Society for Hematopathology SH2017-0106

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Case presentation

EMORY
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Patient history

- 6 year old patient with a 1 year history of chronic intermittent vomiting, 1-5X/day, abdominal pain, weight loss, and recent fever
- Endoscopies/colonoscopy performed at an outside facility showed gastric ulcers, and mild chronic inflammatory changes of ileum (Feb and June 2008)
- EGD at CHOA shows gastric antrum inflammation and gastric ulcers (July 2008)

Physical exam – July 2008

- General: Alert, interactive, nontoxic appearance
- Lymph nodes: No significant cervical/axillary tenderness or adenopathy
- Abdomen: Soft. Non tender. Non distended. Normal bowel sounds. No hepatosplenomegaly.

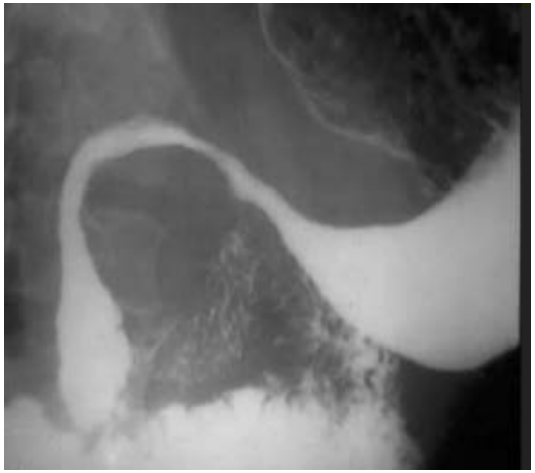
Labs

- IBD Serology 7 panel shows consistent with IBD/Ulcerative colitis

- CBC: microcytic anemia
  - Hb: 9.9 (11.5 - 15.5 GM/DL)
  - MCV: 69.3 (77.0 - 95.0 FL)
  - WBC, ANC, platelets normal

CT scan

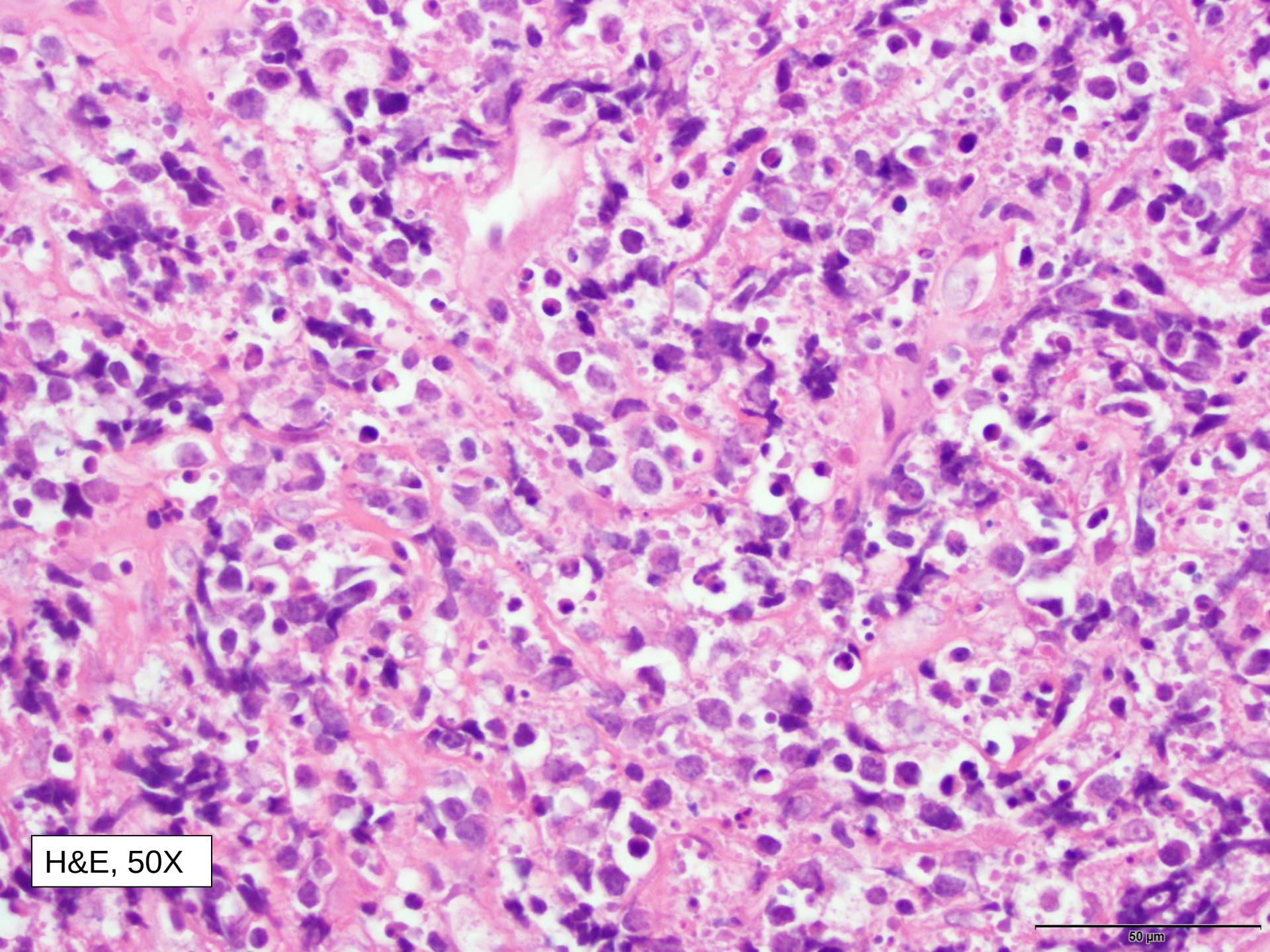
- Inflammatory changes involving the distal aspect of the stomach, proximal small bowel, and terminal ileum
- Suggestive of "ram's horn" sign and may be seen in Crohn's disease, lymphoma, eosinophilic gastroenteritis or other infiltrative disease process
- Multiple enlarged rounded mesenteric lymph nodes scattered throughout the abdomen

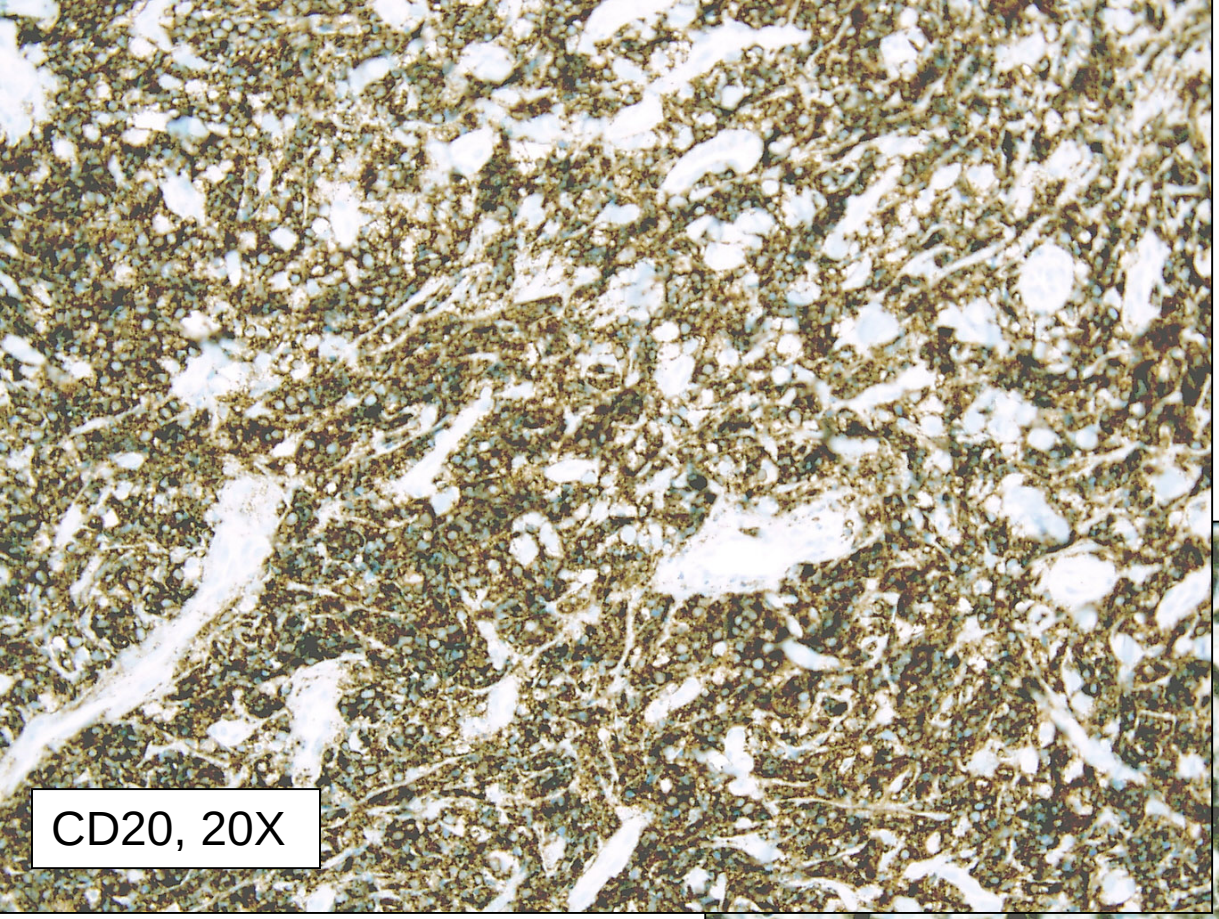


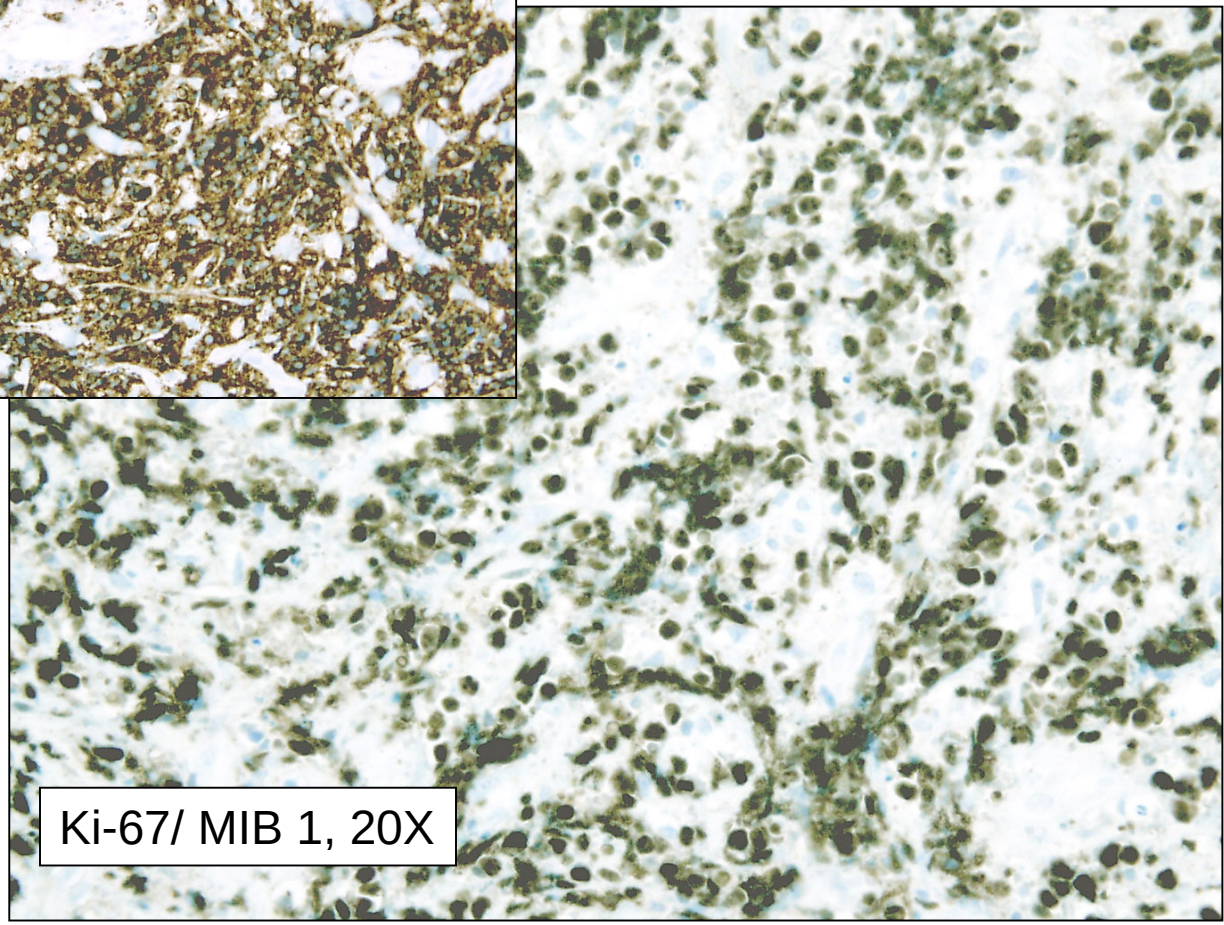
https://www.slideshare.net/dsherif1412/git-signs

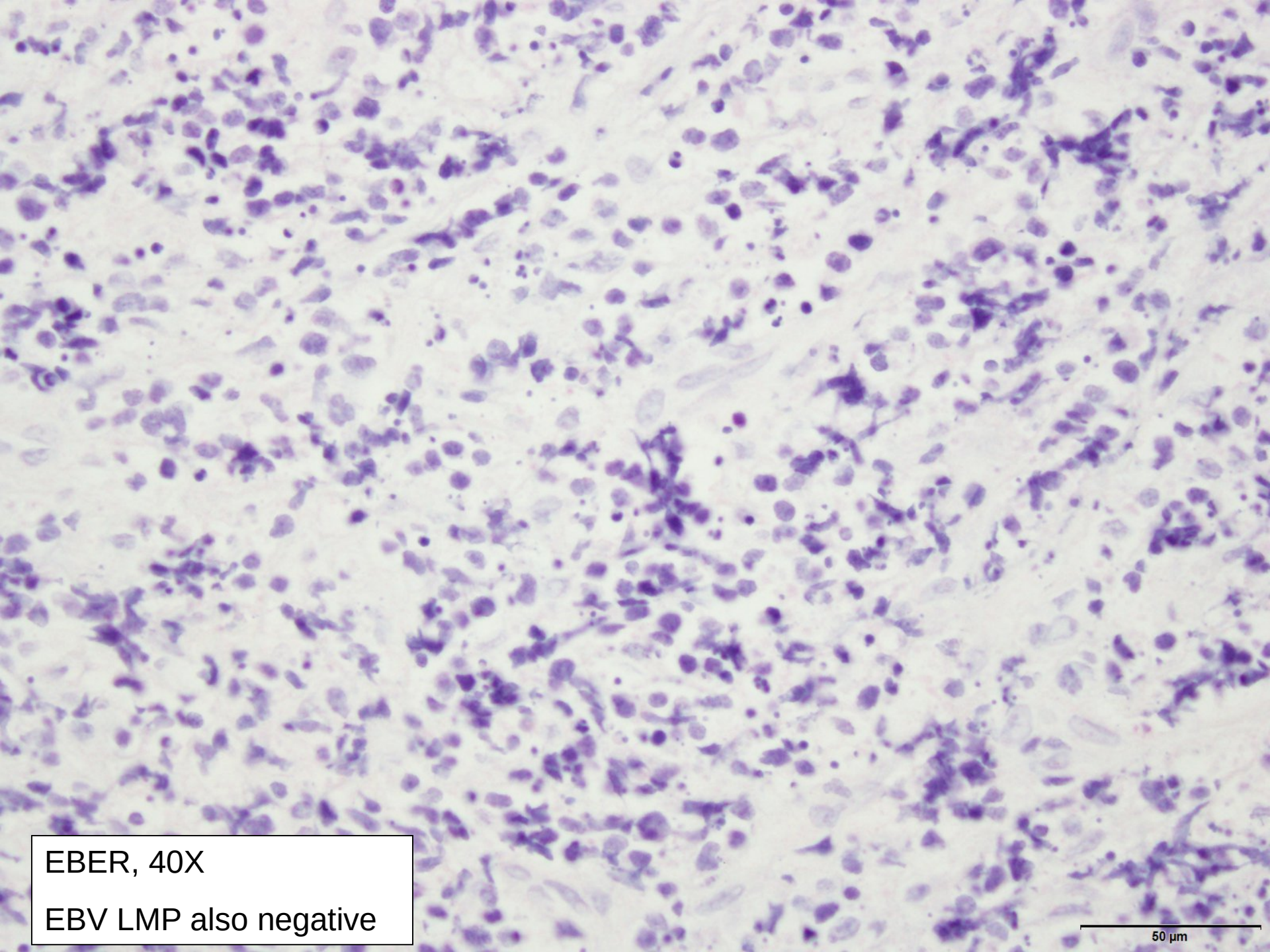
Sept 2008

- Underwent exploratory laparoscopy at CHOA
- Surgeon noticed an inflamed appearing ileocecal mass during exploration, which was biopsied
- Patient had been pre-treated with steroids


H&E, 50X
50 µm


CD20, 20X


Ki-67/ MIB 1, 20X



EBER, 40X

EBV LMP also negative

Ancillary studies

- Flow cytometry: Non contributory due to poor viability
- Cytogenetics: No growth
- Fluorescence in situ hybridization (FISH) for c-myc in fresh tissue: Negative
- FISH studies repeated in paraffin:
  - **C-MYC rearrangement:** Positive in **62%** of cells
  - **C-MYC and IgH** dual fusion: **63%** of cells positive for the **t(8;14)**

- Diagnosis: Burkitt lymphoma

Labs at time of diagnosis

- EBV serologies: No evidence of primary or past infection
- EBV PCR (blood, 1/09): Negative
- Immunoglobulins:
  - IgA: 145 (32-223 mg/dl)
  - IgG: 259 (L) (635-1284 mg/dl)
  - IgM: 82 (44-190 mg/dl)

CBC at time of diagnosis/Imaging

- CBC:
  - WBC: 9.99 (4.5-13.5 Thou/ul)
    - ANC: 5.00 (1.80-7.97 Thou/ul)
  - Hb: 12.3 (L) (13.0-16.0 g/dL)
  - MCV: 78.5 (78.0-98.0 FL)
  - Plts: 681 (H) (150-450 Thou/ul)
- PET Scan:
  - Disease limited to abdomen
  - FDG uptake in:
    - Main mass
    - Adjacent to left 10th rib in LUQ
    - Periaortic LN

Funny thing…

- Heme/onc clinician comes to review the slides, and mentions that his younger brother, who is currently 4 yo, also had Burkitt lymphoma 3 years ago
- This history prompted additional testing to be done…

Molecular analysis

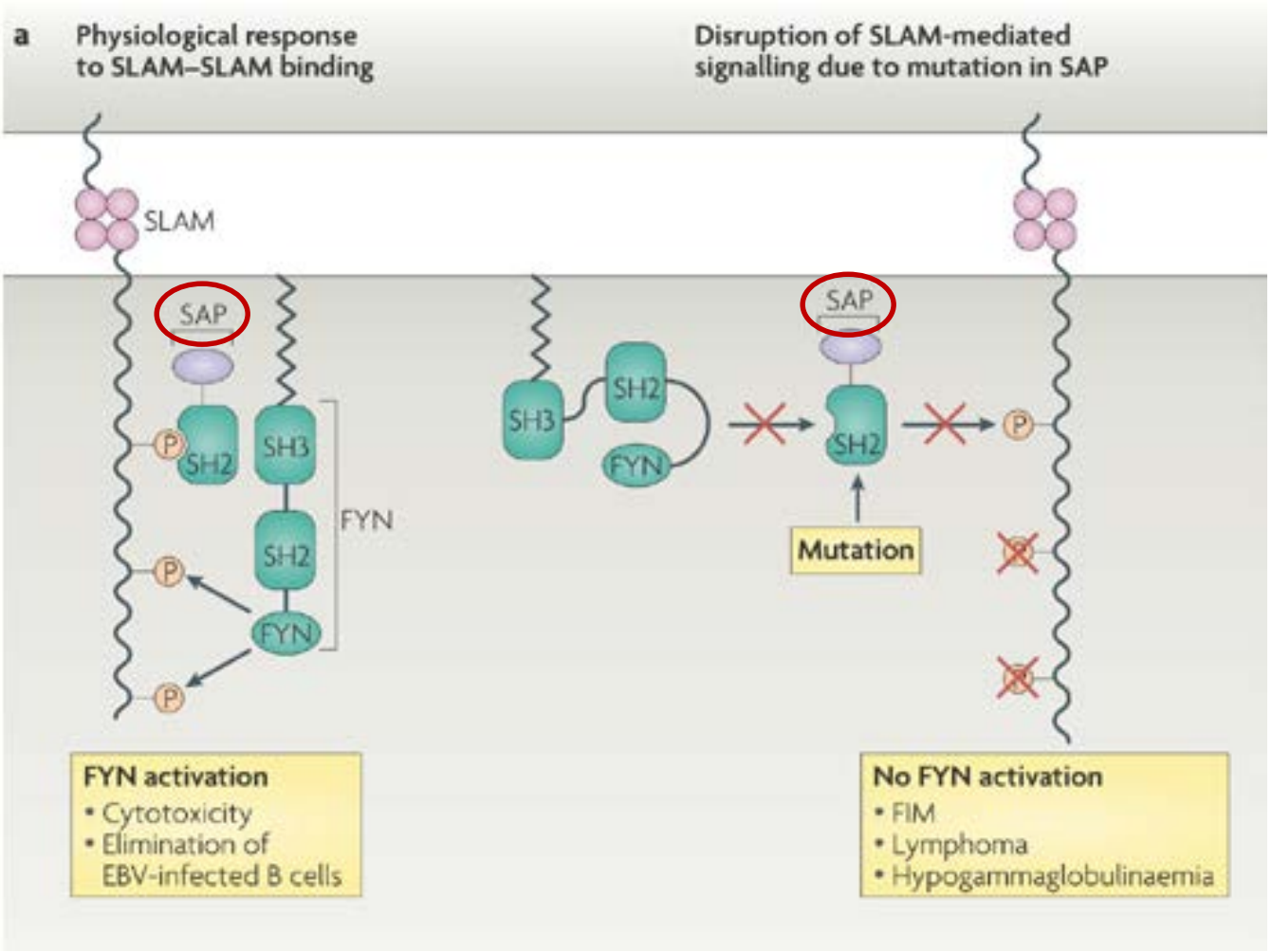
- SAP protein testing by flow cytometry
  - Insufficient cells
- SH2D1A gene testing:
  - POSITIVE for 163 C>T (performed at Cincinnati Children's)
- BIRC4 gene testing: negative
- Diagnosis: X-linked lymphoproliferative disease (XLP1)

XLP

- XLP is a rare primary immunodeficiency disorder with a frequency of 1 per million males (XLP1)
- Two types:
  - XLP1 with SH2D1A mutation
  - XLP2 with XIAP/BIRC4 mutation
- Symptoms of XLP1 are EBV associated HLH, hypogammaglobulinemia, and lymphoma
- No significant difference in the incidence in lymphoma between EBV+ and EBV- patients
- Most patients will die in childhood if untreated, but bone marrow transplant has proven curative

SH2D1A gene (SAP protein)

- SH2D1A gene encodes the SAP protein (signaling lymphocyte activation molecule (SLAM) associated protein)
- SAP is involved in cytotoxic T cell function, NK cell development, and triggering apoptosis to limit the immune response
- When SAP is impaired or decreased, an exaggerated immune response can occur with EBV, leading to HLH



Modified from: Marodi, L. and Notarangelo, L. Immunological and genetic bases of new primary immunodeficiencies. Nature Reviews, Immunology, Volume 7, November 2007 (figure 3, pg 859)

Family testing and patient course

- The family consisted of 4 children, one older girl and 3 younger boys (9 months, 4 years, and 6 years at presentation)
- All 3 of the boys were affected by XLP upon gene testing
  - 2 of the 3 were a BMT match with the sister, and one required an unrelated donor
- All 3 boys underwent BMT at Cincinnati Children's in 2009
- 2 brothers with sister as donor need IVIG, as they have absent class switched of B cells and hypogammaglobulinemia
- 3rd brother with unrelated donor and sister have normal B cells and immunoglobulin levels

Thank you

- Dr. Mihaela Onciu

Final panel diagnosis: Burkitt lymphoma in a patient with X-linked lymphoproliferative syndrome (germline *SH2D1A* mutation)

Questions?

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