Acute Liver Failure Unmasking XIAP-Deficiency in Very Early Onset IBD

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INTRODUCTION

- XIAP deficiency has a broad spectrum of manifestations, including HLH, IBD, uveitis, and episodic fevers
- VEO-IBD may be the presenting symptom of many inborn errors of immunity (IEI) and intestinal epithelial cell defects
- Liver manifestations of XIAP have rarely been reported
- Here we describe a case of severe acute liver failure in a patient with VEO-IBD, found to have XIAP deficiency

PATIENT PRESENTATION

- Age 5: presented with hematochezia, perianal skin tags, intermittent fevers
- Age 6: diagnosed with VEO-IBD - endoscopic and histologic colitis and granulomas
- Age 6: IFX 10mg/kg with achievement of clinical remission
- Age 8: presented with fever, hepatitis, cholestasis, and abdominal pain, EBV IgM+
- 5 days later: Progressive cholestasis, rising transaminases, new synthetic dysfunction, hepatic encephalopathy.
- Admitted to tertiary care facility ICU, listed for liver transplant
- Initial labs with moderately elevated sIL2R, IFN gamma, ferritin, possible evolving HLH (Table 1)
- Treated with methylprednisolone and emapalumab with improvement (Figure 1)
- XIAP flow revealed absence of XIAP expression (Figure 2)

RESULTS

Infectious Workup	**EBV IgM weak +**, EBV IgG, Hep A/B immune, negative EBV, CMV, adenovirus, HHV6, HSV, HIV PCRs, negative toxoplasmosis, negative strongyloides, negative TB testing, negative blood cultures
Autoimmune/Metabolic	ANCA 1:80, anti-F actin weak +, normal LKM and anti-smooth muscle, normal ceruloplasmin, normal metabolic screens
Immune	Normal DHR, low NK cells (52), mildly elevated IgE (87) ANC 1620, Hgb 9.2, plt 177 Ferritin 290, fibrinogen 103, Triglycerides 162 sIL2 1500,**IFNG 128** IL6 7.6, IL8 86, IL10 10, TNFa 4.7, **IL-18 12,000** Normal perforin/granzyme

Table 1: Select labs at time of presentation

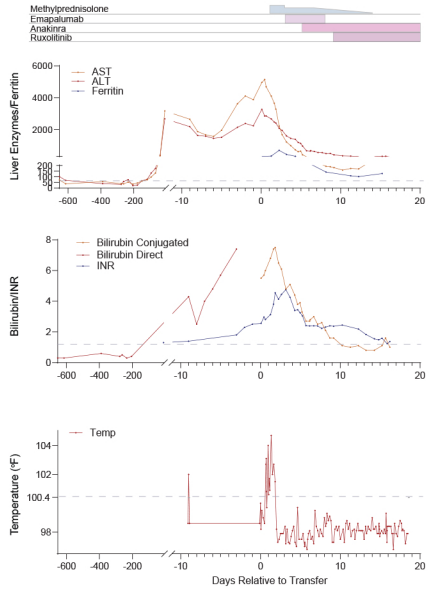

Figure 1: Transaminase and inflammatory marker trends (top), synthetic dysfunction (middle), and fever curve (bottom)

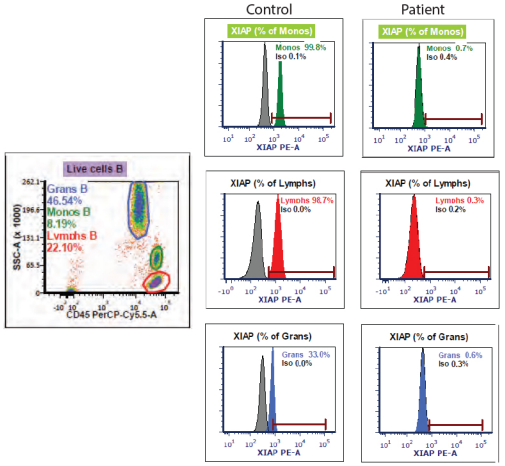

Figure 2: Diagnostic flow cytometry showing absence of XIAP expression in major lineages *(courtesy of Cinncinati Diagnostic Immunology Lab)*

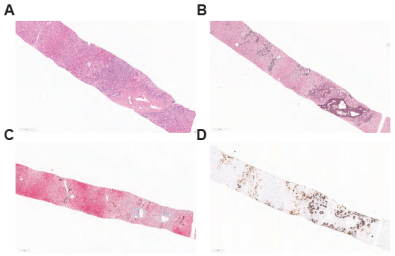

Figure 3: Liver biopsy (D17 post-admission) (A) H&E staining showing periportal and centrilobular collapse, hepatocellular injury (B) Reticulin staining highlighting hepatocellular cord collapse (C) Trichrome staining without fibrosis (D) CK7 staining showing re-generation of bile ducts

MANAGEMENT AND OUTCOMES

- Targeted sequeincg confirmed an XIAP frameshift variant (c.1021_1022del, p.(N341Yfs*8))
- Anakinra started
- Liver biopsy: mild inflammation, hepatocellular injury without fibrosis, and regenerating bile ducts (Figure 3)
- Liver function and mental status improved, transitioned to ruxolitinib pre-discharge while awaiting HSCT
- Underwent mismatched unrelated donor transplant with pre-phase emapalumab and conditioned with campath, fludarabine, thiotepa, and melphalan.

DISCUSSION

- Acute liver failure is a rare manifestation of XIAP deficiency
- Antecedent EBV infection likely triggered this case of liver failure
- High suspicion for underlying IEI/immune dysregulation should be considered in cases of acute liver failure and VEO-IBD
- HSCT can be curative in XIAP-deficiency, and should be considered in cases of intestinal inflammation and severe manifestations such as liver failure

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