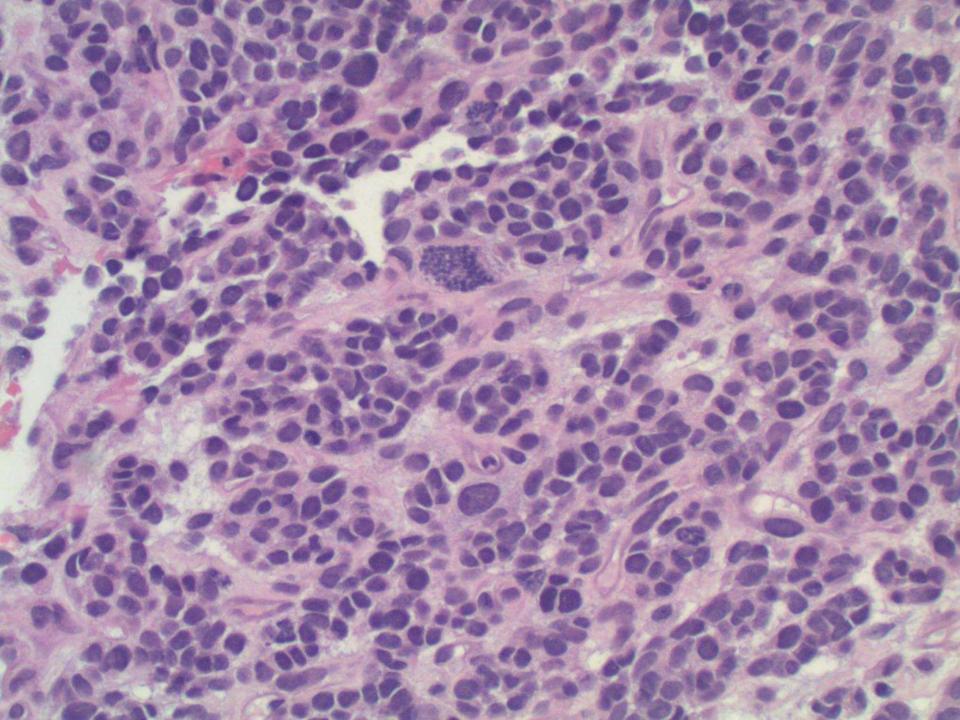
53-year-old F with pleural effusion and underlying 10cm pulmonary mass. Patient had hysterectomy in 2016 for stage I leiomyosarcoma. Core biopsy of lung performed.

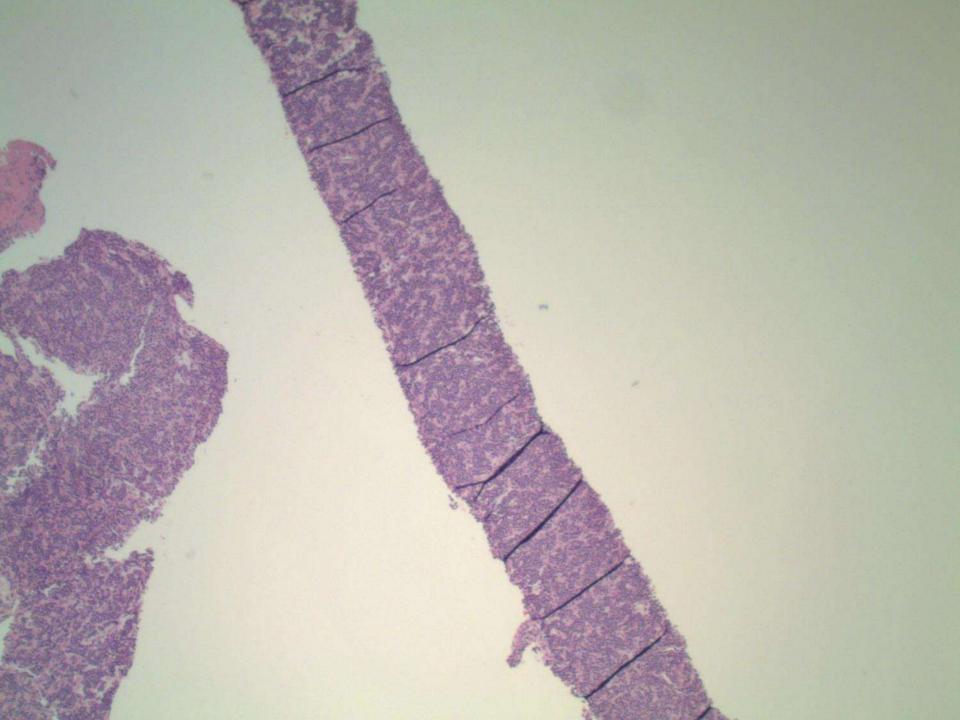


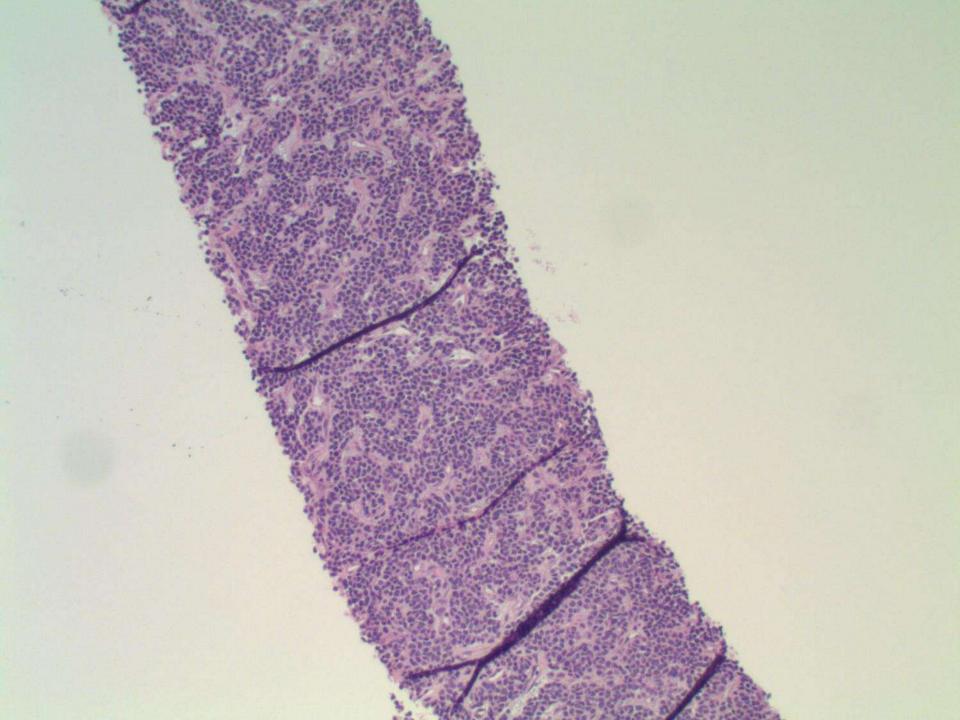


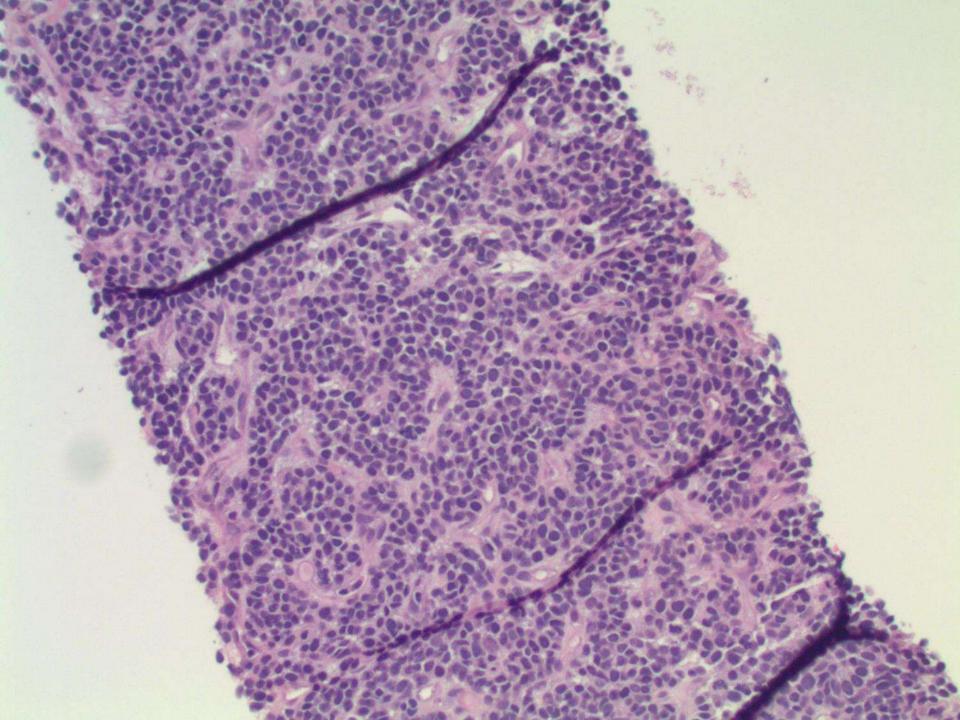


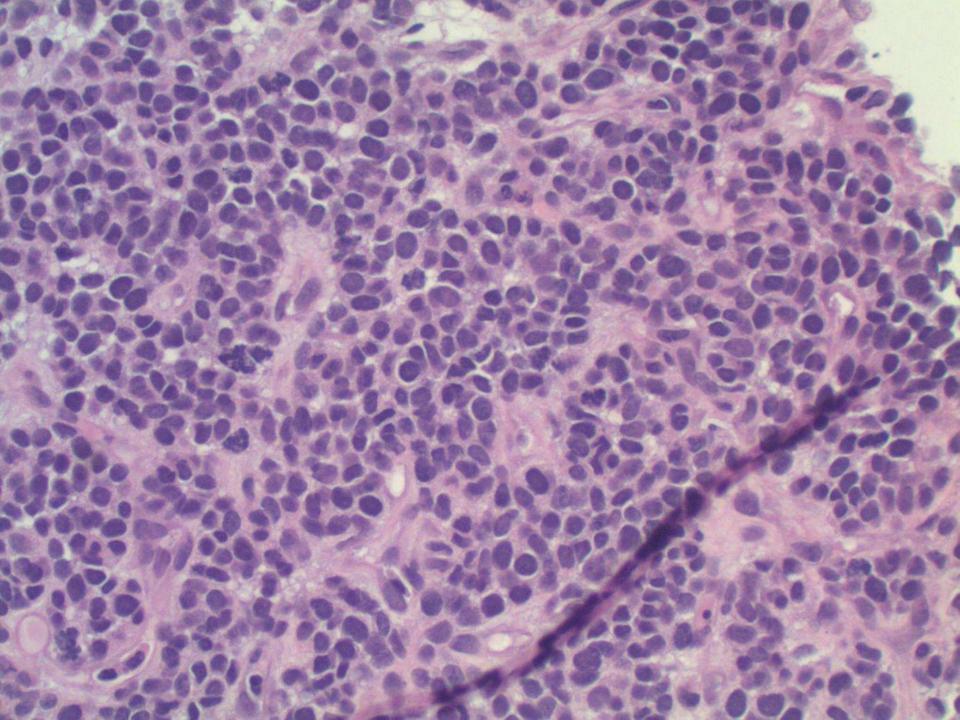












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Small Cell Malignant Tumor of the Lung

Primary poorly diff. carcinoma

TTF-1		- negative
Synaptophysin		- negative
p40		- negative
Metastatic carcinoma		
AE1/AE3	- negative	

Malignant mesothelioma

Metastatic non-epithelial malignancy

Melanoma, other epithelioid malignancies

Clinical History

Prior hysterectomy for leiomyosarcoma

Review of prior hysterectomy slides: High grade leiomyosarcoma Spindle and pleomorphic Extensive necrosis No definite epithelioid or small cells

Our diagnosis: Metastatic epithelioid leiomyosarcoma

A Few Points

- Uterine leiomyosarcoma
 - Spindle, epithelioid, myxoid and pleomorphic
- Sampling issues in needle core biopsies
 - Peeking at a tumor through a keyhole
- Keratin stains can be positive in LMS
 - AE1/AE3 pos in 38% (11% strong, widespread)
 - EMA positive in 44% (6% strong, widespread)

Clinical History

- CLINICAL HISTORY, CLINICAL HISTORY, CLIN.....
- Clinical history is the cheapest ancillary test
- Obtain clinical history before embarking on a myriad IHC stains

desmin

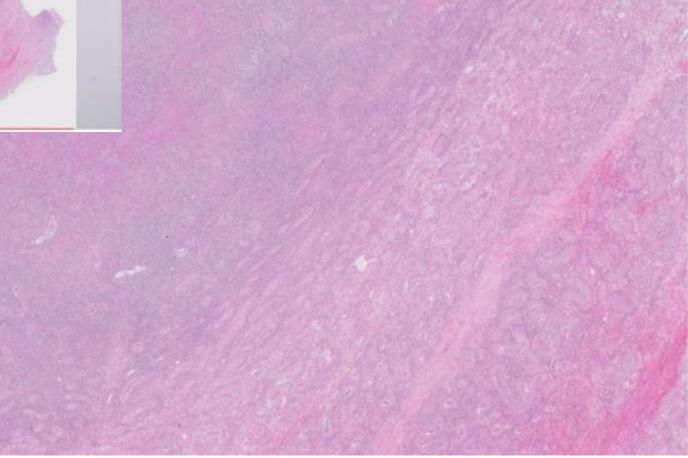
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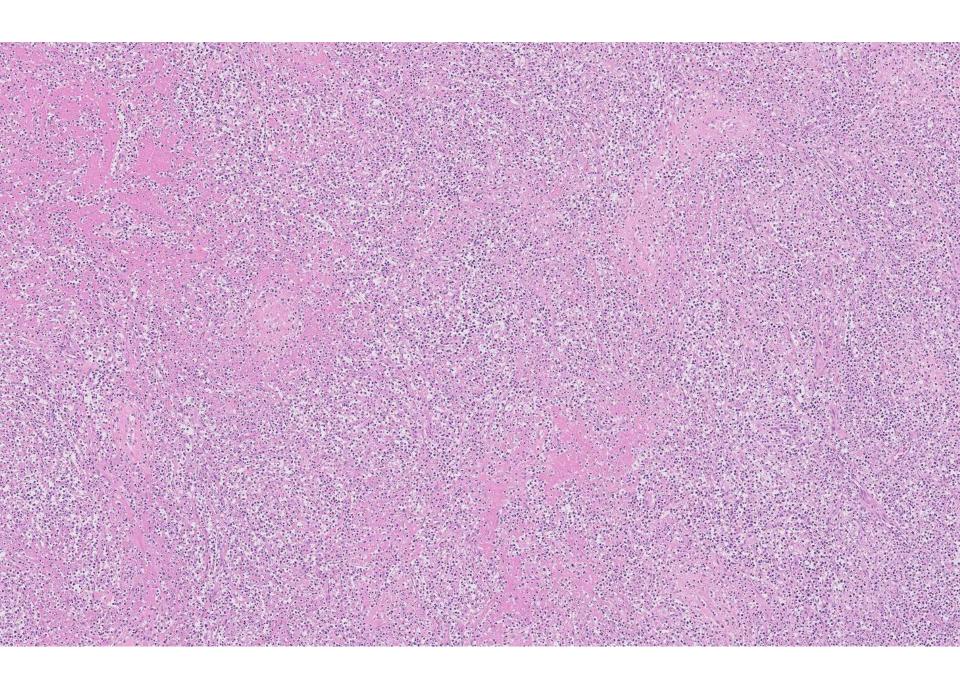
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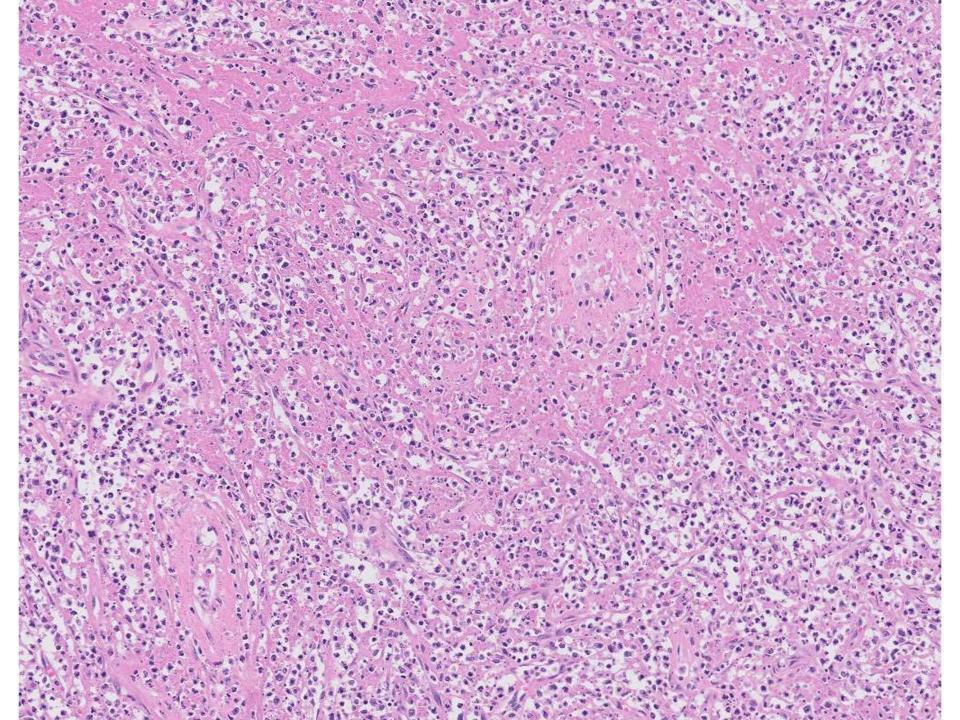
Ashley Volaric/Yaso Natkunam; Stanford

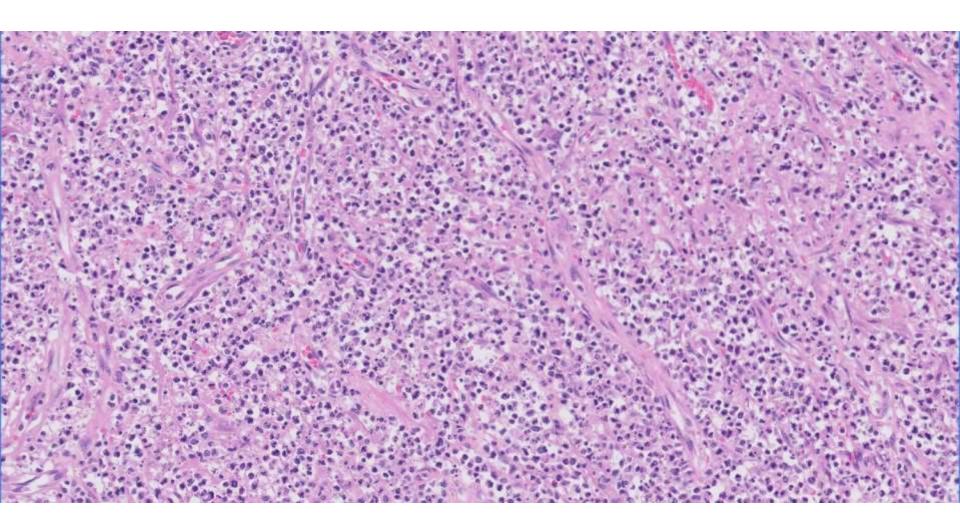
55-year-old M with left testicular mass and remote h/o extranodal NK/T cell lymphoma, nasal type.

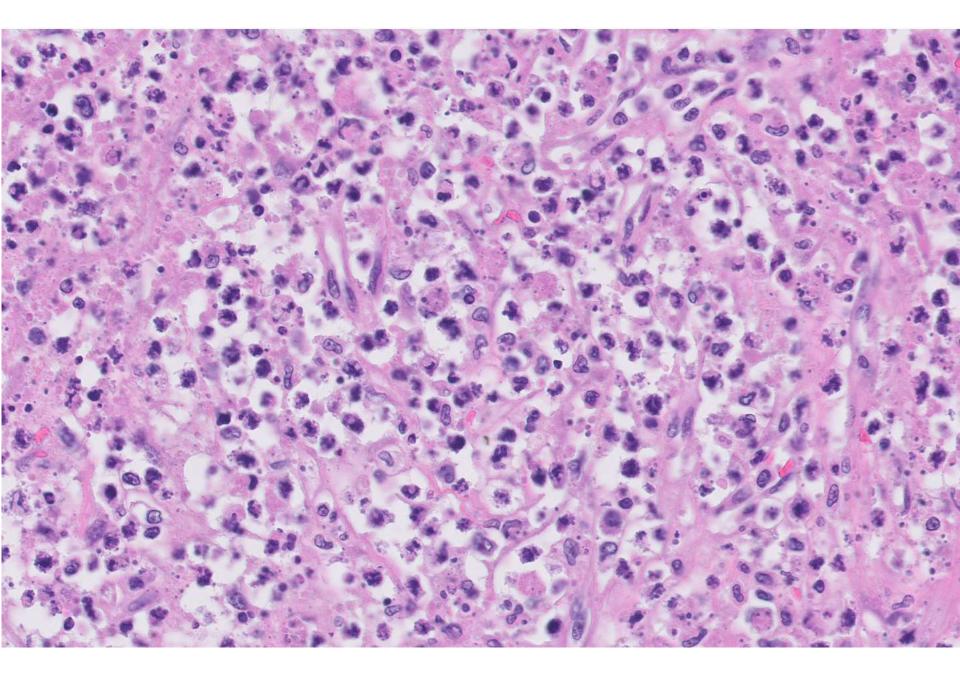










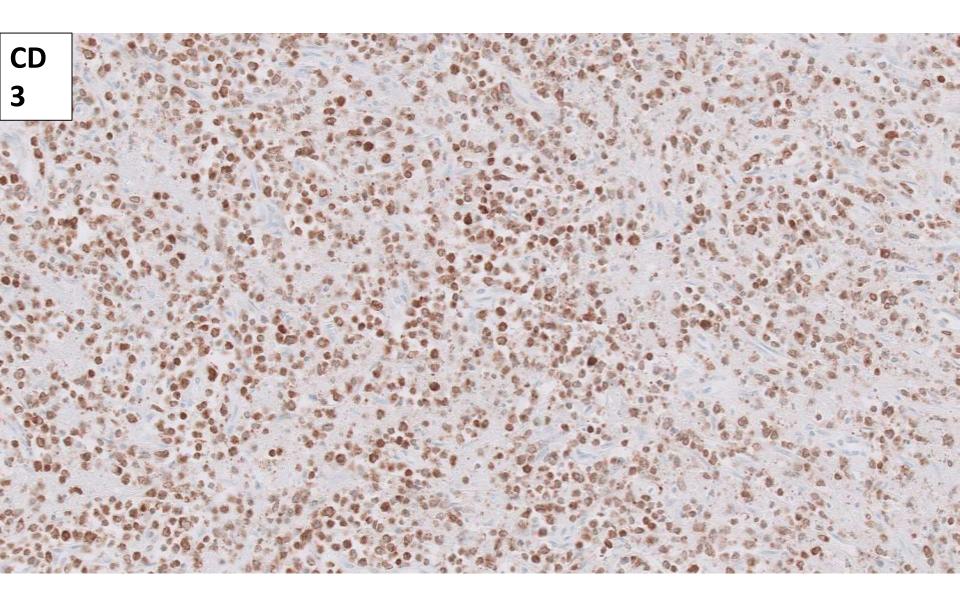


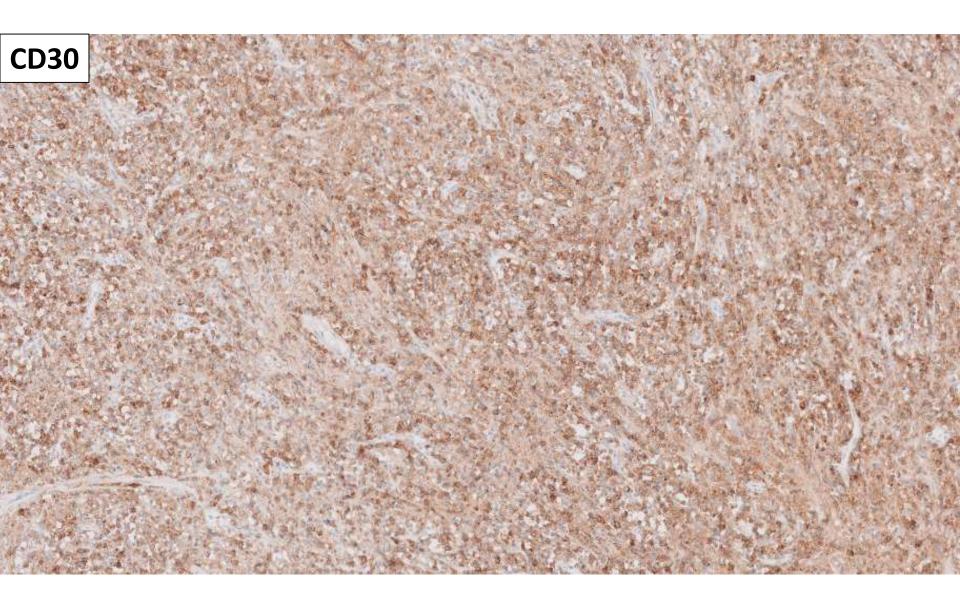


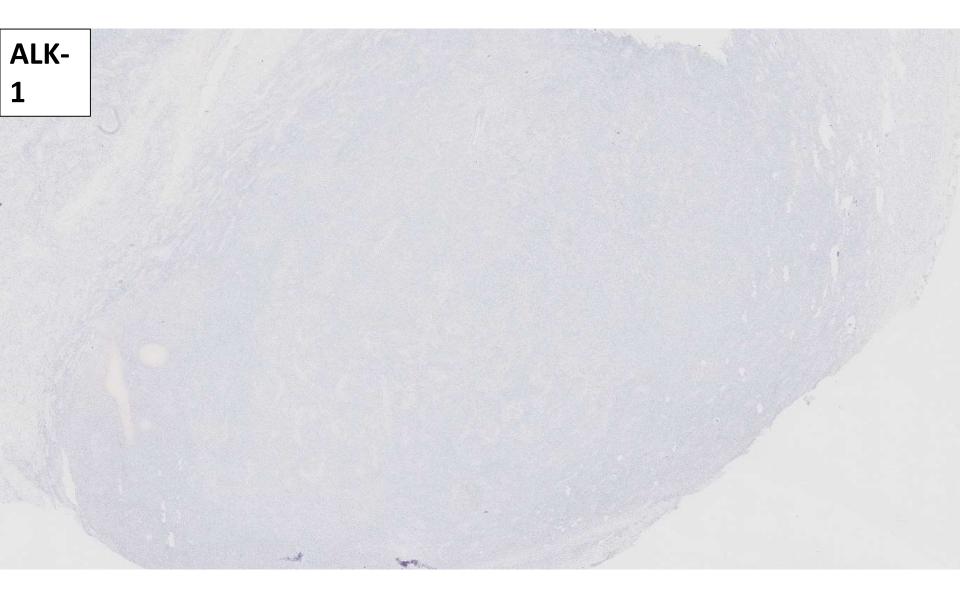


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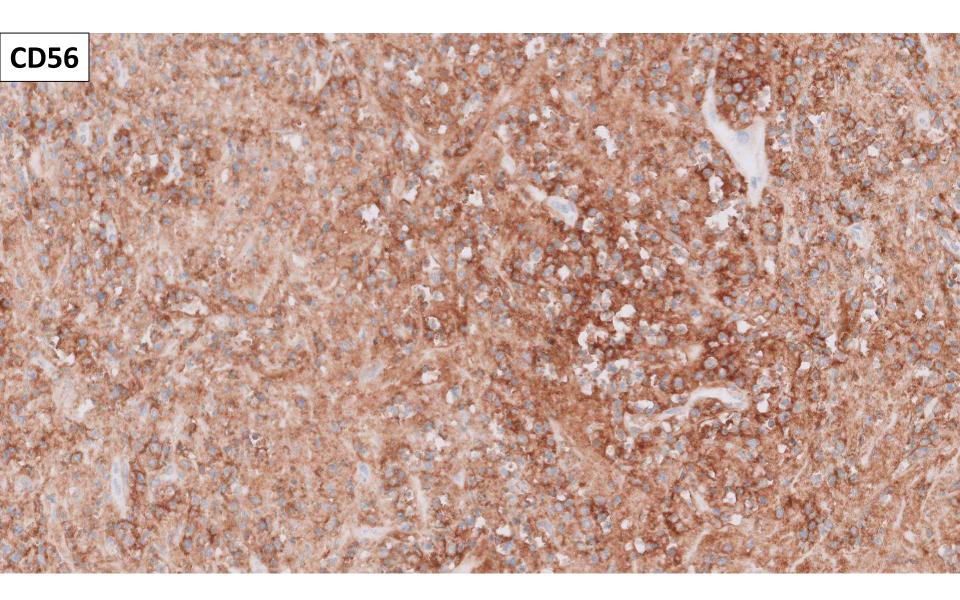


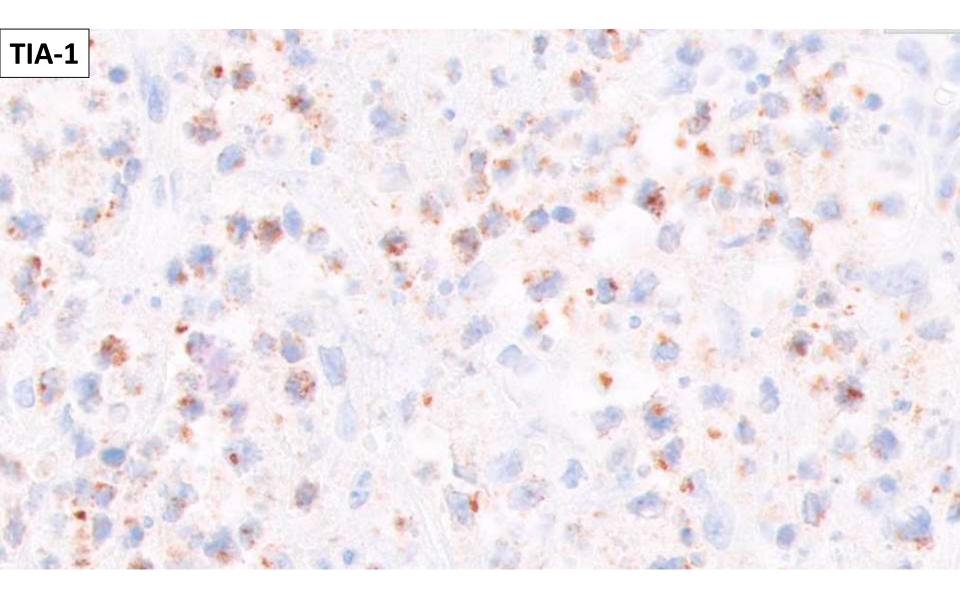


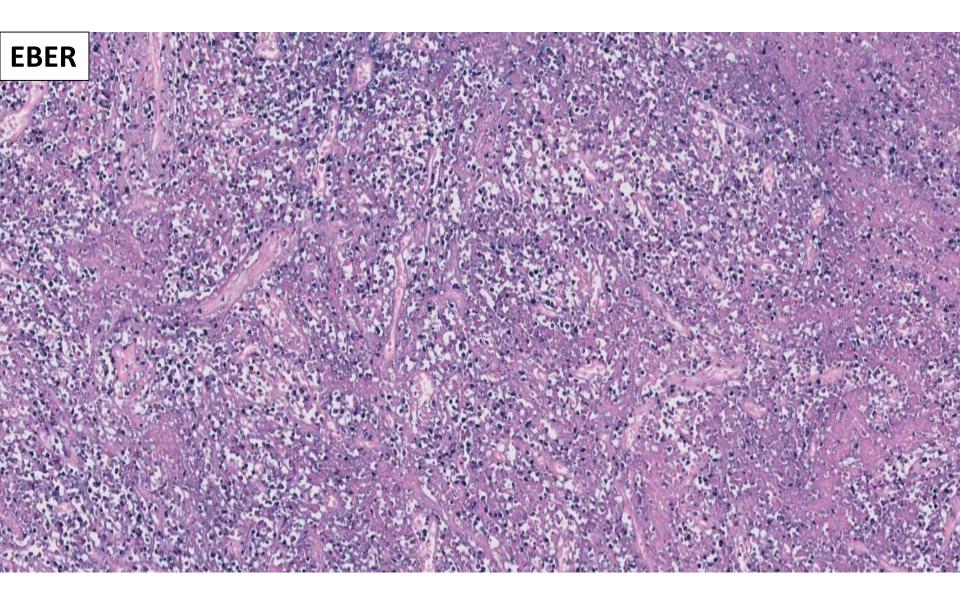




CD 4







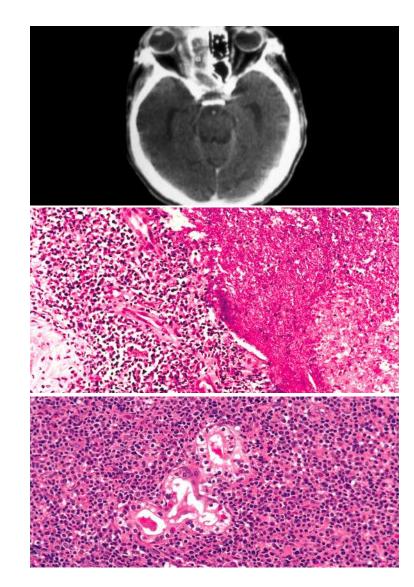


TESTIS, LEFT, ORCHIECTOMY:

-- RECURRENT EXTRANODAL NK/T CELL LYMPHOMA

Extranodal NK/T cell Lymphoma, Nasal Type

- NK or T cell phenotype
- Angiocentric, angiodestructive
- Clinically aggressive
- Prominent necrosis
- Strongly associated with EBV
- Males>females; 44-54 yo
- Upper aerodigestive tract, extranasalskin, soft tissue, GI tract, testes, secondary lymph node involvement



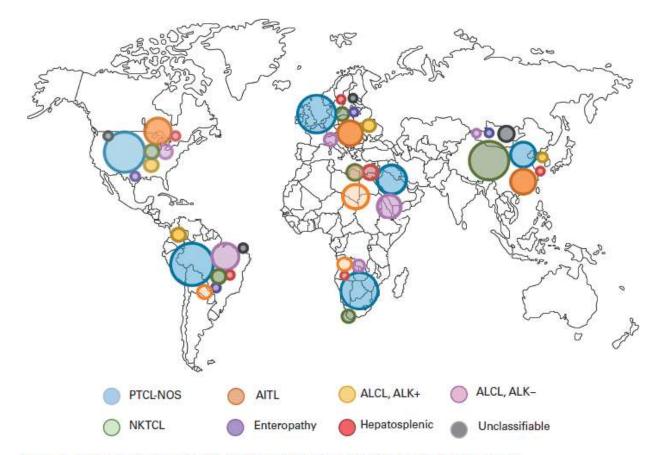
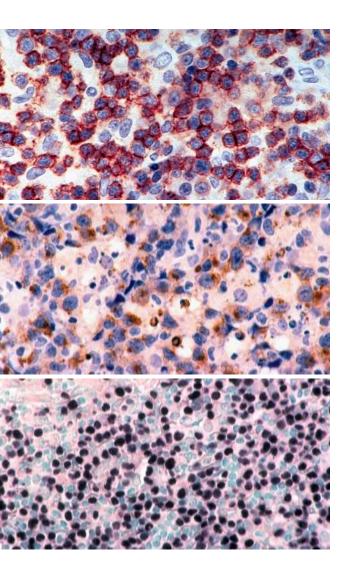


Figure 1. Epidemiologic Variability of Peripheral T-Cell Lymphomas According to Geographic Location.

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALK = anaplastic lymphoma kinase; NKTCL = natural killer/T-cell lymphoma; PTCLNOS = peripheral T-cell lymphoma not otherwise specified.

Data from: Bellei et al. Hernatol Oncol. 2017[4]; Bellei et al. Rev Bras Hernatol Hernoter. 2012[5]; Perry et al. Haernatologica. 2016[6]; Vose et al. J Clin Oncol. 2008.[7]

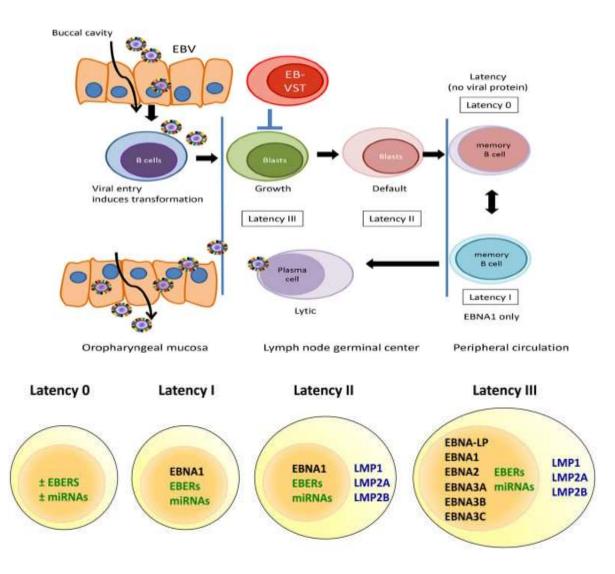


NK/T cell Lymphoma Immunophenotype

- CD2(+)
- CD5(-)
- CD56(+)
- Surface CD3(-)
- Cytoplasmic CD3-epsilon(+)
- Cytotoxic molecules (+)
- CD30(+/-)
- If cytotoxic T cell phenotype: CD5(+), CD8(+), TCR(ab/gd)
- EBV(+)

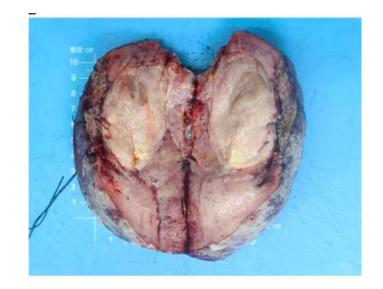
EBV Infection

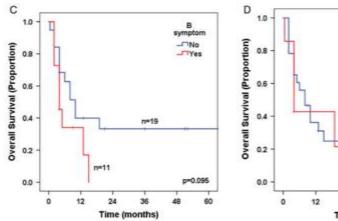
- Virus in episomal form
- Type II latency: EBNA1(+), EBNA2(-), LMP1(+)
- Most cases are of subtype A
- EBV circulating DNAindicator of disease progress, treatment effect

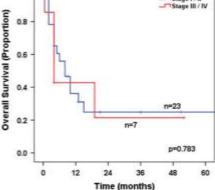


Extranasal NK/T cell Lymphoma: Testes

- Primary site, very rare
- Associated with even more aggressive clinical course and disseminated disease
- Testicular swelling, pain, B symptoms
- Asian men







-Stage 1 / II

Table 2. Risk Factors Included in the Different Prognostic Indices for NK/T-Cell Lymphoma

Prognostic Index of NKCL	PINK with EBV (DNA)
ge > 60 yr	Age > 60 yr
tage III or IV disease	Stage III or IV disease
	Distant lymph node involvement
lon–nasal-type disease	Non–nasal-type disease
	EBV (DNA) present
	ge > 60 yr tage III or IV disease istant lymph node involvement on–nasal-type disease

EBV = Epstein-Barr virus; ENKTL = extranodal NK/T-cell lymphoma; KPT = Korean Prognostic Index; LDL = lactate dehydrogenase; NK = natural killer; NKCL = natural killer cell lymphoma; PINK = prognostic index of natural killer cell lymphoma; PINK-E = prognostic index of natural killer cell lymphoma with EBV.

Data from: Lee et al. J Clin Oncol. 2006[16]; Kim et al. Lancet Oncol. 2016.[17]

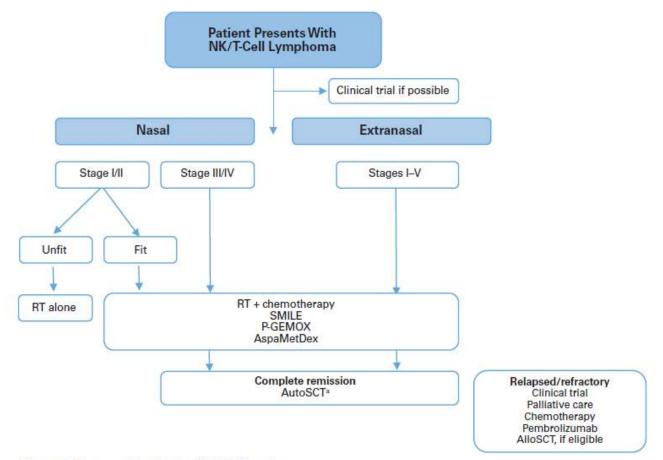


Figure 2. Treatment Algorithm for NK/T-Cell Lymphoma.

AutoSCT should be considered for patients with stage I/II disease, but it is not absolutely needed.

AlloSCT = allogeneic stem cell transplantation; AspaMetDex = pegylated asparaginase, methotrexate, and dexamethasone; autoSCT = autologous stem cell transplantation; NK = natural killer; P-GEMOX = pegylated asparaginase, gemcitabine, and oxaliplatin; RT = radiotherapy; SMILE = dexamethasone, methotrexate, ifosfamide, Lasparaginase, and etoposide.

Data from: NCCN guidelines 2017.[23]

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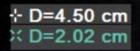
Neslihan Kayraklioglu/Robert Ohgami/Joshua Menke; UCSF

17-year-old M with 3-month history of nontender, mobile, and rubbery right neck mass. He denies B symptoms and CBC is within normal limits. FNA biopsy showed monoclonal CD10 positive B-cell population concerning for non-Hodgkin lymphoma. Ultrasound, PET-CT, and right neck lymph node excision were performed. Right neck ultrasound shows 4.5 cm submandibular lymph node

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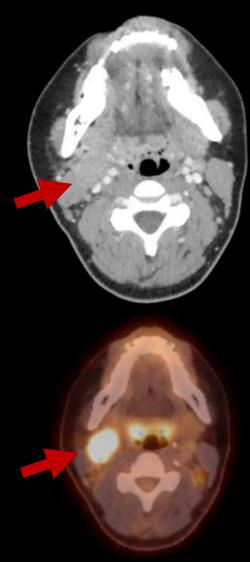
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PET-CT around time of biopsy shows right level 2 nodal conglomerate (3.3 cm) with SUV max of 19

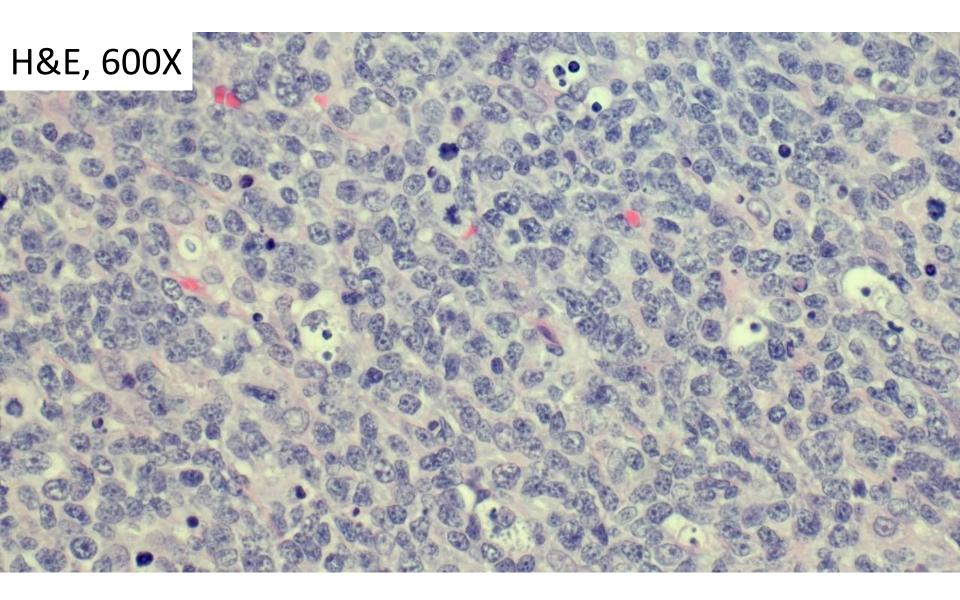


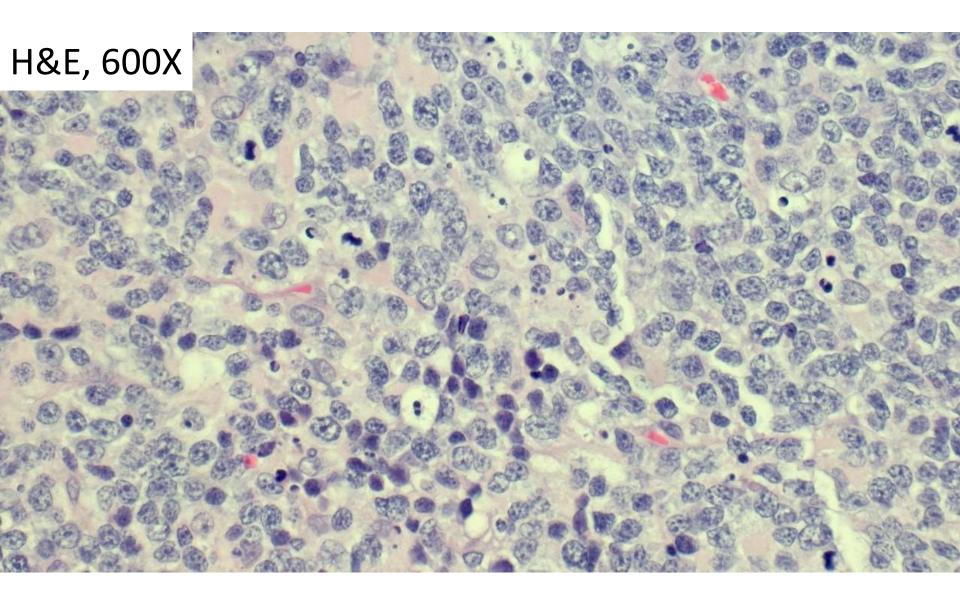


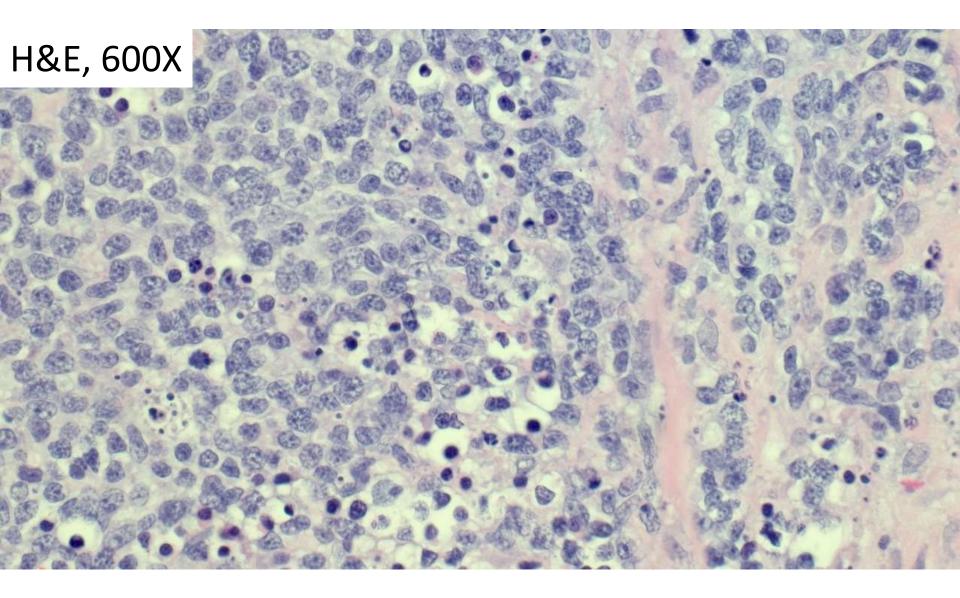
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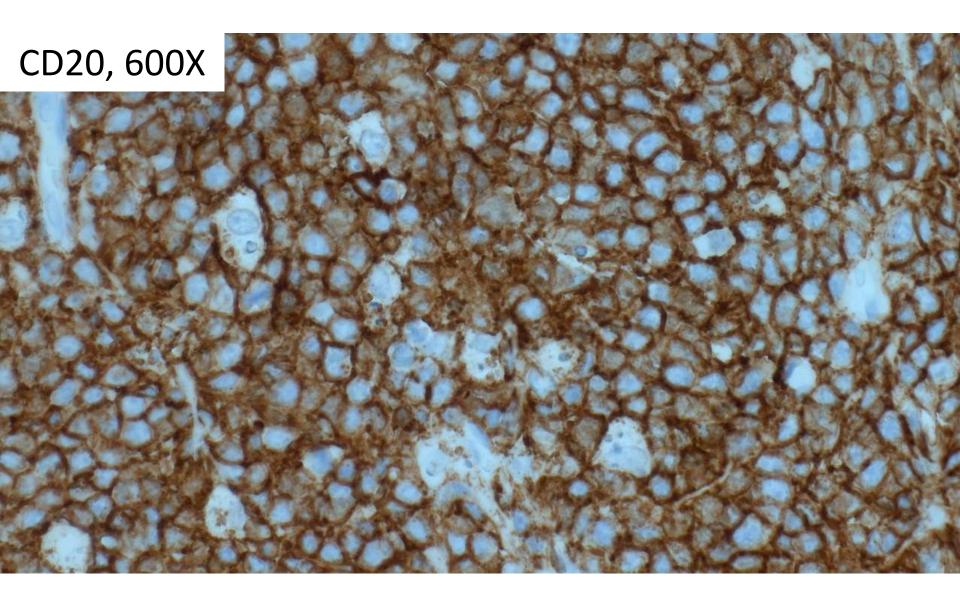
Right neck lymph node excision

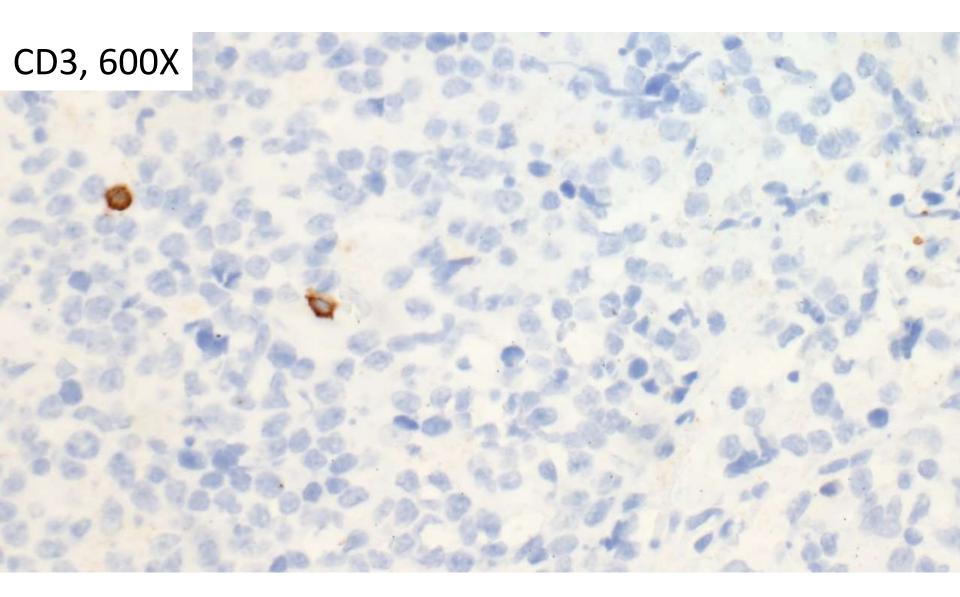
H&E, 200X

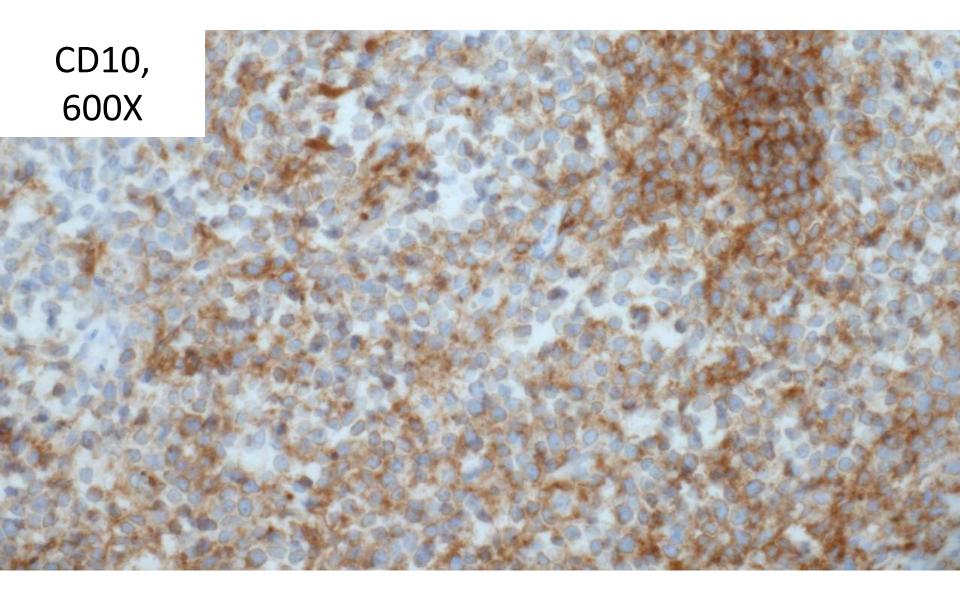


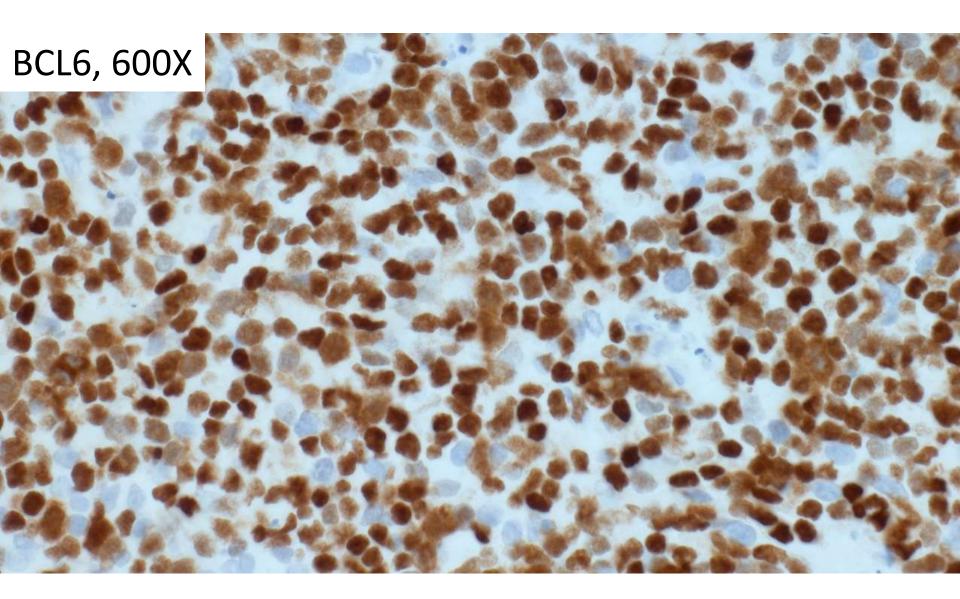


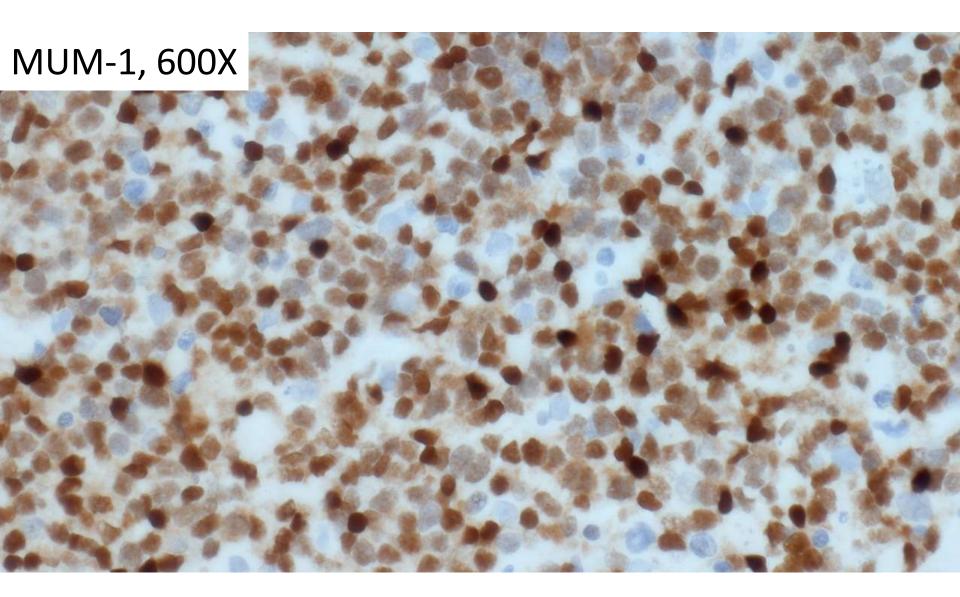


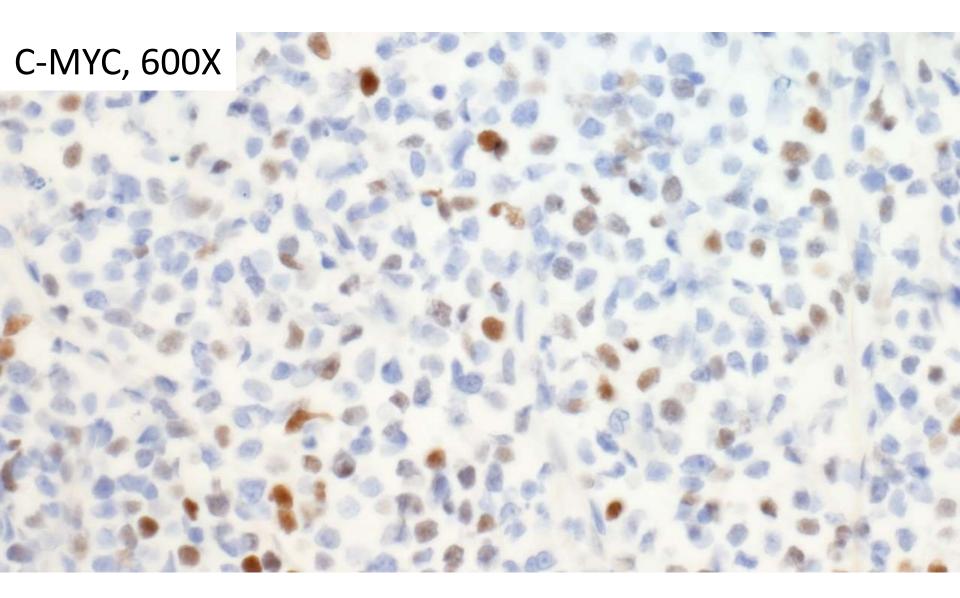


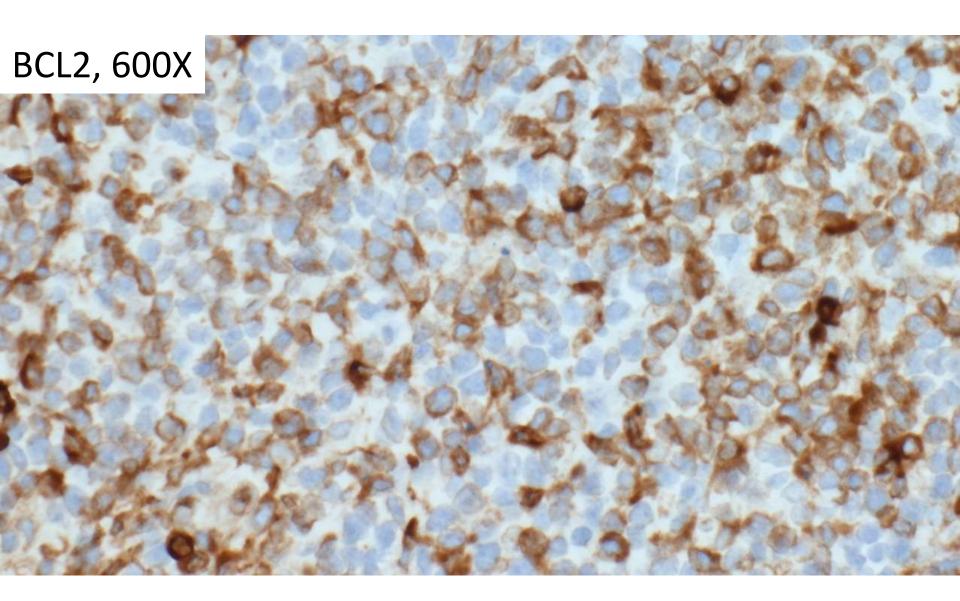


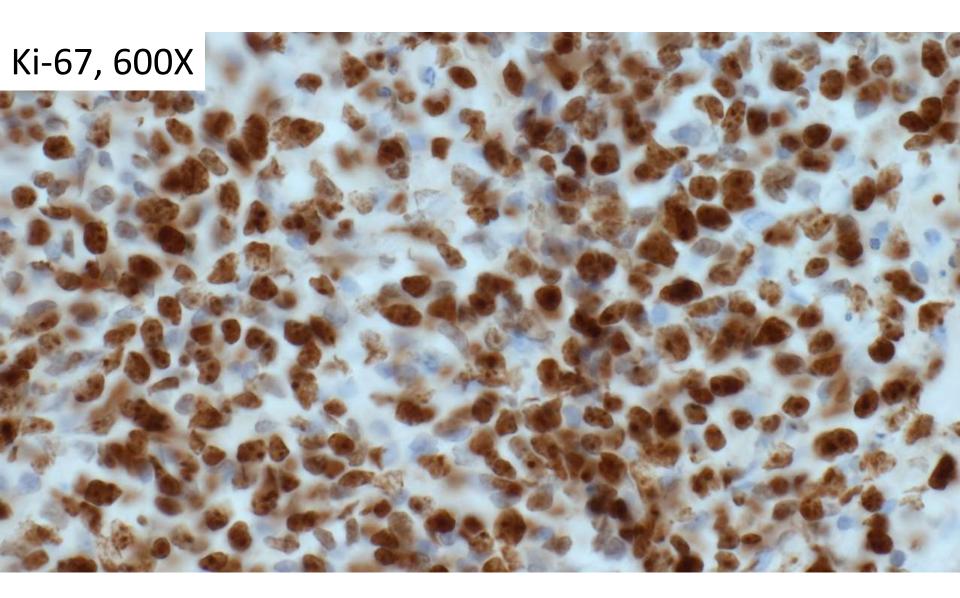


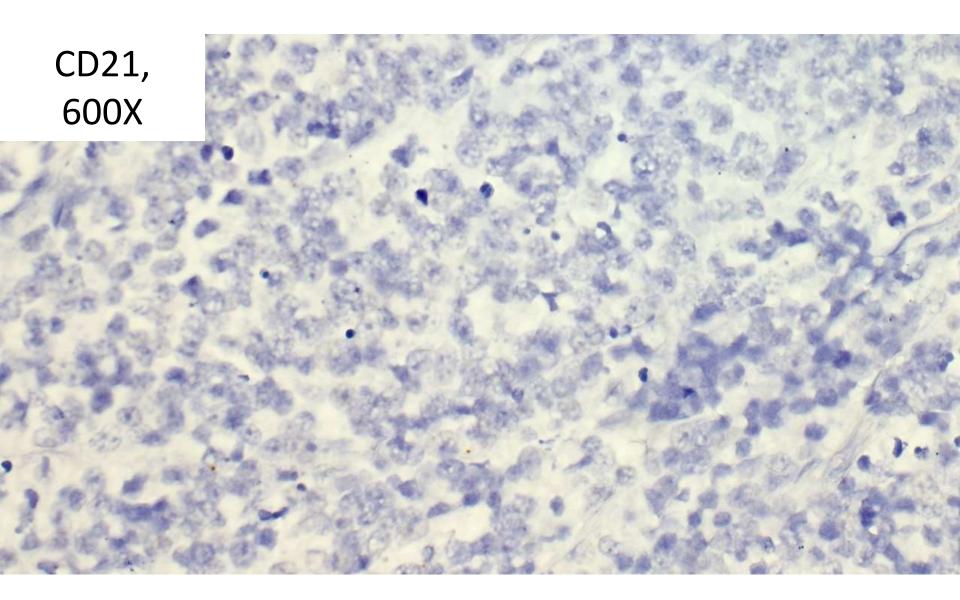


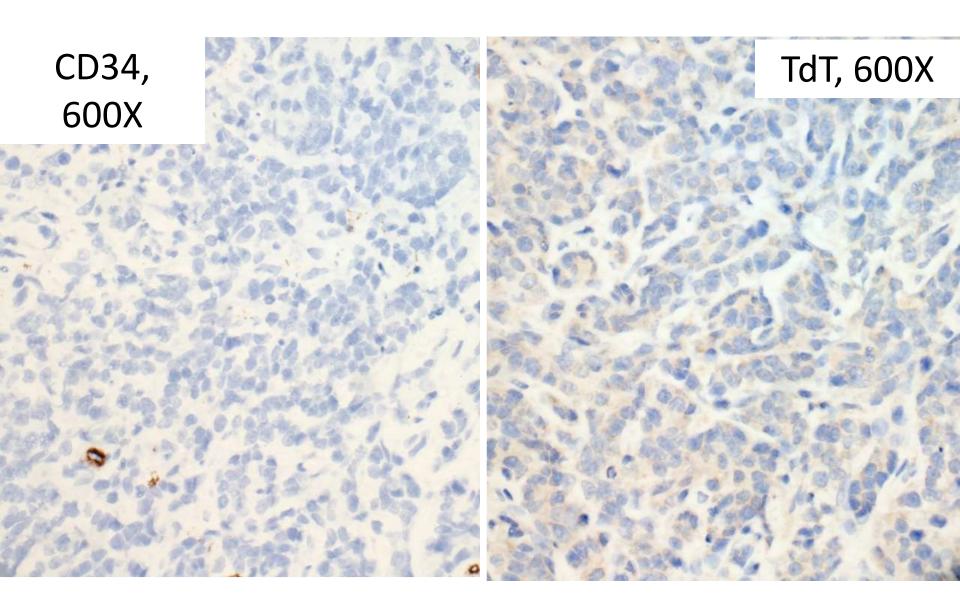






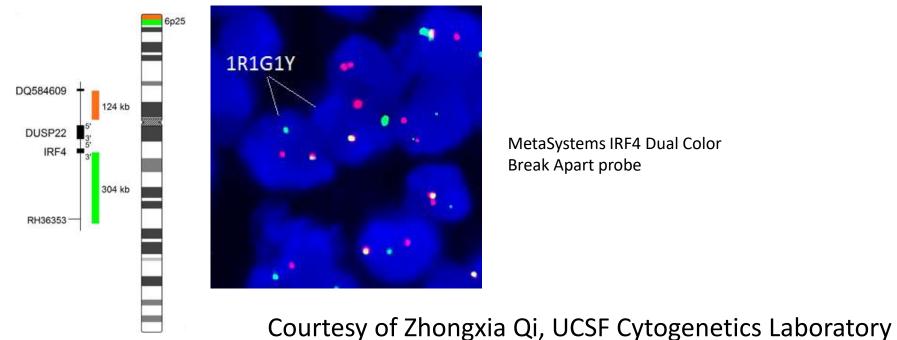






FISH results

- IRF4 rearrangement found in 39 of 50 (78%) of interphase cells
- No MYC, BCL2, or BCL6 rearrangements detected



Diagnosis and Staging

- Large B-cell lymphoma with *IRF4* rearrangement
- Stage 1A disease based on imaging, negative lumbar puncture, and negative bone marrow biopsy

Treatment and Follow up

- AANHL 1131 R-CYM 2 (rituximab, cytarabine, methotrexate) and prophylactic intrathecal chemotherapy
- PET-CT shows interval resolution of right neck mass without residual hypermetabolism

Large B-cell lymphoma with *IRF4* rearrangement (LBCL-*IRF4*)

- Rare B-cell lymphoma seen mostly in children and young adults
- Frequently involves head or neck and Waldeyer ring
- Architecture ranges from entirely follicular to diffuse
- Immunophenotype characterized by expression of MUM-1 and BCL6 with variable expression of CD10 and BCL2
- Associated with favorable prognosis

Salaverria et al. Blood 2011

Subset of LBCL-IRF4 has high grade features

- Per the 2017 WHO, mitotic figures are infrequent and starry sky pattern is absent in LBCL-*IRF4*
- However, the current case shows high mitotic rate (4-17 mitoses per high power field) and prominent starry sky pattern
- Other differential diagnoses such as high-grade B-cell lymphoma with *MYC, BCL2,* and/or *BCL6* rearrangements and Burkitt's lymphoma were ruled out with negative *MYC* FISH

LBCL-IRF4 genotype

- Has a distinct molecular profile when compared to other pediatric large B-cell lymphomas
- Characterized by mutations in IRF4 and NK-kB pathway genes (CARD11, CD79B, and MYD88), losses of 17p13 and gains of chr7, 11q12.3-q25 (Ramis-Zaldivar et al. Blood 2019)
- The current case (and a similar case with high grade features) is being studied with whole exome sequencing and will be compared to the known genetic profile of LBCL-*IRF4*

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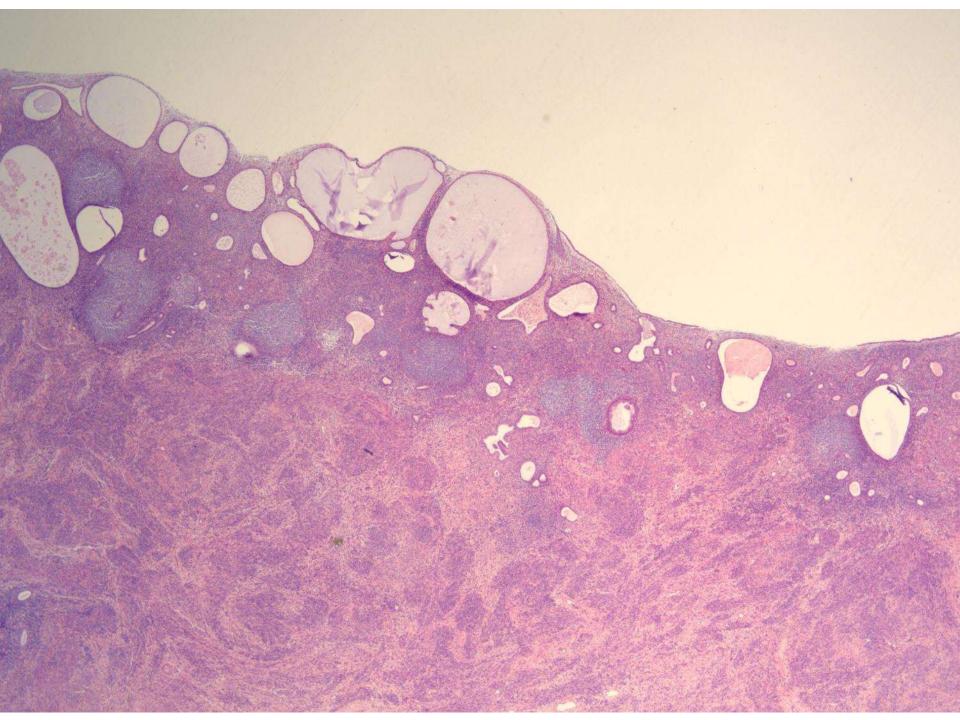
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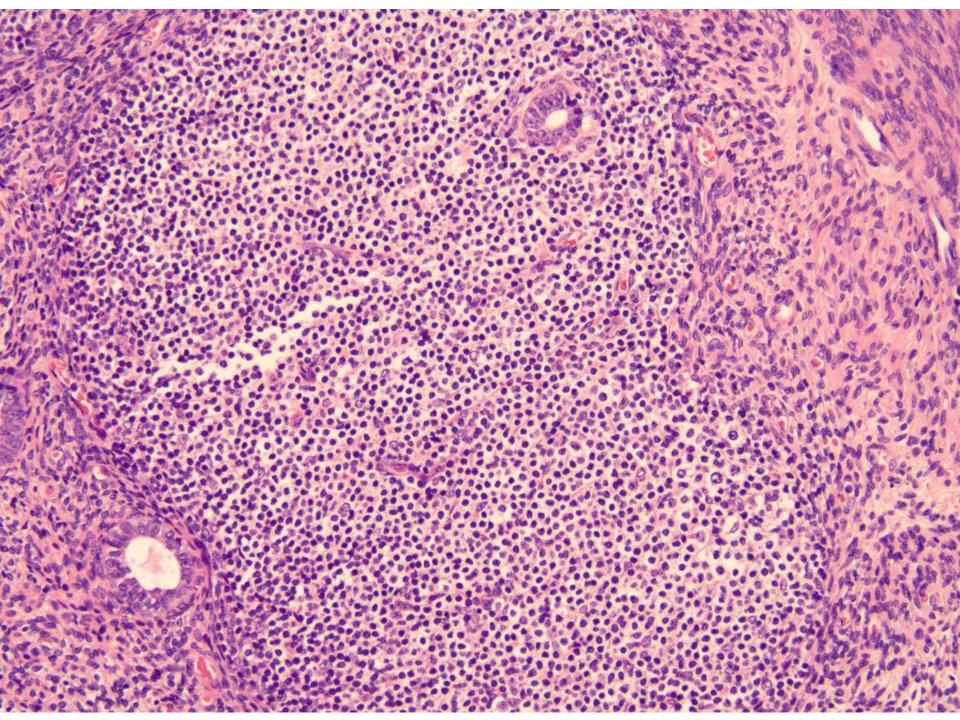
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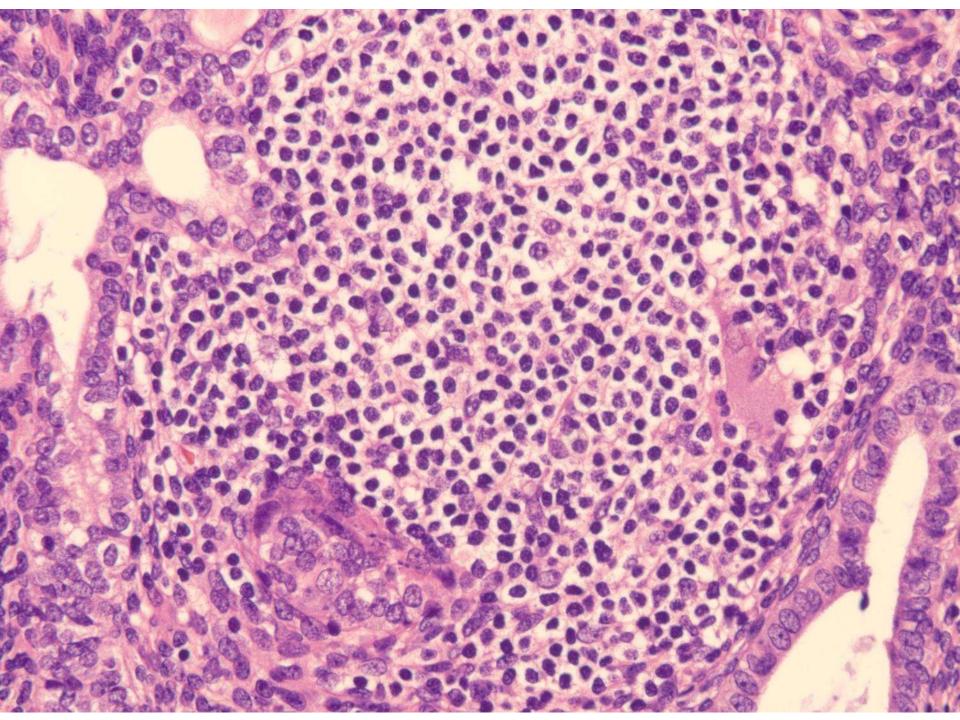
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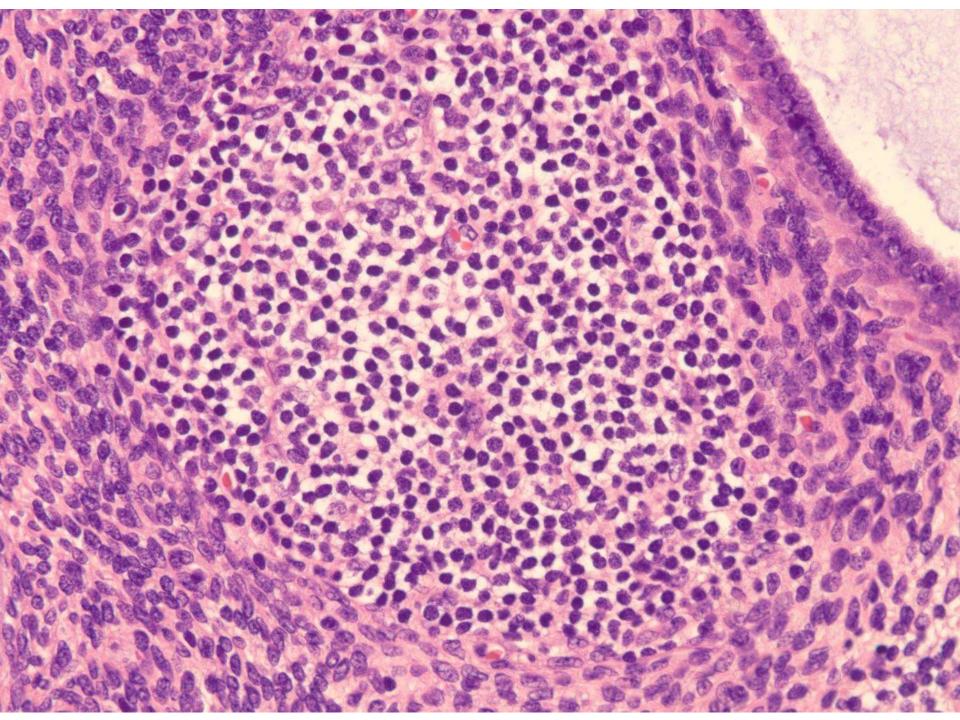
Charles Lombard; El Camino Hospital

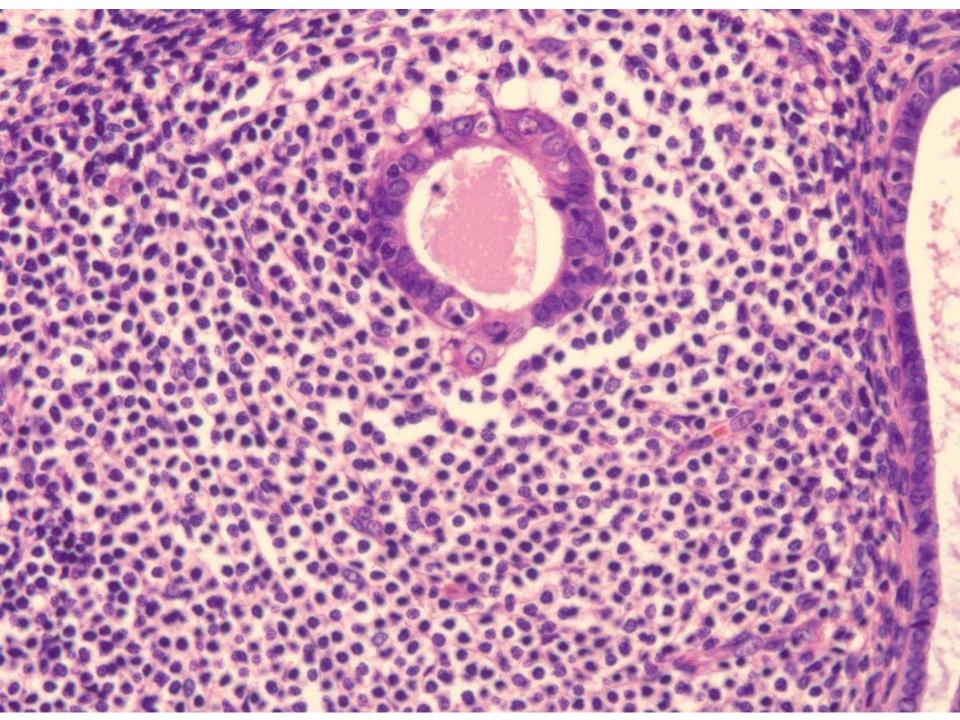
81-year-old F undergoes total hysterectomy for uterine prolapse. Section of endomyometrium shown.

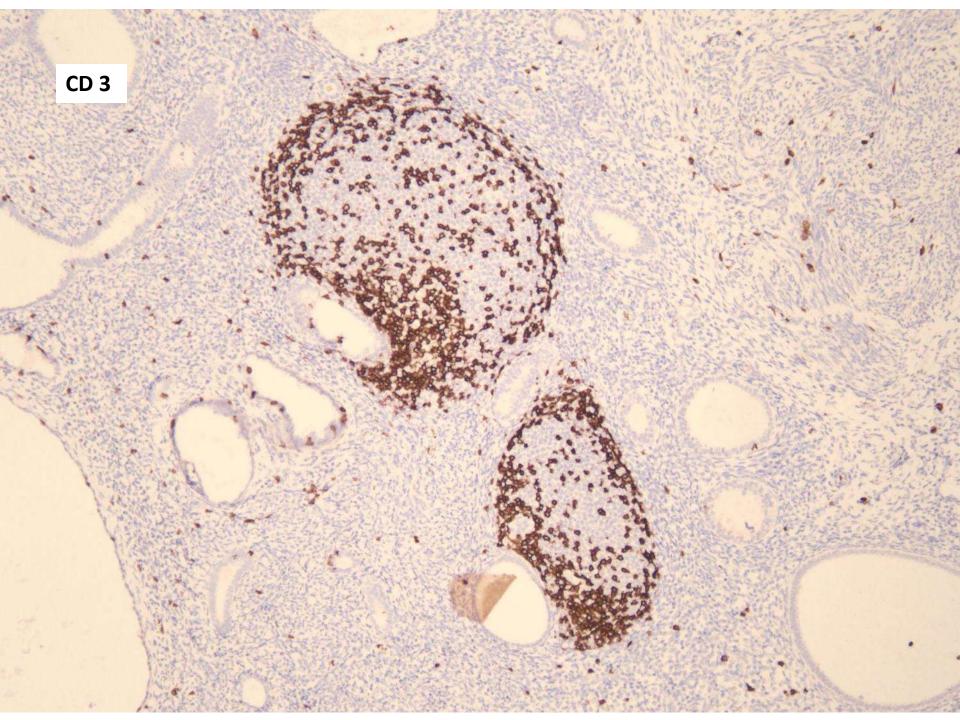


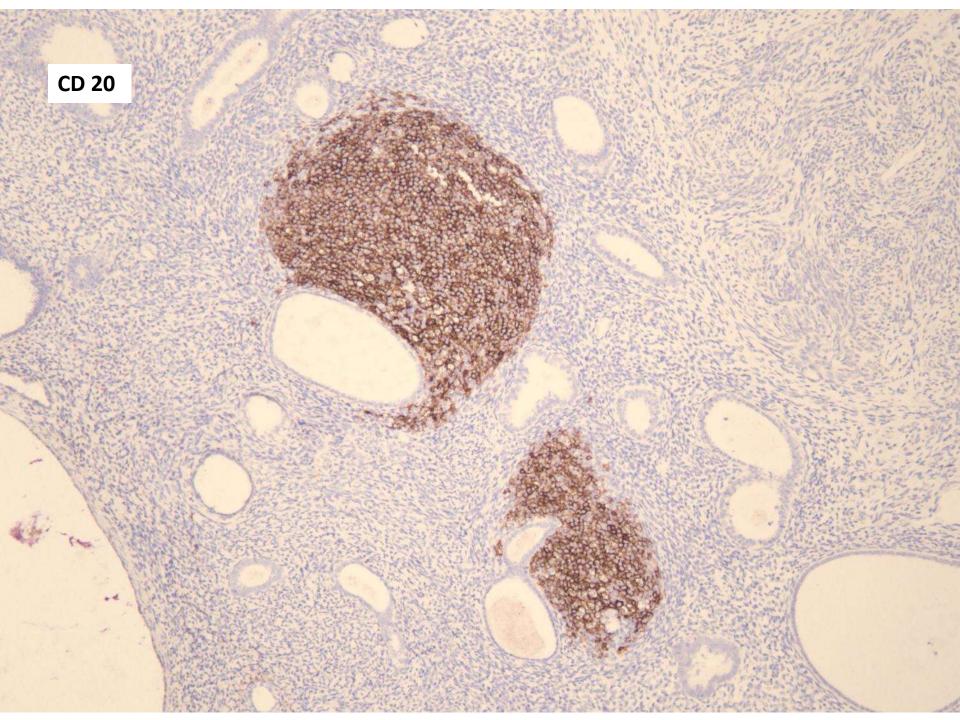


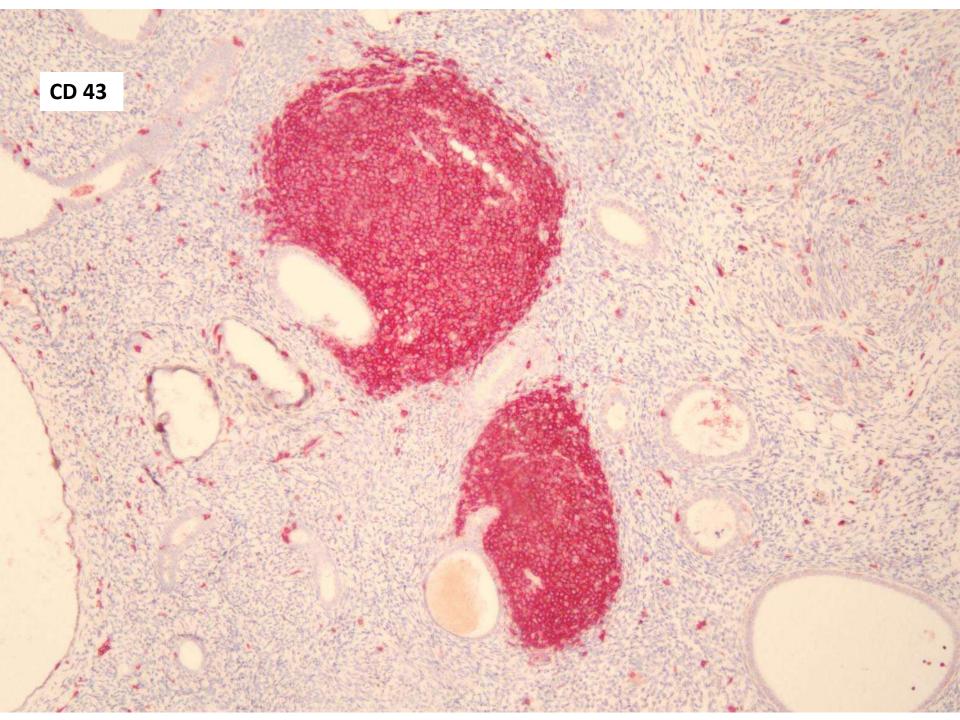


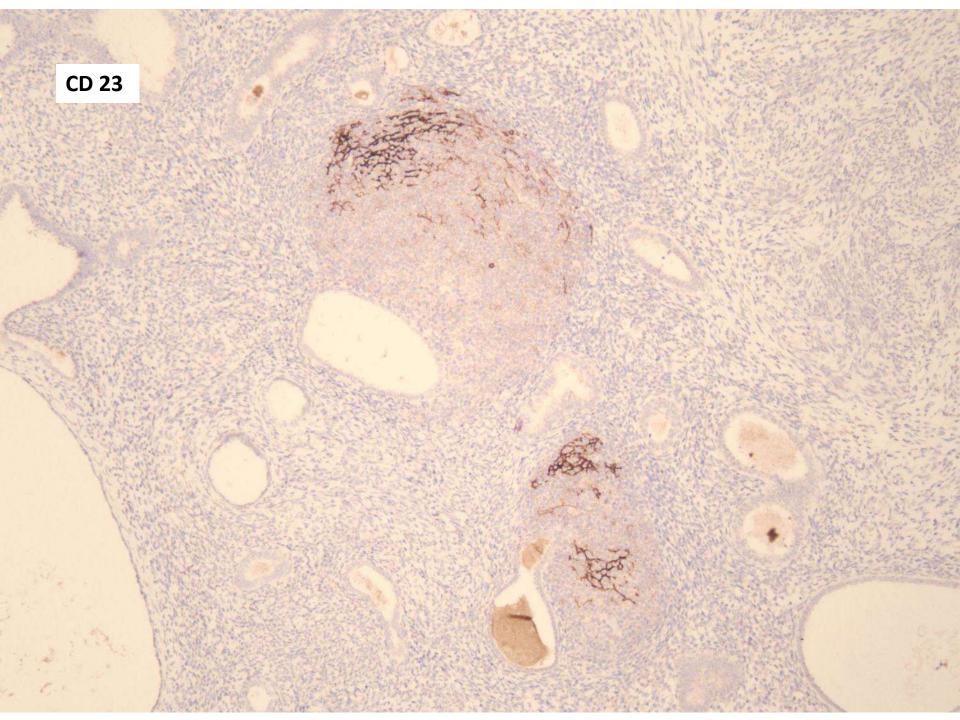


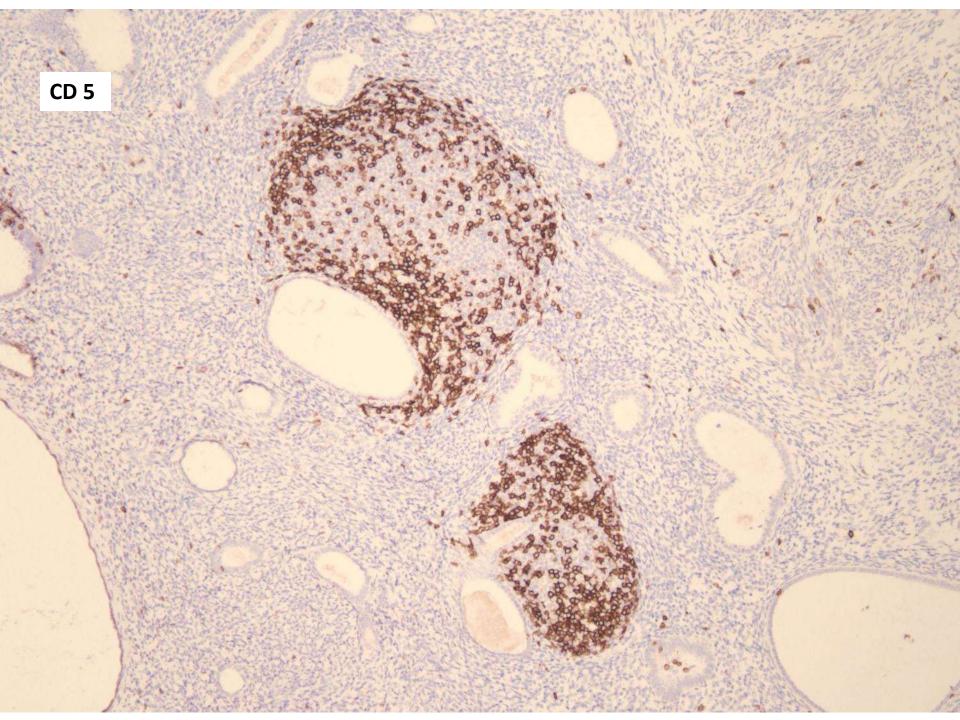












Primary Endometrial Marginal Zone Lymphoma (MALT Lymphoma)

Bennett et al: Primary Endometrial Marginal Zone Lymphoma (MALT Lymphoma). AJSP 2016;40: 1217-1223.

- Clinical
 - All lesions incidentally discovered
 - There are no gross lesions
 - They are small, microscopic and nearly all limited to the endometrium
 - They have excellent prognosis without any further therapy

Endometrial MALT lymphoma

- Pathology
 - Nodular infiltrates
 - Lack lymphoepithelial lesions
 - CD 20 + with coexpression of CD 43
 - Lack CD 5, CD 10, LEF1, Cyclin D1 and SOX11
 - They have expanded follicular dendritic network demonstrated by CD 21
 - Lack clonal plasmacytic differentiation

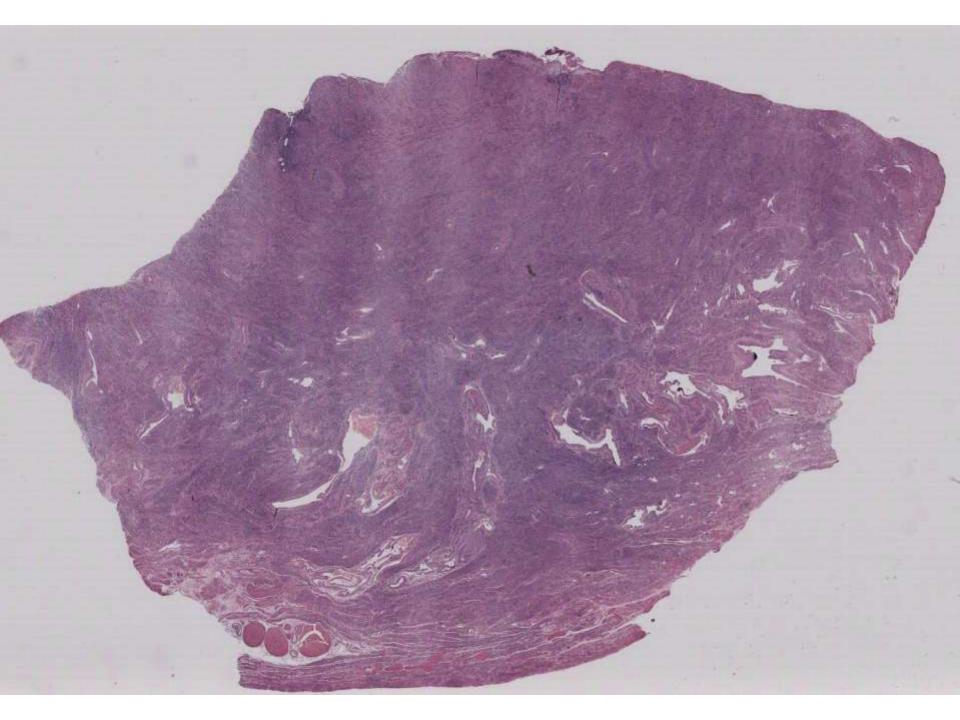
Question ???

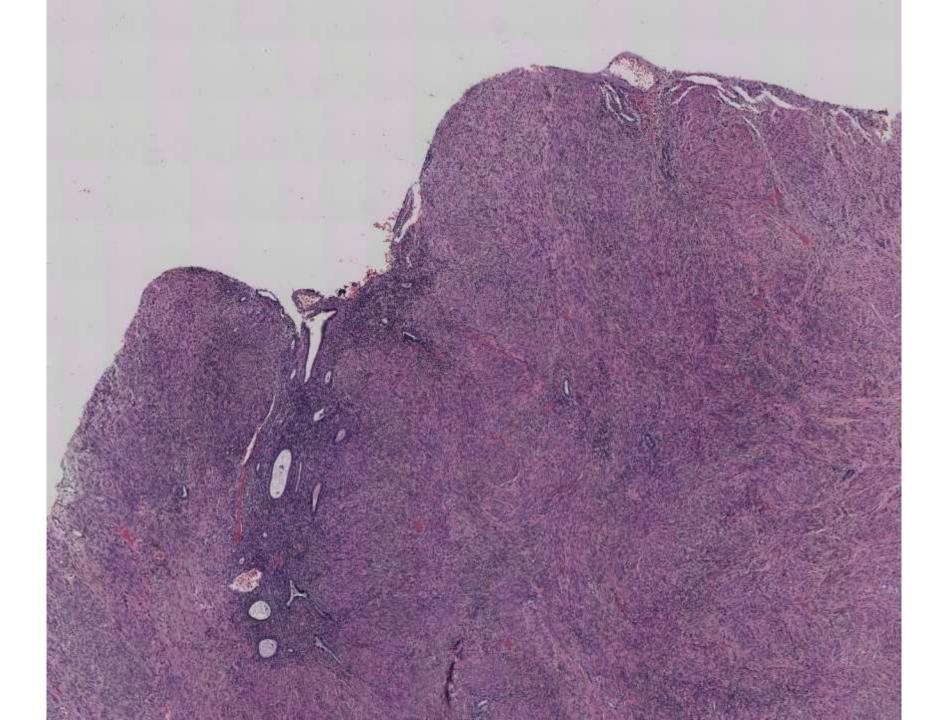
- Might it be better to regard these lesions as:
 - "MALT-like lymphoid proliferations"
 - Clonal B cells are present in a variety of proliferations not fulfilling criteria for lymphoid malignancy
 - Clonal B cells in RFH
 - Monoclonal B cell lymphocytosis
 - In-situ FL/Mantle cell lymphoma
 - Bennet et al. Still favor DX: MALT lymphoma
 - Clonal proliferation
 - Aberrant CD 43
 - Abnormal dendritic cell network
 - With understanding of favorable prognosis

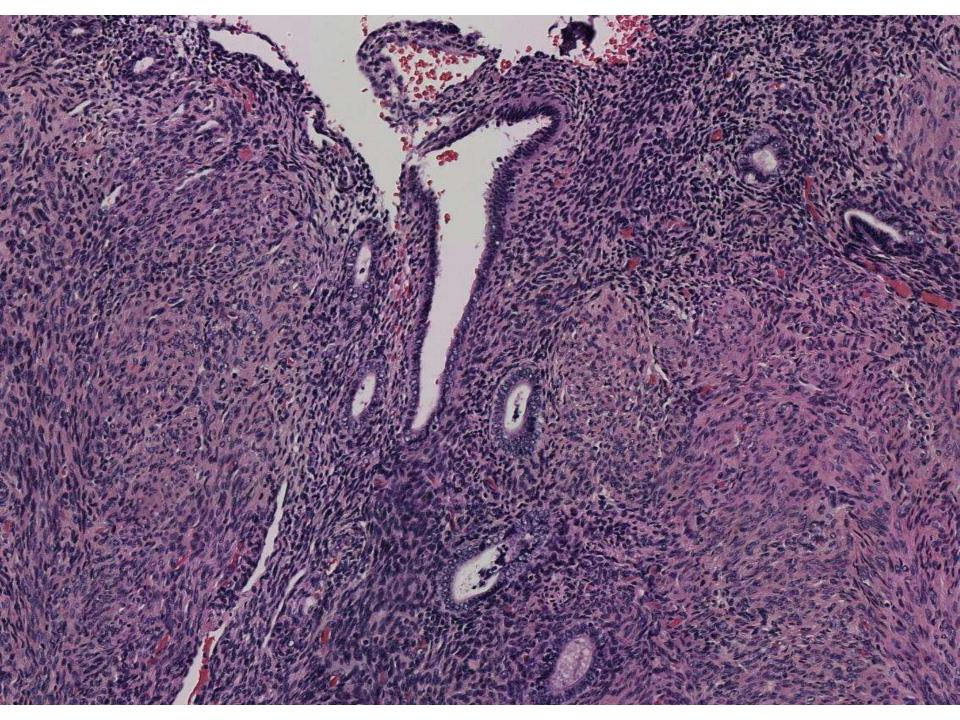
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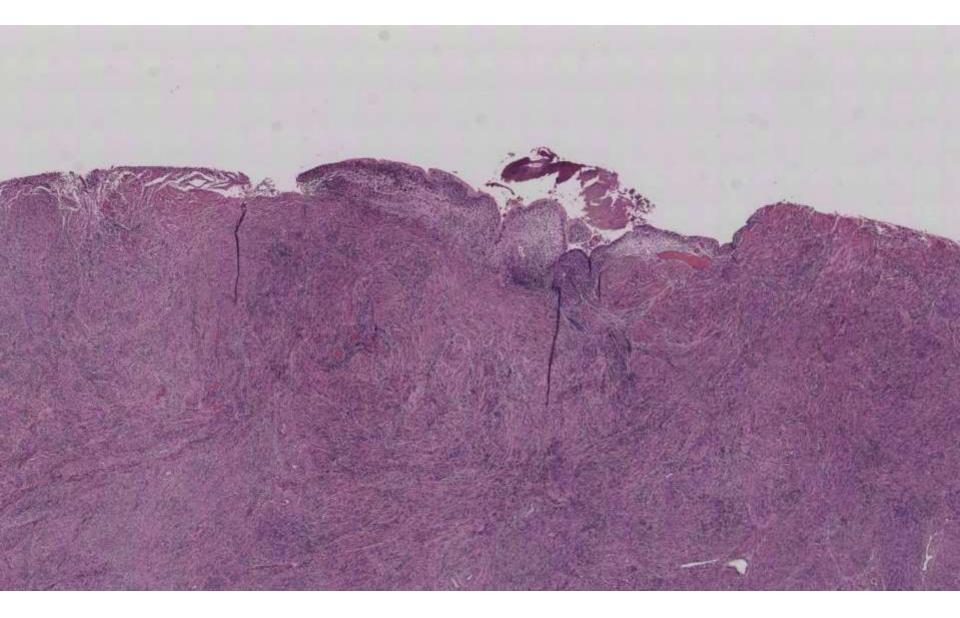
Ankur Sangoi; El Camino Hospital

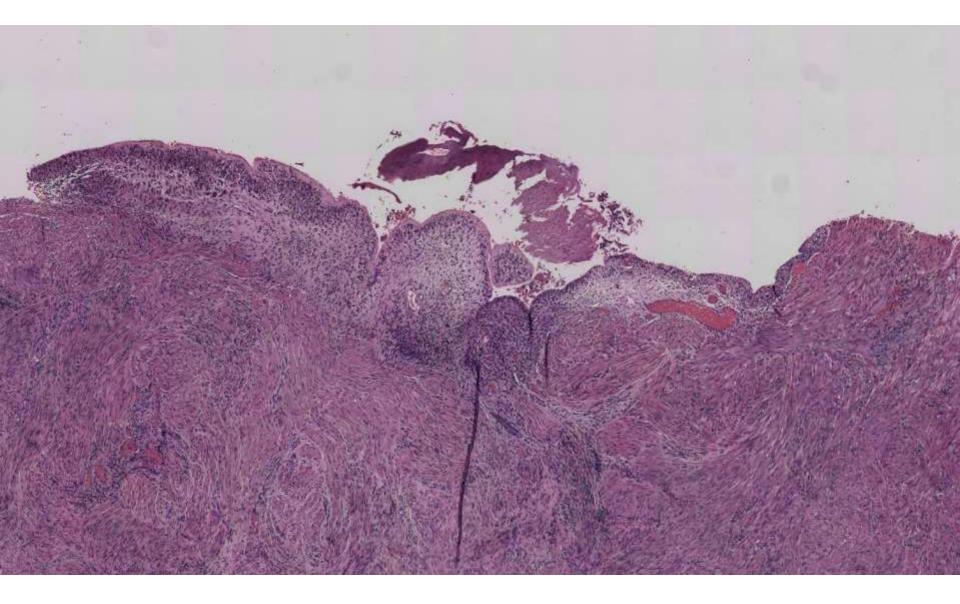
51-year-old F undergoes total hysterectomy for uterine prolapse. Section of endomyometrium shown.

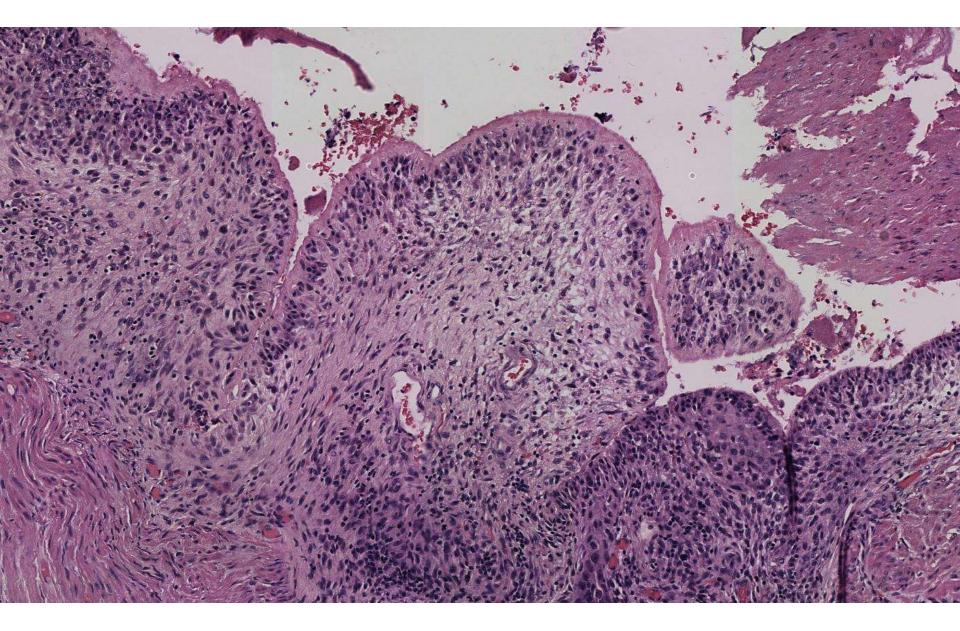


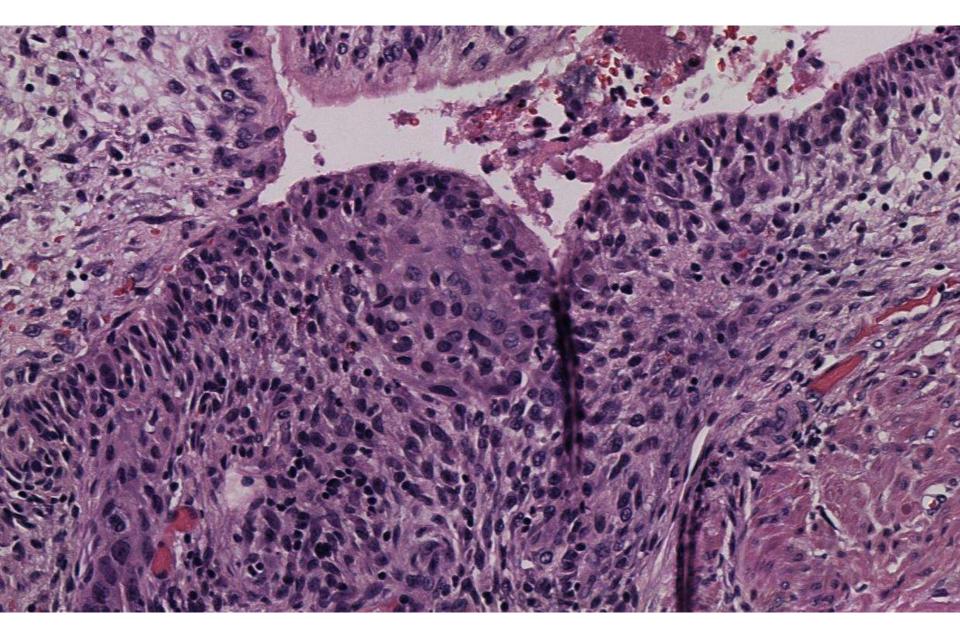


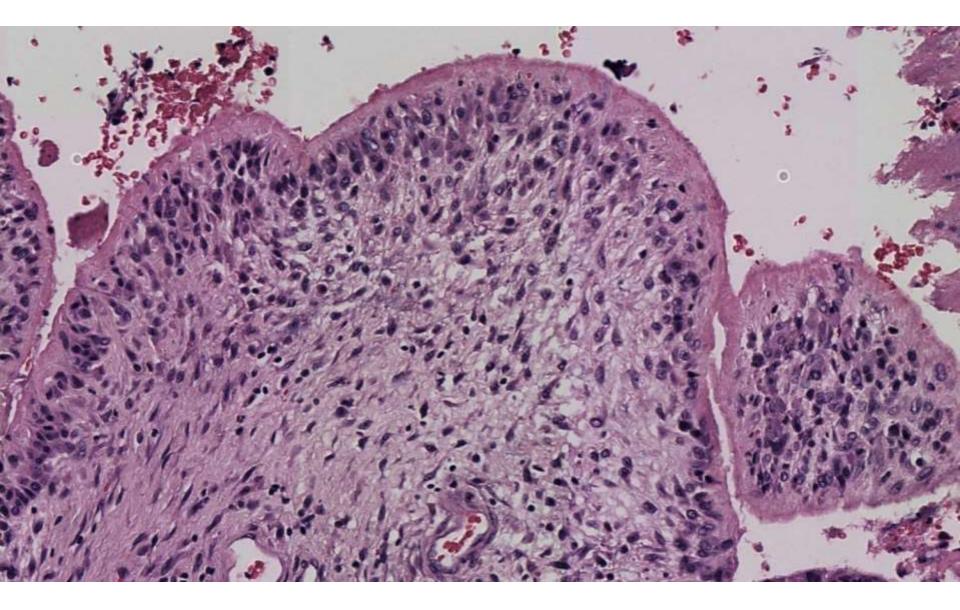


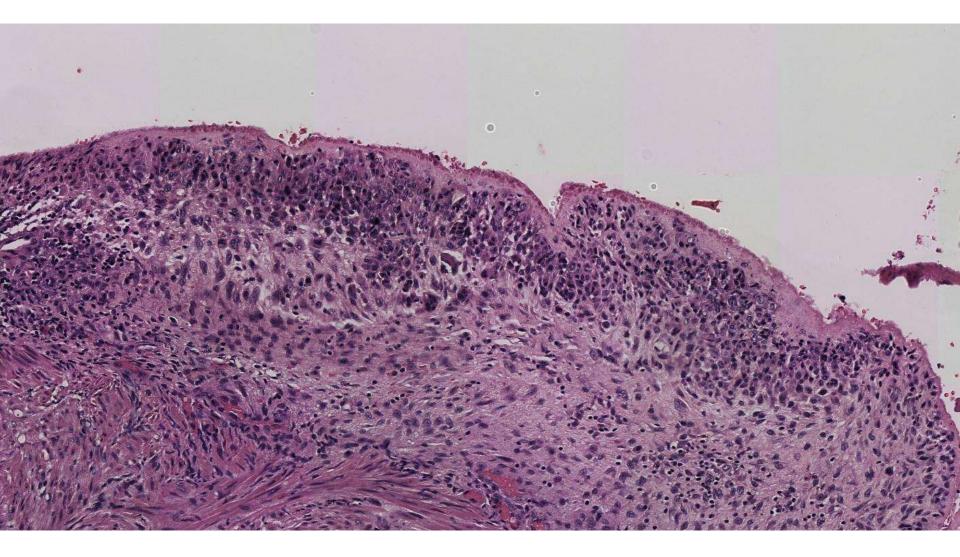


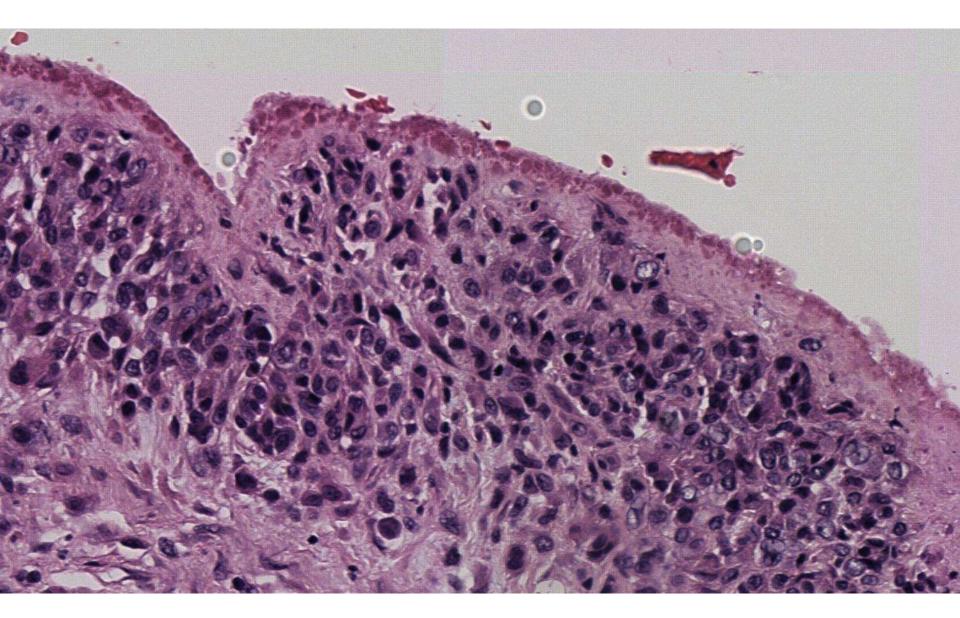












DDx

- Synovial-like metaplasia
- Papillary syncytial metaplasia
- Histiocytic endometritis
- Granulomatous endometritis
- Post-ablation endometrial changes
- Adenosarcoma

Endometrial Synovial-like Metaplasia Associated With Levonorgestrel-releasing Intrauterine System

Colin J. R. Stewart, F.R.C.P.A. and Robyn Leake, F.R.A.N.Z.C.O.G.

Summary: The levonorgestrel-releasing intrauterine system (L-IUS) is widely used in contraception and in the treatment of menorrhagia, dysmenorrhea, adenomyosis, and endometriosis. L-IUS is also increasingly considered in the management of endometrial neoplasia and its precursors. Histologic changes in the endometrium can be due to the effects of high-dose progestogen or may be caused by the local irritant or mechanical effects of an intrauterine foreign body. In the present study, we describe a novel endometrial alteration associated with L-IUS that most closely resembles synovial metaplasia reported at other extra-articular anatomic sites. Eleven cases were identified with a mean age of 49.6 yr. In most patients L-IUS was used for management of menorrhagia or endometrial hyperplasia. Endometrial synovial-like metaplasia was always a focal finding and was associated with areas of surface epithelial erosion. The synovial-like cells showed a distinctive palisaded arrangement with orientation perpendicular to the endometrial surface. Multinucleate cells were present in 2 cases, but granulomas were not identified. The synovial-like cells were vimentin immunoreactive and a variable proportion of cells expressed CD68. Only focal CD10 staining was seen and there was no expression of estrogen receptor, progesterone receptor, or cytokeratin. In summary, L-IUS may be associated with a distinctive synovial-like metaplastic alteration which most likely represents a stromal reaction to an intrauterine foreign body following endometrial surface erosion. The synovial-like cells appear to comprise histiocytes and modified fibroblasts or stromal cells similar to this process in other sites. Key Words: endometrium— synovial metaplasia—Mirena—IUD—progesterone.

Int J Gynecol Pathol Vol. 34, No. 6, November 2015

IUD utility

- L-IUS = levonorgesterel-releasing intrauterine system
- Contraception
- Tx of menorrhagia, dysmenorrhea, adenomyosis, endometriosis

Typical IUD histologic changes

- Thinning of endometrial functional layer, stromal decidual-type alteration, glandular atrophy
 - Also metaplastic epithelial changes, mucinous/myxoid stromal changes
- Occasionally irritative effects
 - Surface erosions, inflammation, infarction, hyalinization, calcification

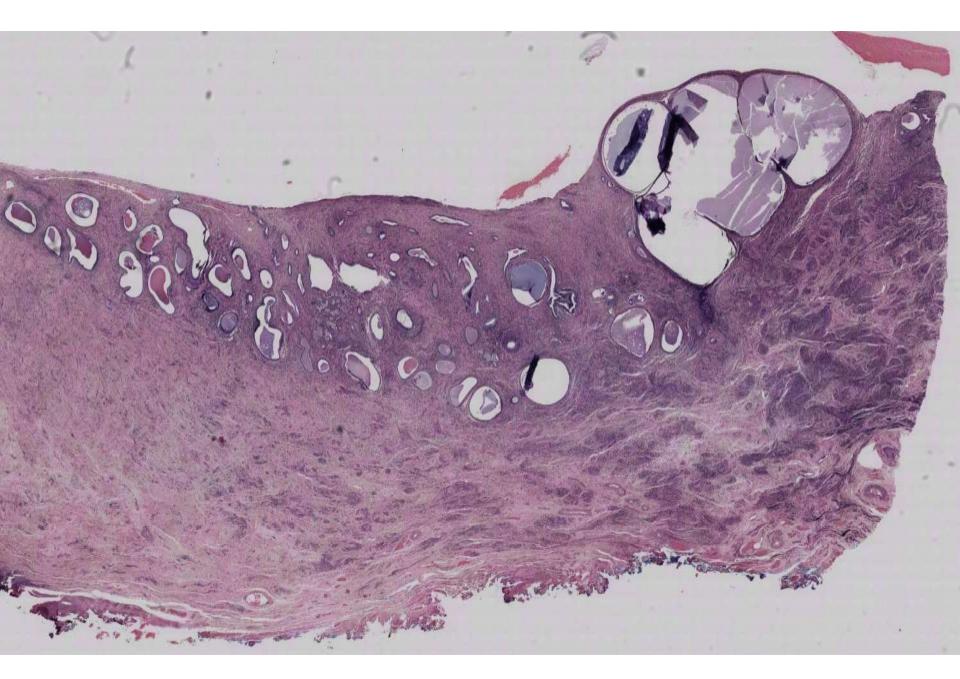
Endometrial synovial-like metaplasia

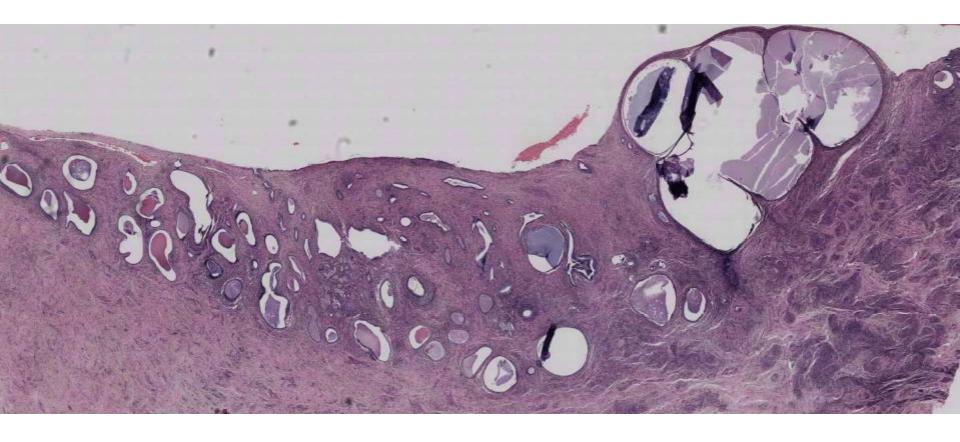
- Closely resembles pseudosynovial reaction in other body sites
 - Most notably breast
 - Relation to prosthetic implants
 - Rarely: testicular/vocal cord silicone implant procedures, around, oral mucoceles, skin (cutaneous metaplastic synovial cyst)
 - Usually associated with IUD
 - Typically focal histologic finding
 - Associated with surface epithelial erosion

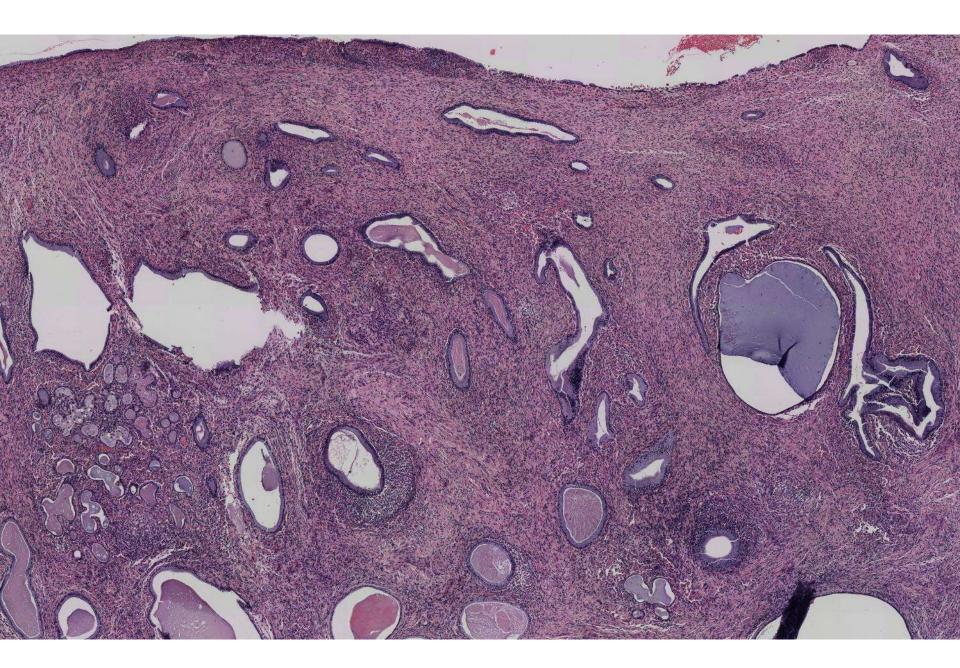
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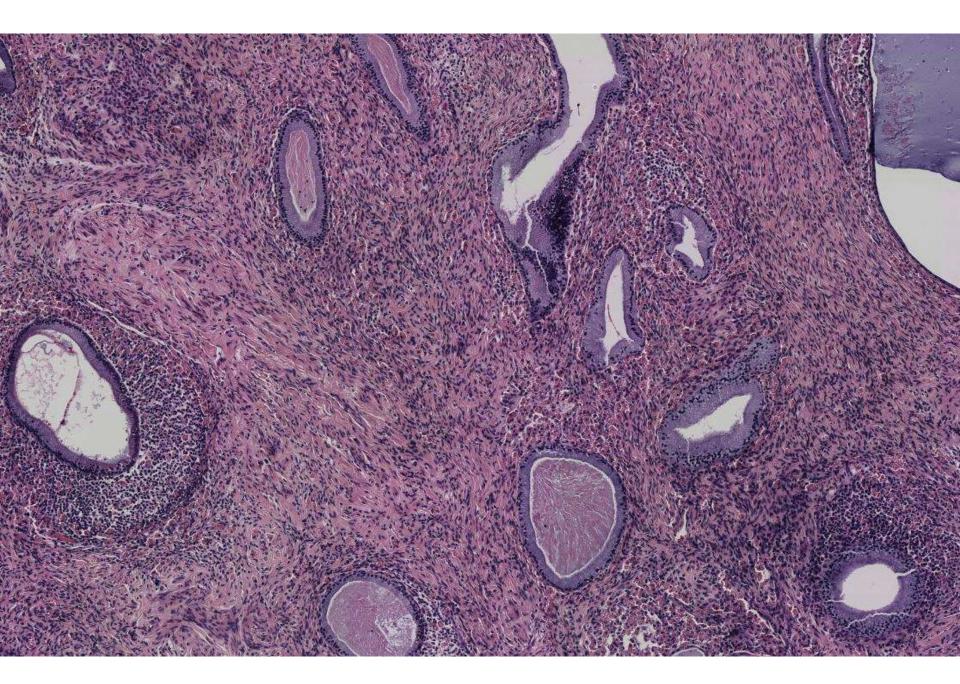
Ankur Sangoi; El Camino Hospital

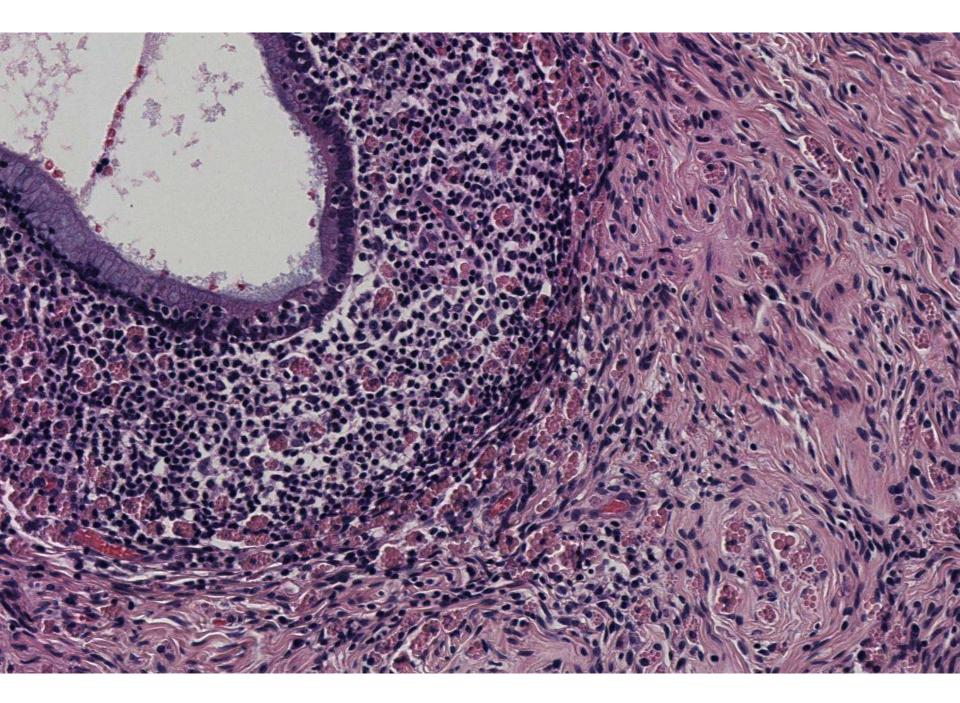
70-year-old F undergoes total hysterectomy for uterine prolapse. Section of cervix shown.

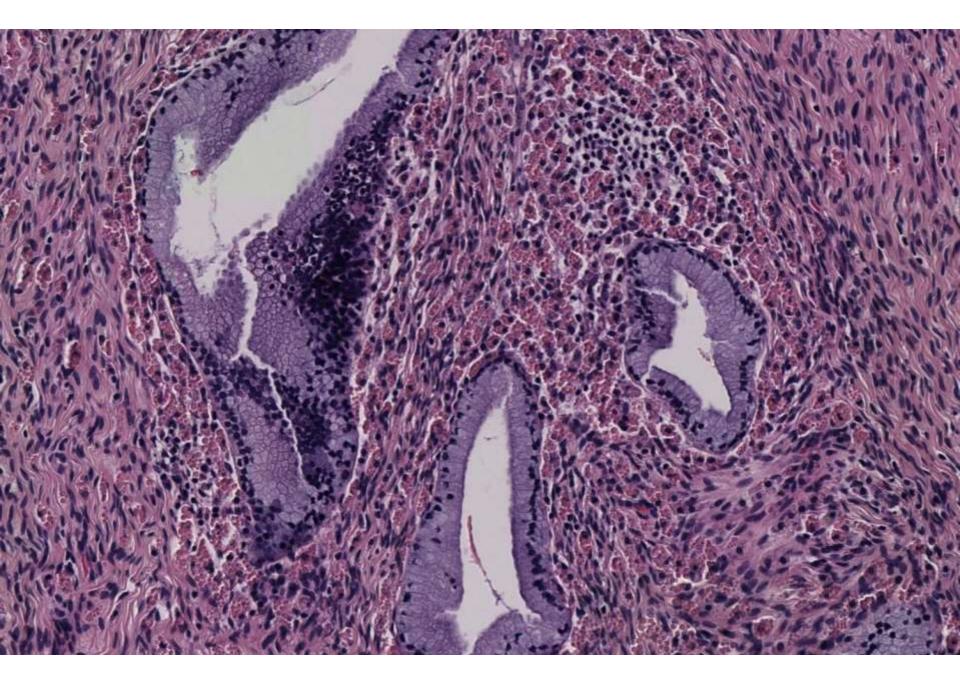


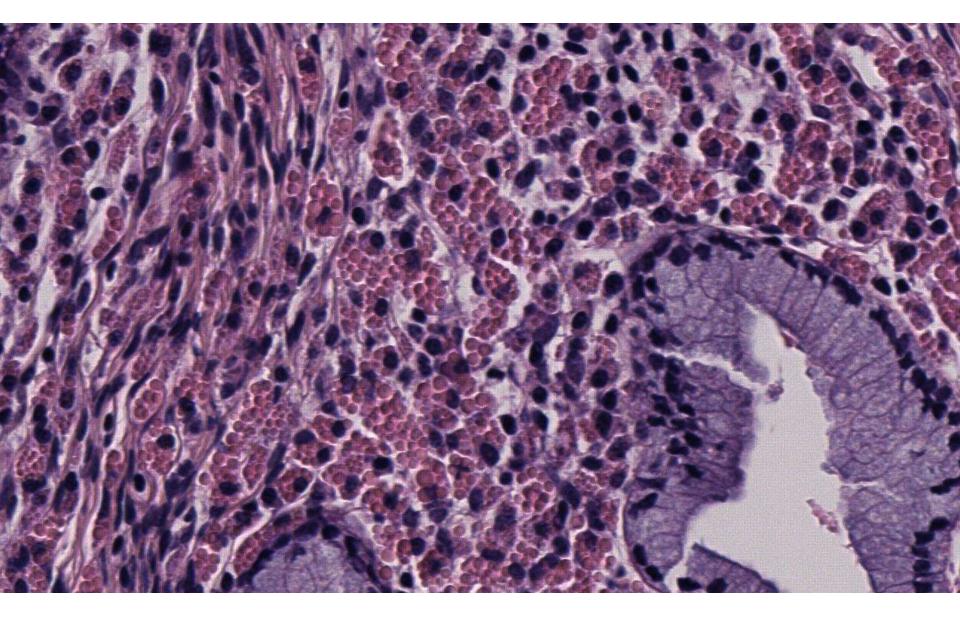


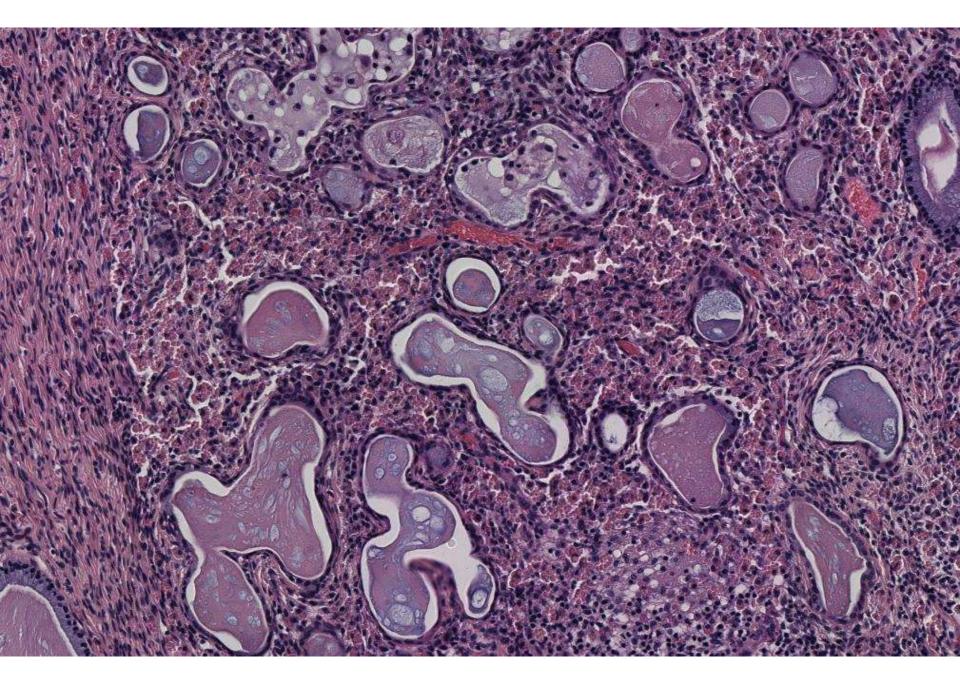


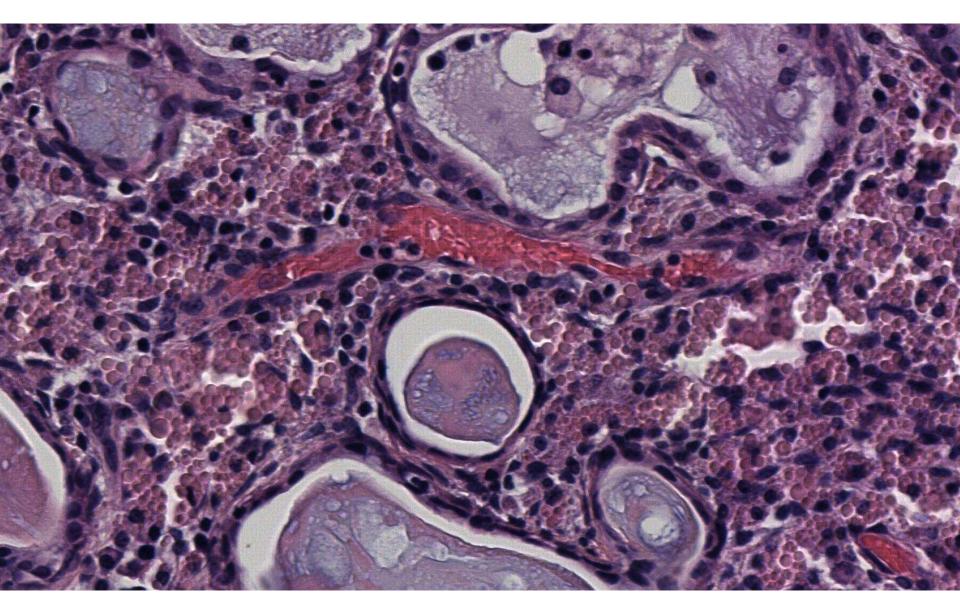


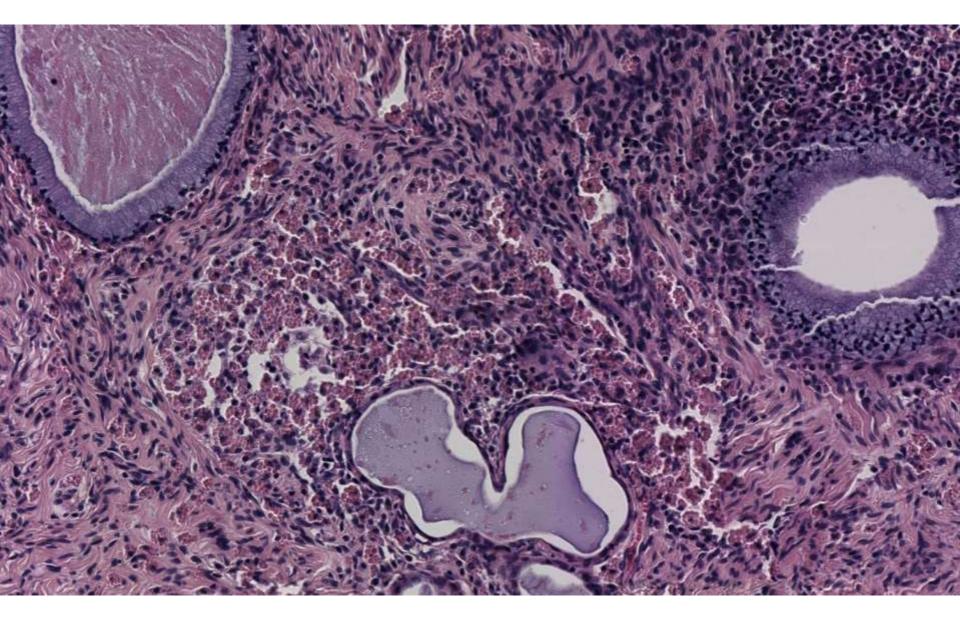


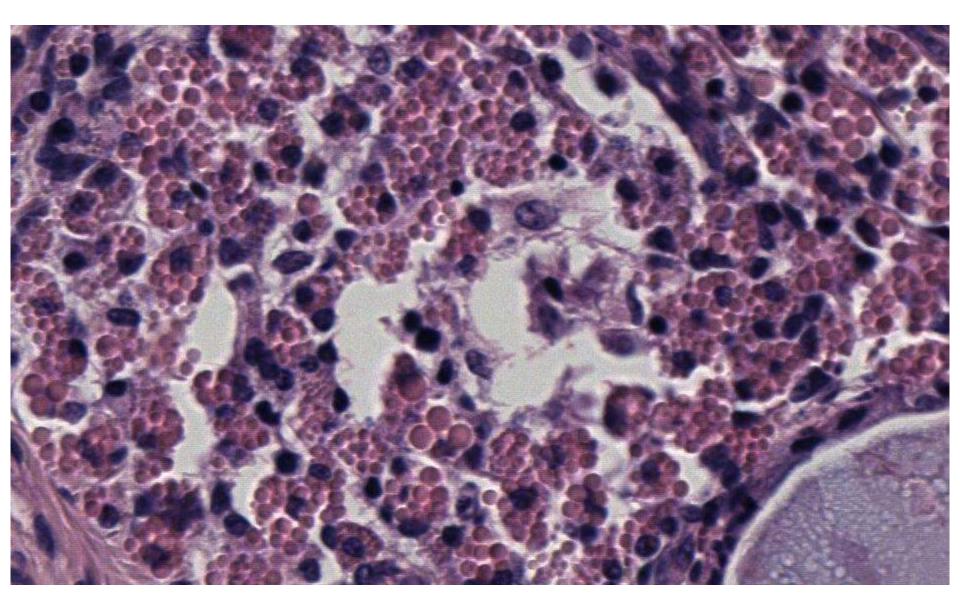








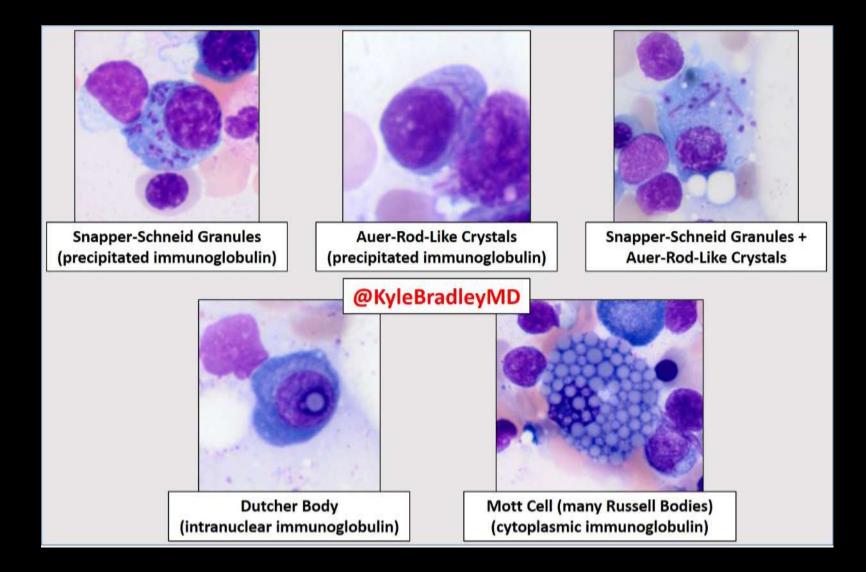




DDx

- Lymphoplasmacytic lymphoma
- Plasmacytoma
- Signet ring cell carcinoma
- Erythrophagocytosis
- Eosinophilic cervicitis
- Russell body cervicitis

Variety of plasma cell inclusions





DEFINITIONS



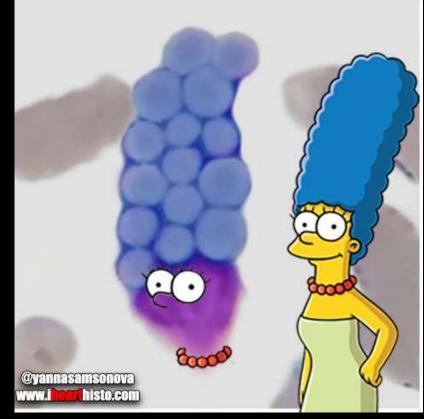
Bleb full of immunoglobulin = Russell body

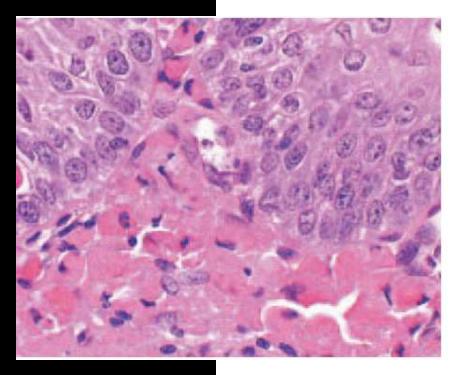
Cell full of Russell bodies = Mott cell

Cervix full of Mott cells = really cool Southbay case

Russell bodies

- Can be seen in chronic inflammation and hematologic malignancies
- "Russell body gastritis" most famous mucosal lesion
- Rare in other sites





Pathology (2006), 38(2), April

Reactive plasmacytic infiltration with numerous Russell bodies involving the uterine cervix: 'Russell body cervicitis'

Sir,

The cervix in healthy women includes a population of lymphocytes and plasma cells which are considered to represent part of the normal mucosal immune tissue.^{1,2} In patients with cervicitis there is a more marked chronic inflammatory infiltrate accompanied by a variable neutrophil polymorph response. Cervicitis may be caused by a wide variety of organisms and can also have a non-infective actiology but in most cases the histological changes are not specific.³

Russell bodies are distinct cosinophilic inclusions seen within the cytoplasm of plasma cells and occasionally in extracellular locations. They are present in reactive plasma cell infiltrates at many anatomical sites, and may be prominent in benign endocervical polyps.4 In most cases, only a minority of plasma cells show these inclusions and their presence is of little interest to diagnostic histopathologists. However, Tazawa and Tsutsumi described a case of Helicobacter-associated gastritis in which the mucosal inflammatory infiltrate predominantly consisted of plasma cells with conspicuous cytoplasmic Russell bodies.5 They coined the term 'Russell body gastritis' for this lesion and since then two additional cases have been reported.^{6,7} To our knowledge this unusual pattern of inflammation has not been described in other mucosal sites. Herein, we report a case of 'Russell body cervicitis'.

An asymptomatic 35-year-old female with no significant medical history underwent a routine Papanicolaou smear which showed a low-grade squamous intracpithelial lesion (SIL) consistent with cervical intracpithelial neoplasia (CIN)1. Colposcopic examination showed only some periglandular cuffing, consistent with minimal human papillomavirus (HPV) effect, and a punch biopsy was taken. The biopsy comprised squamous lined mucosa and superficial stroma with a small focus of endocervical epithelium. The squamous epithelium appeared slightly oedematous and some superficial cells exhibited mild nuclear enlargement and irregularity, however, distinct morphological features of HPV infection were not seen. There was no evidence of CIN. The stroma showed a diffuse and essentially confluent infiltrate of plasma cells with abundant cytoplasm distended by numerous variablysized cosinophilic cytoplasmic inclusions typical of Russell bodies (Fig. 1, 2). Many of the cells had degenerative and compressed nuclei but some cells had characteristic plasmacytic cytomorphology. The plasma cells extended to the base of the squamous epithelium and, in some cases, appeared to lie within the parabasal epithelium. Occasional extracellular Russell bodies were also seen.

Immunohistochemistry demonstrated expression of CD79a and CD138 by the plasma cells, although the Russell bodies were not stained, appearing as 'negative' intracytoplasmic images (Fig. 3). The plasma cells showed

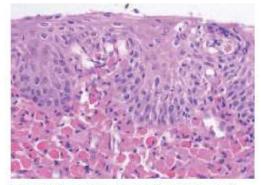


Fig. 1 The subepithelial stroma shows a diffuse and monomorphic infiltrate of plasma cells with abundant eosinophilic cytoplasm (H&E, \times 250).