Severe COVID 19 associated acute liver failure from Hemophagocytic Lymphohistiocytosis (HLH) and Herpes Simplex Virus-1 (HSV) hepatitis

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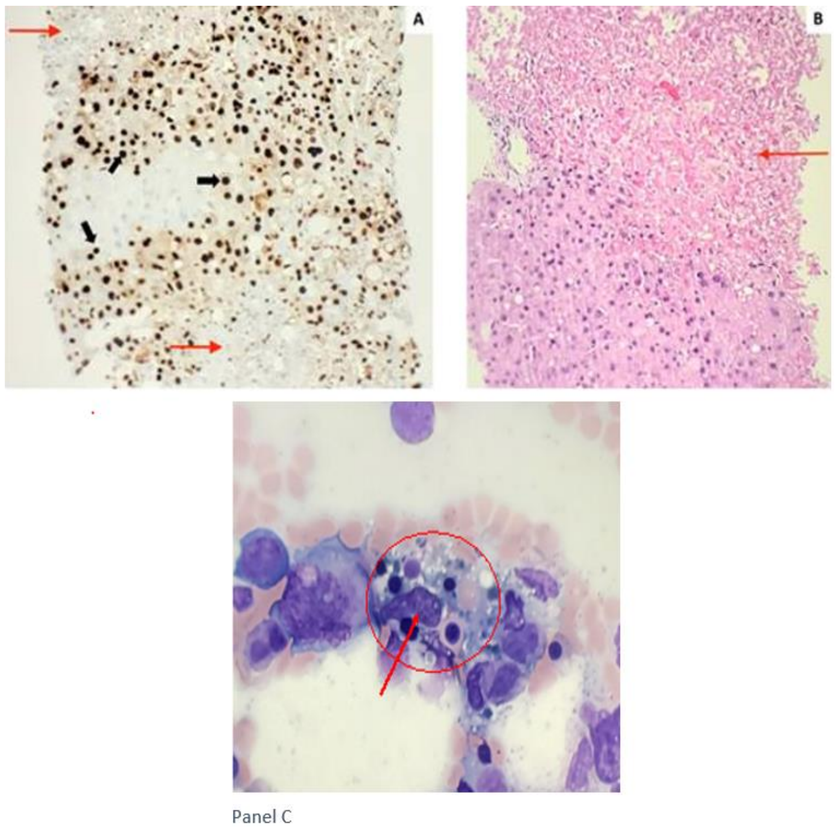
Introduction

- Acute liver failure from HSV hepatitis and Hemophagocytic lymphohistiocytosis (HLH), a syndrome characterized by an uncontrolled inflammatory response with cytokine storm, are uncommon associations with COVID-19 infection.
- We report an unusual case of acute HSV-hepatitis and HLH in an otherwise healthy male with a severe COVID 19 infection.

Case Report

- A 39-year-old male without significant medical history presented to the ER with progressive dyspnea after testing positive for COVID-19 a week before and was admitted for acute hypoxic respiratory failure.
- He was treated with Dexamethasone, Remdesivir, and Baricitinib.
- Liver enzyme elevation of Aspartate transaminase (AST) 57 and Alanine transaminase (ALT) 35 at the time of admission, was attributed to COVID-19.
- Thirteen days later, enzymes increased to AST 2457 and ALT 3119, with normal Total Bilirubin (TB) and INR. N-acetyl Cysteine was initiated, and Baricitinib was discontinued.
- He was transferred to a liver transplant center for impending liver failure. Serologies for HAV, HBV, HCV and the autoimmune panel were negative. Ultrasound abdomen did not show acute abnormalities.
- HLH was suspected based on hypofibrinogenemia, fasting hypertriglyceridemia, cytopenias, elevated ferritin (>100,000 ng/ml), and Interleukin-2
- The diagnosis was confirmed with a Bone marrow biopsy showing hemophagocytosis

- A diagnosis of primary HSV-1 hepatitis was made based on positive serum HSV-1 DNA PCR and histologic evidence of sub-massive hemorrhagic necrosis of the liver with diffuse nuclear positivity for HSV-1 in the hepatocytes.
- Anakinra and dexamethasone for HLH treatment and Acyclovir for HSV hepatitis were administered.
- He progressed to acute fulminant liver failure with shock and multiorgan failure and died three days after the confirmed diagnosis and treatment initiation.



Figure

(Panel A) Liver biopsy with HSV immunohistochemical stain. Nearly all hepatocytes are infected by the HSV virus, as demonstrated by dark brown nuclear staining (black arrow). Red arrows indicate large areas of necrotic liver tissue (panel B). Hematoxylin and eosin stain showing large areas of liver necrosis (red arrow) and viral cytopathic effect in remaining viable hepatocytes. (Panel C) Bone marrow aspirate smear demonstrating an HLH histiocyte (outlined in red, nucleus indicated by red arrow) engulfing mature and precursor red blood cells and platelets.

Table

Laboratory parameters	Day of admission	Hospitalization day 13	Hospitalization day 21
Complete blood picture			
WBC	7.4 K/uL	6.9 K/uL	4.1 K/uL
Hemoglobin	15.3 g/dL	17.3 g/dL	7.2 g/dL
Platelets	163 K/uL	112 K/uL	64 K/uL
Prothrombin time (PT)	12.0 seconds	14.2 seconds	33.6 seconds
INR	1.0	1.2	2.9
Complete metabolic panel			
Sodium	139 mmol/L	123 mmol/L	133 mmol/L
Potassium	3.7 mmol/L	4.4 mmol/L	4.7 mmol/L
Chloride	100 mmol/L	86 mmol/L	97 mmol/L
C02	26 mmol/L	25 mmol/L	14 mmol/L
Anion Gap	13	12	22
BUN	23	24	11
Creatinine	0.94 mg/dL	1.14 mg/dL	2.17 mg/dL
Albumin	4.1 g/dL	3.3 g/dL	2.8 g/dL
Bilirubin Total	0.5 mg/dL	0.7 mg/dL	7.1 mg/dL
AST	57 U/L	2457 U/L	15750 U/L
ALT	35 U/L	3119 U/L	9150 U/L
Alkaline Phosphatase	65 U/L	98 U/L	339 U/L
Others			
Ferritin			>100000 ng/mL
Triglycerides			317 mg/dL
Interleukin-2 (IL-2)			6461 mg/mL
Fibrinogen			41 mg/dL
EBV DNA, QN PCR (copies/ml)			18816 copies/ml
HSV 1 DNA, real-time PCR			Detected

Conclusions

- Elevated transaminases are commonly seen in patients with COVID 19, and clinicians often attribute them to COVID 19 infection or drug-induced liver injury.
- Occurrence of primary HSV infection or reactivation could happen in severe COVID 19 infection.
- Similarly, HLH could be part of the spectrum of Immune-mediated complications in patients with severe COVID-19.
- Our case has both HSV hepatitis and HLH leading to acute fulminant liver failure, which is detrimental.
- Clinicians should be aware of these conditions and consider them as differential diagnoses for elevated transaminases seen in COVID-19.