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Riley Children's Health
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A Case of EBV Induced HLH Following Covid-19 Vaccination in a Pediatric Patient

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The authors have no conflict of interest.

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Introduction:

- The COVID-19 pandemic resulted in widespread mRNA vaccinations against SARS-CoV2.
- Side effects include fatigue, headache, myalgia, fever, nausea, and lymphadenopathy, frequently experienced in younger recipients (16-55 years) following the second dose.
- Hemophagocytic Lymphohistiocytosis (HLH) is a rare syndrome of uncontrolled systemic inflammation identified by clinical and laboratory signs of immune activation.
- In pediatric patients, HLH occurs in 1.2 cases per million persons per year.
- If untreated, HLH is often fatal, with a median survival of 2 months.

References:
Possible Side Effects After Getting a COVID-19 Vaccine | CDC
Egeler RM, Shapiro R, Loechelt B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. J Pediatr Hematol Oncol. 1996 Nov;18(4):340-5. doi: 10.1097/00043426-199611000-00002. PMID: 8888739
Henter JI, Elinder G, Soder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand. 1991;80:428–35.
Anderson, E. J. et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults.N. Engl. J. Med.383, 2427–2438 (2020)
Sadarangani, M., Marchant, A., Kollmann, T.R., 2021. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nature Reviews Immunology 21, 475–484.. doi:10.1038/s41577-021-00578-z
B cell responses in SARS-CoV-2 naive and recovered individuals following mRNA vaccination. Sci. Immunol. 6, eabi6950 (2021)
*Kerr JREpstein-Barr virus (EBV) reactivation and therapeutic inhibitorsJournal of Clinical Pathology 2019;**72:**651-658.*
Latour, S., Fischer, A., 2019. Signaling pathways involved in the T-cell-mediated immunity against Epstein-Barr virus: Lessons from genetic diseases. Immunological Reviews 291, 174–189.. doi:10.1111/imr.12791

Case Presentation:

- Previously healthy 17-year-old Caucasian male.
- Presented with 7-day history of headaches, stiff neck, nausea, dark urine, and fever two weeks after receiving his second Pfizer COVID-19 vaccination.
- Significantly elevated EBV PCR of 54,000 IU/mL (normal <500 IU/mL).
- Initial laboratory testing significant for anemia, thrombocytopenia, acute kidney injury, transaminitis, hyponatremia, and coagulopathy.
- Concern for macrophage activation syndrome (MAS) raised so work-up for MAS/HLH was initiated.
- Bone marrow biopsy showed normocellular marrow with prominent hemophagocytosis.
- HLH labs showed anemia, elevated ferritin, low fibrinogen.
- Ten days into his illness, patient developed chest and back pain, rash, fatigue, myalgias, and fever.
- Started on the HLH2004 protocol with oral dexamethasone 15mg and IV etoposide 150mg/m2.
- Decrease in HLH markers and EBV PCR and discharged home 3 weeks later.
- At week 6, clinical status and labs were significantly improved.

	Admission	10 days later	1 month later
Hgb (13.4-17.4 g/dL)	9.2	7.3	8.9
Platelets (150-440x10^9 k/cumm)	107	100	50
Creatinine (0.74 to 1.35 mg/dL)	4.16	.74	.43
BUN (9-23 mg/dL)	71	17	18
AST (5-40 Units/L)	205		8
ALT (7-56 Units/L)	74		4
Sodium (132-145 mEq/L)	122	137	137
PT (9-11.7 seconds)	16.5	16.9	
PTT (55-75 seconds)	22.2	25.4	
INR (.9-1.2)	1.45	1.48	
D-Dimer (>0.5 ng/mL DDU)	13222		
Ferritin (24-336 ng/mL)	733.3	35,676.6	
Fibrinogen (203-337 mg/dL)	142	465	
sIL2r (122-496 pg/mL)		10,671.4	8004.0
CXCL9 (38.4-383.9pg/mL)		5719	522
EBV IgM+ (<500IU/mL)	54,000	1349	<500

Table 1 displays lab values upon admission, 10 days after, and 1 month later.

Discussion:

- HLH Treatment = immunosuppressive therapy + treatment of underlying condition.
- Differential: multisystem inflammatory syndrome in children (MIS-C).
- Studies have shown low levels of CD8+ T cells responses after COVID-19 vaccination.
- Either prior infection or vaccination with Pfizer vaccine primed memory B cell responses so that the second exposure (reinfection or vaccination dose 2) resulted in amplification of memory B cell response.
- EBV infects B lymphocytes leading to their immortalization.
- In vitro, latent EBV can reactivate by stimulating the B cell receptor, for example, to unrelated infections.
- In immune response of healthy individuals, EBV-specific T cells counteract and eliminate EBV infected proliferating B cells.
- When T-cell expansion is impaired, i.e. vaccination, EBV infected B cells accumulate, causing uncontrolled activation of T cells that cannot kill the EBV infected B cells but proliferate and produce large amounts of pro-inflammatory cytokines including IFN-ɣ which further activates macrophages, leading to HLH.

Conclusion:

- HLH is a rare syndrome of immune dysregulation.
- The immune response created by vaccinations can lead to HLH if an underlying infection has already compromised the immune system.
- Identification and treatment of HLH is vital to patient care.