Case Report

Successful early plasma exchange therapy in hemophagocytic lymphohistiocytosis due to hyperacute liver failure; A case report and review of published cases.

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare severe inflammatory syndrome of excessive cytokine production. A 16-year-old girl presented with hyperacute liver failure due to idiopathic HLH. Liver failure due to HLH is uncommon, and survival in an adult after hyperacute liver failure is rare. Early diagnosis of the disease and timely treatment with plasma exchange followed by immunosuppressive therapy were associated with the survival of this patient.

Keywords: Hyperacute liver failure, hemophagocytic lymphohistiocytosis, Plasma exchange, Liver transaminase, Immunosuppressive therapy

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare form of severe inflammatory syndrome with excessive cytokine production due to the activation of T cells and histiocytes [1]. There are three forms: primary, acquired, and idiopathic [1]. The primary or familial form is commonly seen in children, but around 14% of adults have genetic mutations. [2, 3]. The acquired form in adults is associated with malignancies, autoimmune diseases, and infections [3, 4]. The Epstein–Barr (EBV), cytomegalovirus (CMV), dengue, and hepatitis viruses can initiate HLH [3]. However, in most adult patients with HLH, the underlying cause cannot be identified, and that form is considered idiopathic [4].

Acute liver injury has been found in most cases in the HLH, which is reported as an elevation of liver enzymes up to 3 times from baseline with bilirubin levels ranging from 3 to 25mg/dl [5].

However, HLH has rarely been reported as the cause of hyperacute liver failure. Treatment regimens for patients with hyperacute liver failure with HLH are not available. HLH with or without hyperacute liver failure has high mortality and morbidity [6]. Here, we report a case of a 16-year-old girl with hyperacute liver failure and idiopathic HLH who was successfully treated with plasma exchange and immune-modulatory therapy.

Case report

A 16-year-old schoolgirl presented to a regional hospital with a one-day history of low-grade fever, chest tightness, and vomiting. Later she developed a high-grade continuous fever with five episodes of bile-stained vomiting and jaundice. However, her stool was not pale, and her urine was yellow. She had no significant past illness and used no prescription or over-the-counter drugs. There was no history of blood transfusion, alcohol consumption, contact history of hepatitis, or previous jaundice. She had no tattoos. There was no significant family history of liver disease. She was drowsy and irritable on the fourth day of the illness and had high transaminase levels with elevated bilirubin and an increased international normalized ratio (INR).

Table 1: Haematological and biochemical parameters of the patient

Day	3	4	5	7	9
Place	RH	RH	TH	TH	TH
AST *(12-40 U/L)*	258	4870	9652	963	74
ALT *(<40U/L)*	178	3995	6929	2211	3
Total bilirubin (*0.3-1.5mg/dL*)	ND	45	83.9	73	54
INR (*<1.5*)	ND	3.2	8.85	2.25	1.7
Haemoglobin (*11.5-15.5g/dL*)	8.7	9.0	8.5	8.0	9.1
Platelet (*150-450 $\times 10^3/\mu L$*)	74	76	88	64	87
White cell count (*4-11 $\times 10^3/\mu L$*)	13.9	10.9	9.85	7.24	8.54

Abbreviations; AST- aspartate transaminase, ALT- alanine transaminase, INR- international normalized ratio, ND-not done, RH- regional hospital, TH- teaching hospital.

On the fourth day, she was electively intubated and transferred to a teaching hospital with a diagnosis of hyperacute liver failure. Her Glasgow Coma Scale was 8/15 (E-3, V-ET, M-5) with pupils 3mm in size equal and reactive to light. She was jaundiced with no lymphadenopathy, peripheral oedema, finger clubbing, ecchymotic patches, or skin rashes. There were no signs of chronic liver disease or portal hypertension. Her abdomen was soft, with no organomegaly, and cardiac and respiratory examinations were unremarkable.

Her ultrasound scan showed normal-sized liver with increased echogenic texture without intrahepatic or extrahepatic bile duct dilations and a mild amount of free fluid in the hepato-renal pouch. Serum ceruloplasmin levels were normal at 26.4 mg/dL (15-60) with normal 24-hour urinary copper excretion 0.85 µmol/24h (0.23-1.09) and negative Kayser–Fleischer rings (KF rings). Moreover, she was also negative for dengue antigens and antibodies, SARS-CoV-2 virus polymerase chain reaction, and mycoplasma antibodies. Her Hepatitis A, B, C, E, and EBV serology were negative. CMV and HCV PCR tests were negative. Furthermore, her retroviral screening and venereal disease research laboratory test (VDRL) were negative, her blood and urine cultures were sterile, and her inflammatory markers, including ESR and C reactive protein levels, were normal range. Her anti-nuclear antibody (ANA) was positive in 1:400 titers (<1:40). But her dsDNA antibody levels and anti-smooth muscle antibody levels were negative. Her serum Immunoglobulin G levels were within the normal range of 923 mg/dL (650-1600). Her blood paracetamol level was normal (2.8 mg/dl, normal<3). Her renal functions remain normal throughout her clinical course. Blood film showed normochromic normocytic red cells with neutrophil leukocytosis, suggesting possible iron deficiency with co-existing infection and inflammation. Serum ferritin level 7581 ng/mL (8-388) was very high. The rotational thromboelastography (ROTEM) study showed a deficiency of vitamin K-dependent clotting factors, platelet dysfunction, and low fibrinogen levels. Her fibrinogen level was low, 152 mg/dL (220 – 426). And her triglyceride level was 142mg/dL (less than 150). The bone marrow biopsy revealed reactive marrow with increased macrophage activity with evidence of hemophagocytosis (Figure 1).

HLH was diagnosed with a fever of more than 38.5°C, cytopenia involving more than two cell lines, low fibrinogen level, high ferritin level, and hemophagocytosis in the bone marrow [7].

She had a hyperacute liver failure on the fifth day of the illness and was directly admitted to the intensive care unit. Therapeutic plasma exchange was started on the fifth day of the disease and continued every other day for five cycles using 1200 ml of fresh frozen plasma.

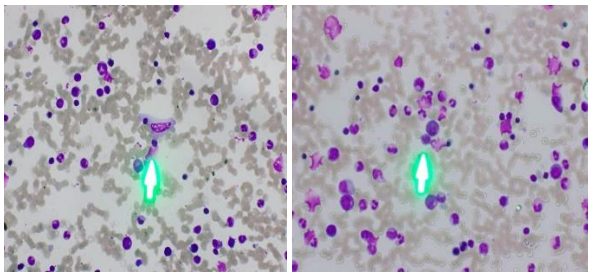

Figure 1: Micrographs showing the activated histiocytes/macrophages with cytoplasmic projections engulfing mature red blood cells (green arrow). (Leishman stain and magnification X 400)

Intravenous N-acetyl cysteine 150 mg/kg per hour over one hour, followed by 12.5 mg/kg per hour for four hours, continued as 6.25 mg/kg per hour for 72 hours until her liver functions improved. From the sixth day of the illness, treatment was started with intravenous dexamethasone 10mg/m^2/day dose after plasma exchange. The patient was extubated on the 10th day. Intravenous dexamethasone was converted to oral, and she was discharged from the hospital on the 14th day. After discharge, she was followed up regularly and has not developed any disease relapses for one year.

Discussion

We report a probable idiopathic primary HLH presenting as a hyperacute liver failure with AST of more than 9500 and ALT of more than 6000 units per litre. She was treated successfully with plasma exchange and steroids. Liver injury following the secondary HLH is common. However, it is associated with liver transaminase elevation less than three times from the baseline and a mild increase in the bilirubin (3-25 mg/dl).

We reviewed the current medical literature under "adults with acute liver failure" and "HLH". There were 22 reported cases (Table 1). Most presented with fever, nausea, vomiting, and jaundice, including our patient. All reported patients were diagnosed according to the 2004 criteria except one with a postmortem diagnosis [11].

After the diagnosis, most (18 out of 22) were started on immunosuppressive therapy with dexamethasone. However, the outcome with dexamethasone alone was poor. Of the 22 cases, only four survived, all young (4 days, 16, 23, 25). All of them had viral aetiology. Our patient is 16 year old girl, but we could not find a viral aetiology. Four of the 22 patients had transaminases of more than 5000, like ours, and two survived, indicating that high transaminase levels may not predict poor prognosis.

One possible mechanism for a high survival rate among the young population could be the age-related changes in the human immune system and its ability to remove pro-inflammatory cytokines and reactive oxygen species. HLH is due to cytokine overproduction, and the removal of produced cytokines is efficient in young [8].

Of the 22 patients reviewed, only one was treated with plasma exchange twice weekly, but that patient did not survive [17]. We have performed plasma exchange every other day for up to five cycles.

Moreover, plasma exchange was critical in this patient as a therapeutic option for her survival. A possible helpful mechanism of plasma exchange in HLH is the removal of active cytokines, defective proteins, and autoantibodies by replacing them with fresh plasma [9]. The role of plasma exchange in patients with acute liver failure and secondary HLH needs further evaluation as a therapeutic option.

We could not perform HLH-related genetic studies. Hence, the primary (heterozygous) nature of the disease could not be established conclusively [10].

Table 2: Reported cases of liver failure with HLH and clinical and therapeutic characteristics

Reference	**Age (years) Sex**	**Liver functions**	**Onset of liver injury**	**Underlying disease**	**Presenting complain**	**Treatment**	**Outcome**
Hino T et al. 1997(11)	50 F	AST 1028 ALT 647 Bil 14.4 INR NA	Acute	Malignant lymphoma	jaundice hematemesis	No treatment	death
Yamada K et al. 2008 (12)	Four days M	AST 3237 ALT 851 Bil 2.8 INR	Acute	Herpes simplex virus type 1	Fever	**Dexamethasone** Acyclovir	**Survived**

Tierney LM et al. 2011 (13)	60 F	AST 1317 ALT 399 Bil 3.4 INR 1.5	Acute on chronic	unknown	fever jaundice	**Dexamethasone** etoposide	death
Wright G et al. 2012 (14)	44 M	AST 2407 ALT 4096 Bil 298 INR 7.6	Acute	unknown	fever nausea jaundice	**Dexamethasone** etoposide liver transplant	death
Pinto-Patarroyo GP et al. 2013 (15)	23 F	AST 383 ALT 154 Bil 0.8 INR 1.69	Acute	Epstein Barr virus and Hepatitis A virus	fever anaemia jaundice	**Dexamethasone** etoposide	**Survived**
Lacey B et al. 2014 (16)	66 M	AST NA ALT NA Bil 46 INR NA	Acute	unknown	abdominal pain jaundice	No treatment	death
Lin S et al. 2016 (17)	34 M	AST 2006 ALT 1827 Bil 510 INR 1.56	Acute	unknown	fever nausea vomiting jaundice	**Prednisolone plasma exchange**	death
Schneier A et al. 2016 (18)	44 F	AST 235 ALT 210 Bil 73.3 INR 2.3	Acute	unknown	dark urine jaundice fatigue fever	**Dexamethasone** etoposide	death
	62 F	AST 4124 ALT 2614 Bil 23.8 INR 2.6	Acute	unknown	jaundice fatigue	**Dexamethasone** etoposide	death
	53 F	AST 4271 ALT 3049 Bil 35.8 INR 2.5	Hyper acute	unknown	fever nausea vomiting jaundice	**Dexamethasone**	death
Giard J-M et al. 2016 (19)	35 F	AST 2781 ALT 1497 Bil 11.6 INR 1.7	Acute	unknown in pregnancy	fever jaundice	**Dexamethasone**, etoposide	death
Patel R et al. 2017 (20)	57 M	AST 261 ALT 395 Bil 19 INR 4.2	Acute	B cell lymphoma	fatigue confusion jaundice	Supportive care	death
Cappell MS et al. 2018 (21)	47 M	AST 70 ALT 167 Bil 45.1 INR 1.9	Acute	unknown	fever, jaundice, widespread macula rash	**Prednisolone** supportive care	death
Zhang L-N et al. 2018 (22)	16 M	AST 8496 ALT 6499 Bil 16.8 INR 1.65	Acute	Varicella infection	fever rash abdominal pain	**Dexamethasone**, etoposide Acyclovir	**survived**
Kumar M et al. 2018 (23)	56 days M	AST 5440 ALT 5570 Bil 11.85 INR	Acute	unknown	fever diarrhoea vomiting	**Dexamethasone**	death
Lutfi K et al. 2018 (24)	51 F	AST 647 ALT 194 Bil 10.1 INR NA	Acute	Epstein Barr virus	fever jaundice abdominal pain	Bone marrow transplant, alemtuzumab	death

Najib K et al. 2020 (25)	3 F	AST 8840 ALT 1420 Bil 1.5 INR 2.09	Acute	unknown	fever tachycardia	**Dexamethasone**	death
Coppola A et al. 2021 (26)	76 M	AST 106 ALT NA Bil 28 INR 2	Acute	B cell lymphoma	fever confusion jaundice	**Methyl prednisolone**	death
Blaney M et al. 2021 (27)	33 M	AST 72 ALT 38 Bil 0.9 INR 1.7	Acute	Hepatitis B virus with HIV	fever cough	Supportive care	death
Qureshi H et al. 2022 (28)	51 M	AST 344 ALT 217 Bil 3.4 INR 1.6	Acute	Renal cell carcinoma	fatigue diarrhoea jaundice	**Dexamethasone** etoposide	death
Termsinsuk P et al. 2022 (29)	25 M	AST 5652 ALT 5397 Bil 7.3 INR 1.34	Acute	Hepatitis A virus	fever hepatomegaly	**Dexamethasone** Intravenous immunoglobulin	**survived**

Abbreviations; AST- aspartate transaminase, ALT- alanine transaminase, Bil- serum bilirubin, INR- international normalized ratio, F-female, M-male, NA- not available

Conclusion

Hyperacute liver failure with HLH is rare, and diagnosis remains challenging due to the lack of specific clinical features and investigations. Hence it carries significant mortality. A high degree of clinical suspicion is needed to diagnose HLH and its complications. Treatment with therapeutic plasma exchange and immunosuppression may increase survival but needs further evaluation.

Informed consent: The patient has given verbal and written consent to publish her history and images as a case report.

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