

Expanding Clinical Spectrum of Female X-linked Lymphoproliferative Syndrome 2

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Dear Editor,

X-linked lymphoproliferative syndrome type 2 (XLP2) due to pathogenic variants in the X-linked inhibitor of apoptosis (XIAP) gene is a rare cause of primary immunodeficiency. Symptomatic patients, primarily males, present with hemophagocytic lymphohistiocytosis (HLH), inflammatory bowel disease (IBD) and/or transient hypogammaglobinemia (1). However, XLP2 in female patients is complicated with the rarity of symptomatic cases and clinical heterogeneity (2). We report a female affected by XLP2 with previously unreported findings.

A currently 18-year-old female presented with fever, abdominal pain, diffuse lymphadenopathy, splenomegaly, and pancytopenia three years ago. She was diagnosed with HLH, treated with steroids and found to have low B-cells and borderline hypogammaglobinemia. Additionally, a single pathogenic variant in *XIAP* (c.389_392delACAG [p.Asp130Glyfs*11]) was identified. There is no family

history of immunodeficiency, HLH or IBD; parents tested negative for the variant in *XIAP*, indicating a new mutation. Further workup showed presence of EBV IgG, and normal expression of XIAP protein in only 8-19% of various white blood cell types by flow cytometry indicating skewed X chromosome inactivation. She had intermittent infections, one resulting in an additional HLH flare with elevated IL-18 and CXCL9 levels that was treated with steroids and intravenous immunoglobulin (IVIG).

Repeated EBV PCR testing had been negative.

However, she was found to have EBV reactivation with positive EBV VCA-IgM, high titer VCA-IgG and EA-IgG levels while EBV-PCR was negative in the plasma sample when she presented to our clinic with diarrhea. There was ongoing history of headaches, abdominal pain, joint pain, and ADHD at that time. Later, she underwent work up for recurrent abdominal pain, diarrhea, urgency and elevated fecal calprotectin. MRI-enterography and capsule endoscopy were negative. Endoscopy was remarkable for chronic active proctitis. She was prescribed mesalamine with significant improvement in abdominal pain and resolution of mucous stools.

Due to persistent knee/ankle pain, she was investigated for peripheral neuropathy and was found to have low vitamin B12 levels (112-145 pg/mL; N:180-914) without dietary restrictions, absent anti-intrinsic factor antibodies and negative family history. Her pain improved significantly on vitamin B12 injections and gabapentin with normalization of vitamin B12 levels.

She continued to have fluctuating and borderline low levels of serum immunoglobulins with persistently low B-cells. She was given IVIG supplementation when serum IgG levels were low. No

additional HLH flares have occurred. Mild increase in CD5-dim T-cells (9%) representing T-large granular lymphocytes (T-LGL) and clonal T-cell receptor (TCR) rearrangement pattern were identified in peripheral blood. She continues to have migraine episodes, and very high EA-IgGat >150U/mL (N<9) that may indicate stable phase of chronic active EBV infection.

Female carriers are at risk for extra hematopoietic manifestations, if they have an extremely skewed X chromosome inactivation (3). She was EBV-PCR negative, but EBV VCA-IgM positive repeatedly suggesting a recent reactivation at presentation to our institution. Persistent high EBV EA-IgG titers is suggestive of ongoing EBV challenge due to immune deficiency and emphasizes the significance of EBV serology testing. Clonal T-LGL expansion may be related to EBV and/or immune deficiency (4). Low vitamin B12 raises the possibility of impairment in absorption; the presence of proctitis raises possible subclinical inflammation in the distal ileum. Observed conditions in this case add to the spectrum of this rare entity (Table 1).

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Table 1. Clinical spectrum in symptomatic females with XLP2

Conditions	Reference
HLH, inflammatory bowel disease (IBD)	1, 3
IBD, diverticulitis, erythema nodosum, irritable bowel syndrome, Sweet's syndrome	2
Hypogammaglobulinemia, Low B cells, Proctitis, Persistent high EBV EA-IgG titers and EBV reactivation, Vitamin B12 deficiency, Clonal T-LGL expansion	Present case