Society for Hematopathology
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Case presentation
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
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
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 10\textsuperscript{th} rib in LUQ
    - Periaortlc 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?