An unusual complication of hepatitis A: secondary hemophagocytic lymphohistiocytosis

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European Journal of Medical Case Reports
Volume 4(6):186–189

https://doi.org/10.24911/ejmcr/173-1563277232

ABSTRACT

Background: Secondary hemophagocytic lymphohistiocytosis (HLH) is characterized by severe cytopenias due to uncontrolled hemophagocytosis. Other laboratory signs and clinical symptoms result from disordered immune regulation, and cytokine storm is well recognized. It is often a fatal complication of infections. It is not as uncommon as thought of previously.

Case Presentation: We discuss a 7-year-old boy, born out of non-consanguineous marriage with acute hepatitis A infection, who developed HLH during treatment and was successfully managed with methyl prednisolone pulse therapy followed by oral prednisone therapy.

Conclusion: Secondary HLH is a rare complication in a case of hepatitis A. A high index of suspicion at the early stage of HLH may produce a favorable outcome.

Keywords: Hemophagocytic lymphohistiocytosis, hepatitis A, injectable methyprednisolone, oral prednisolone, ferritin, triglycerides.

Received: 27 September 2019 **Accepted:** 06 May 2020

Type of Article: CASE REPORT **Specialty:** Pediatrics

Funding: None.

Declaration of conflicting interests: The authors declare that there is no conflict of interests regarding the publication of this case report.

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Background

Hemophagocytic lymphohistiocytosis (HLH) has been classified under histiocytosis syndromes of childhood. These disorders feature severe cytopenias due to uncontrolled hemophagocytosis. Other laboratory signs and clinical symptoms result from disordered immune regulation and cytokine storm [1].

HLH is classically divided into two types: (1) primary or familial HLH and (2) secondary HLH. Familial HLH is generally an autosomal recessive condition, whereas secondary HLH is usually associated with infectious, autoinflammatory, and autoimmune diseases (where it is more commonly known as macrophage activation syndrome), malignancy, immunosuppression, hematopoietic stem cell transplantation, organ transplantation, human immunodeficiency virus infection, and metabolic diseases [2].

The clinical signs of HLH include prolonged high-grade fever, multiorgan involvement including cytopenias, hepatosplenomegaly and liver dysfunction, skin rash, coagulopathy, and variable neurologic symptoms [3]. HLH is diagnosed based on HLH diagnostic criteria-2004 (Table 1) [4].

The presence of hemophagocytes in the bone marrow is pathognomonic but may not be obvious at the time of initial diagnosis. However, the prominent sinusoidal Kupffer cell hyperplasia and conspicuous hemophagocytosis with extramedullary hemotopoiesis led to a strong suspicion of HLH in the absence of initial bone marrow hemophagocytes in a study by Chatura et al. [5].

Conventionally, HLH-94 protocol was followed for the management of HLH. HLH-94 protocol included an initial intensive therapy with immunosuppressive and cytotoxic agents for 8 weeks, with the aim to induce remission of the disease activity [6].

Other treatment modalities for the treatment of HLH have been documented in literature. Liposomal doxorubicin treatment combined with etoposide and methylprednisolone showed an encouraging overall response and was well tolerated in adults according to the study by Wang et al. [7]. Nawata et al. [8] suggested the possibility of mycophenolate mofetil as a key drug for treating HLH associated with SLE. According to a study by Naoi et al. [9], an additional therapy (with steroids/immunosuppressive drugs/ IVIg) was significantly more frequently provided in the pediatric group than in the adult group ($p = 0.012$) in the cases of scrub typus-associated HLH.

Corticosteroids with disease-specific therapy have been mentioned as the treatment for clinically stable cases of HLH [10]. However, the duration, dose, and choice of steroids as monotherapy for the management of HLH have not been established. Recent study by Muduli et al. [11] suggested the use of short course of monotherapy

steroids for 14 days with a favorable outcome in pediatric secondary HLH.

The association of HLH with hepatitis A has been rarely reported, and there is an absence of formulated treatment strategy for the treatment of the same. With that background, we report an interesting case of hepatitis A associated with secondary HLH.

Case Presentation

A 7-year-old boy born out of non-consanguineous marriage presented to the institution with a history of fever for 10 days associated with melena for 5 days.

On examination, the child was toxic, irritable, febrile, puffy, pale, and icteric. The examination of gastrointestinal system showed ascites and grade III hepatosplenomegaly.

A provisional diagnosis of acute infective hepatitis was made, and the child was started on conservative management (injection Vitamin K, syrup lactulose, injection Ranitidine, and IV fluids) after sending appropriate investigations (Table 2). The investigations revealed deranged liver function test (LFT) with normal prothrombin time (PT) INR and activated partial thromboplastin time (aPTT). Hepatitis A virus IgM was reactive. Commonly associated tropical infections were ruled out (malaria, typhoid, leptospirosis dengue, EBV, CMV, and herpes).

Despite adequate therapy, the child remained febrile for the next 6 days associated with the deterioration of clinical status. He developed hypotension associated with a decrease in urine output. The child developed petechial rash over the dependent parts of the body.

Repeat LFT continued to be grossly deranged with worsening of PT and aPTT to no coagulation. LDH, ferritin, and triglyceride were elevated (Table 2).

A provisional diagnosis of secondary HLH based on HLH society criteria was made (as there were no stigmata or family history of HLH). The child was started on institutional protocol of IV methyl prednisolone pulse therapy for 3 days (30 mg/kg), followed by oral prednisolone for 11 days (1 mg/kg).

The bone marrow study could not be done due to the non-availability of consent.

On 2nd day of methyl prednisolone therapy, the child became afebrile with normalization of blood pressure. Hence, the ionotropes were tapered off. On day 3 of methyl prednisolone therapy, the blood counts improved with the rapid resolution of anasarca, ascites, and hepatosplenomegaly.

LFT gradually normalized over next 2 weeks. Coagulopathy improved on day 2 without the use of FFP (Vitamin k was administered at the admission and repeated on day 6). Factor V level was low (50%).

Steroids were tapered over next 2 weeks. On follow-up at 1 and 2 months, the child was asymptomatic with the normalization of blood parameters, ferritin, and triglyceride levels.

Table 1. *Diagnostic Criteria of HLH molecular diagnosis of HLH or the presence of at least 5 of 8 criteria.*

1. Fever
2. Splenomegaly
3. Cytopenias (affecting at least two lineages in the peripheral blood) Hemoglobin levels <90 g/l (in infants <4-week old and hemoglobin <100 g/l) Platelets <100 × 109/l Neutrophils <1.0 × 109/l
4. Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglycerides ≥3.0 mmol/l (i.e., ≥265 mg/dl) Fibrinogen ≤1.5 g/l
5. Documented hemophagocytosis in the bone marrow, spleen, or lymph nodes
6. Low or absent natural killer cell activity
7. Ferritin ≥ 500 mg/l
8. Soluble CD25 (i.e., soluble interleukin-2 receptor) ≥2,400 U/ml

Table 2. *Laboratory Parameters during hospital course.*

LABORATORY PARAMETERS	DAY 1	DAY 2	DAY 3	DAY 5	DAY6	DAY 7	DAY 8	DAY 9
CBC (HB/TPC/ANC)	8.6/1.4/8,000		7.9/1.2/6,600		6.4/0.8/5,000			8.8/2.5/5600
Serum urea/creatinine	120/1.1	80/0.9			110/1.1	48/0.8		35/0.6
LFT TB/SGPT/SGOT/ albumin	3.6/540/440/2.6				4/670/308/2.0			1.2/148/102/2.6
PT INR/aPTT (ratio)	1.2/2			No coagulation	No coagulation	No coagulation	2.2/1.5	1.1/1.2
Triglyceride					540			
Ferritin					>1,650			
LDH					1,250			
Crp	165				160			
Esr	35				15			

Discussion

Nonresponse to supportive therapy prompted us to investigate for HLH. The clinical features associated with pancytopenia, elevated ferritin, and triglyceride levels strengthened the initial suspicions. The low factor V levels were probably due to DIC (D dimer levels were elevated) or liver involvement. Etoposide was not instituted in view of abnormal LFTs.

Although hepatitis A infection in association with HLH has been described in adults [12,13], the literature about the pediatric population is scarce.

The strength of this study was that a favorable outcome was achieved in our case with the use of ultra-short course of steroids (14 days) as opposed to the case described by Giri et al. [14], where steroid therapy (injection dexamethasone) was given for 1 month. The non-availability of the bone marrow study to confirm the diagnosis was a major limitation.

Conclusion

A rare case of hepatitis A in association with secondary HLH was managed with ultra-short course of steroids.

What is new?

Secondary HLH is a very rare complication of hepatitis A. Early suspicion and diagnosis of HLH in a case of poor response to conservative management may help in diagnosis, and a short course of steroids produces a favorable outcome as in this case.

List of Abbreviations

ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
CMV	Cytomegalovirus
EBV	Ebstein Barr Virus
FFP	Fresh Frozen Plasma
Hb	Hemoglobin
HLH	Hemophagocytic lymphohistiocytosis
INR	International Normalised Ratio
IVIg	Intravenous Immunoglobulin
LFT	Liver function test
LGH	Lactic Dehydrogenase
PT	Prothrombin time
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLE	Systemic Lupus Erythematous
TPC	Total Platelet Count

Consent for publication

Written informed consent was taken from the family of patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Male, 7 years
2	**Final diagnosis**	HLH in a case of hepatitis A
3	**Symptoms**	Fever, icterus, melena
4	**Medications**	Steroids
5	**Clinical procedure**	Conservative
6	**Specialty**	Pediatrics