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Hemophagocytic Lymphohistiocytosis – Unusual Presentation as Cholangitis- Cholestatic Jaundice

Arun Agarwal[1*], Aakanksha Agarwal[2] and Abu Saad Khan[1]

[1]Department of Internal Medicine, Fortis Escorts Hospital, Jaipur, Rajasthan, India.
[2]Department of Radiodiagnosis, SMS Medical College, Jaipur, Rajasthan, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author Arun Agarwal was the primary consultant in this case. He contributed to the conception, design and analysis of the case study. He wrote the first draft of the manuscript and approved the final work to be published. Author Aakanksha Agarwal managed the tabulation work, literature searches and final grammar correction of the manuscript. Author ASK retrieved all patient data, images and photograph. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare, under diagnosed, fatal and devastating hyper-inflammatory syndrome that has gained increasing recognition over the past decade. HLH can be familial (F-HLH) or acquired; infections, autoimmune diseases, malignancy or immune suppression being the most common triggers of the acquired form. Patients with HLH present with clinical and laboratory evidence of uncontrolled inflammation. They may present with fever, cytopenias, jaundice, and hepatosplenomegaly. Laboratory features may show hyperferritinemia, transaminitis, and low fibrinogen, albumin and natural killer (NK) cells. Delay in diagnosis and management inevitably leads to a rapidly progressive and fatal course. We present a case in which the patient had daily fever, gradually rising bilirubinemia, cytopenias, transaminitis and was initially managed as sepsis, and later as cholangitis and obstructive jaundice before being diagnosed as acquired HLH secondary to Epstein Barr virus associated hepatitis. He succumbed to his illness despite starting

**Corresponding author: E-mail: mpicdrarun@gmail.com;*

therapy for HLH after initial recovery .Delayed diagnosis, refractory progressive HLH and secondary bacterial sepsis were the factors contributing to fatality.

Keywords: Hemophagocytosis; obstructive jaundice; secondary hemophagocytic lymphohistiocytosis syndrome (sHLHS); Ferritin; Epstein Barr virus.

1. INTRODUCTION

Hemophagocytic Lymphohistiocytosis (HLH) is an uncontrolled proliferation and over-activation of lymphocytes and macrophages. It can be primary HLH i.e., consequence of genetic disorders, or secondary HLH (sHLHS) i.e., acquired due to infections, autoimmune diseases, malignancy or immune suppression. Viral infections are one of the commonest cause for sHLHS, often misdiagnosed as sepsis with multi organ dysfunction (MODS) syndrome. The most common virus involved is Epstein-Barr virus, but other virus promoting sustained lymphocyte activation could be a trigger to HLH [1,2].

HLH is a Syndromic disorder defined and diagnosed by a unique pattern of clinical and laboratory findings. It may presents in many forms: fever of unknown origin, hepatitis/acute liver failure, sepsis-like, Kawasaki-like, and neurologic abnormalities. HLH diagnosis (Table 1) was defined by Histiocyte Society, the HLH-2004 criteria [3]. Not all of the HLH diagnostic criteria may be present initially and it becomes important to follow clinical signs and laboratory markers of pathological hyper-inflammation periodically to identify the trends. Patients usually present with fever, cytopenias, and hepatosplenomegaly. Laboratory findings include elevated ferritin, triglycerides, transaminases and soluble interleukin-2 (IL-2) receptor levels. Fibrinogen and albumin are low and natural killer (NK) cells, although low to normal in numbers, have measurable impaired function. Ferritin levels above 10,000 ng/ml appear to be specific and sensitive for HLH with 92.84% specificity to HLH diagnosis [4,5]. Hemophagocytosis is neither sensitive nor specific for HLH and is considered as one of the less important diagnostic criteria as bone marrow biopsy may not have evidence of Hemophagocytosis at disease onset in all patients [6]. However, Liver biopsy may show a hepatitis-like periportal infiltrate of lymphocytes and histiocytes that can cause obstructive jaundice [7,8].

Patients treated following the current guidelines have a 50–60% probability of prolonged survival if HLH is diagnosed early and timely [9,10]. We feel that it should be considered more often in patients presenting with or getting worse with sepsis and multi organ dysfunction syndrome (MODS).

2. CASE PRESENTATION

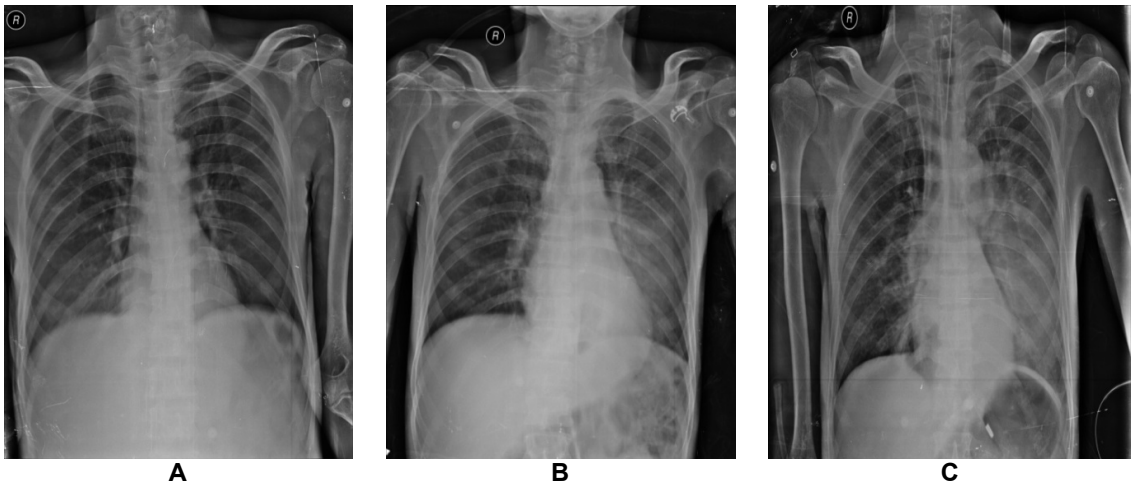
A 63 year-old Asian man presented to Fortis Escorts Hospital, Jaipur, India on March 21, 2018 for evaluation of persistent fever, decreased appetite, oral cavity ulcers ,abdominal pain, anemia and jaundice of almost one month duration. The patient had been generally healthy about a month back when he developed sore throat and fever for which he was treated locally in a village. He was then admitted to another facility from March 05, 2018 to March 21, 2018 for further evaluation of persistent fever. There he was diagnosed to have cholelithiasis, and during hospital stay developed gradually increasing jaundice with pancytopenia. His reports are mentioned in Table 1 and 2. He was initially managed as cholangitis – sepsis and later as obstructive jaundice with antibiotics, 3 unit packed red cells, 8 units fresh frozen plasma and 12 units random donor platelets transfusion during hospital stay. Bone marrow aspiration and biopsy were reported unremarkable. He was then shifted by family to our facility for further management. On examination, he weighed 48.7 kg (BSA 1.54 m2 ,BMI 17.3 kg/m2), his pulse was regular 70 per minute, blood pressure 110/70 mm Hg, respiratory rate 20 per minute, peripheral capillary oxygen saturation (SpO2) 97%, and temperature 98.6°F. He looked toxic, severely jaundiced, had maculopapular non purpuric rash over back and abdomen, anemia, mild hepatosplenomegaly, and mild bilateral pedal edema. Rest of his clinical examination was essentially normal. His XRC is in Figure 1A.He was admitted under gastrointestinal surgery department in intensive care unit with a provisional diagnosis of obstructive jaundice. Suspecting cholangitis, antibiotics were started. An MRCP (magnetic resonance cholangiopancreatography) did not show any evidence of biliary dilation or choledocholithiasis and an upper gastrointestinal endoscopy (UGIE) done earlier had been unremarkable. ERCP (endoscopic retrograde

cholangiopancreatography) was not done. Gastroenterology consult was done to further evaluate him for cholestatic jaundice. Autoimmune Hepatitis panel, IgM HEV antibodies, IgM HAV antibodies, Hepatitis B surface antigen, HCV antibodies, HIV 4th generation antigen/antibody test, Anti-streptolysin O titres, IgM scrub typhus antibodies, IgM/IgG dengue antibodies, Malaria parasite, Widal test, Weil Felix test for rickettsial infections, Blood cultures, urine routine examination and culture, sputum grams stain/acid fast bacilli stain/fungal stain and cultures, serum Procalcitonin were all negative or unremarkable. His cardiac work up including Electrocardiogram and Echocardiogram were normal. His bone marrow was reviewed. Histology showed a normocellular bone marrow with adequate trilineage haematopoiesis and mild megakaryocytic hyperplasia. There was no evidence of myelodysplastic syndrome, myeloproliferative neoplasm or HLH was observed.

With no evidence of cholangitis (sterile cultures) and no obvious cause for cholestasis,an internal medicine consult was done. Persistent bicytopenia, daily spikes of fever, deranged liver function tests (LFT), severe hypoalbuminemia with mild bilateral pleural effusions, hepatosplenomegaly and no evidence of infection, he was further evaluated for inflammatory disorder. His serum ferritin, Triglyceride, Fibrinogen, natural killer (NK) cells, DNA detection of bacteria/fungus / viruses from blood sample were done and bone marrow biopsy was reviewed. There was no evidence of Hemophagocytosis in bone marrow and liver biopsy was refused by family. The reports are mentioned in Table 2, 3 and 4. MRCP is in Fig. 2. Marked hyperferritenemia (>80,000 ng/ml), hypertriglyceridemia, low NK cells, bicytopennia, hepatosplenomegaly, no evidence of malignancy and other abnormal clinical and laboratory findings including jaundice, edema, skin rash ,hepatic enzyme abnormalities, hypoproteinemia, high VLDL, low HDL and detection of Epstein-Barr virus DNA in blood led us to diagnose him as EBV associated sHLHS.

On March 24, 2018 he was initiated on HLH - 2004 recommendations and suggested therapy for EBV-HLH with Etoposide, Dexamethasone and cyclosporine was added upfront along with acyclovir, cefoperazone- sulbactum, teicoplanin and supportive treatment. We did not do his cerebro- spinal fluid (CSF) analysis as he had no neurological signs or symptoms and because of thrombocytopenia. Intrathecal methotrexate was not given. He responded to the treatment and became afebrile. His laboratory abnormalities including deranged LFT's, cytopenias started improving (Tables 2 and 3). He was discharged on March 29, 2018 on twice weekly etoposide, cyclosporine, dexamethasone, acyclovir, cefuroxime axetil and supportive treatment.

He was readmitted through triage on 31.03.2018 with high grade fever, cough, and breathlessness of 6 hours duration. His pulse was regular 108 per minute, blood pressure 60/30 mm Hg, respiratory rate 22 per minute, peripheral capillary oxygen saturation (SpO2) 96%, and temperature 98.6°F.Systemic examination show left side coarse crept and he was admitted to medical ICU.He had to be mechanically



A B C

Fig. 1. X ray chest A.21.03.2018; B.31.03.2018 6am; C.31.03.2018 2pm

ventilated and required vasopressor support. His laboratory parameters show severe pancytopenia with hemoglobin, total leukocyte count and platelets dropping from 8.8 gm/dl, 5.9x103/cmm, and 105x103/cmm to 7.3 gm/dl, 0.7x103/cmm, and 25x103/cmm respectively. This happened within 72 hours despite him being on therapy for HLH. His procalcitonin was very high and this led us to suspect refractory HLH with secondary bacterial sepsis. His XRC is in Fig. 1B and 1C which show left side lobar pneumonia. His weekly dose of Etoposide was due on March 31, 2018 and the same was given along with intravenous dexamethasone, meropenem, moxifloxacin, loading dose of colisitn, acyclovir,one unit packed red cells,4 units of random donor platelets, nebulized colisitn, oral cyclosporine and supportive treatment. We also gave him rituximab 500 mg for progressive EBV- HLH. However he succumbed to his illness on April 01, 2018. Central and peripheral blood culture reports received on April 02, 2018 show extensively drug resistant (XDR) Acinetobacter Baumannii ,sensitive only to colisitn. Autopsy was refused by the family.

3. DISCUSSION

HLH was considered to be a rare disease in adults but has been increasingly reported over last few years, likely due to awareness, rather than rise in its incidence. Authors have earlier reported a small case series and emphasized that the cases reported in literature probably represent a tip of an iceberg of large number of undiagnosed cases mostly labeled as sepsis with MODS in critical care units [11].

HLH is the aggressive proliferation of activated macrophages and histiocytes, which phagocytes other cells, namely RBCs, WBCs and platelets, leading to the clinical symptoms. However, this pathologic finding is neither necessary nor

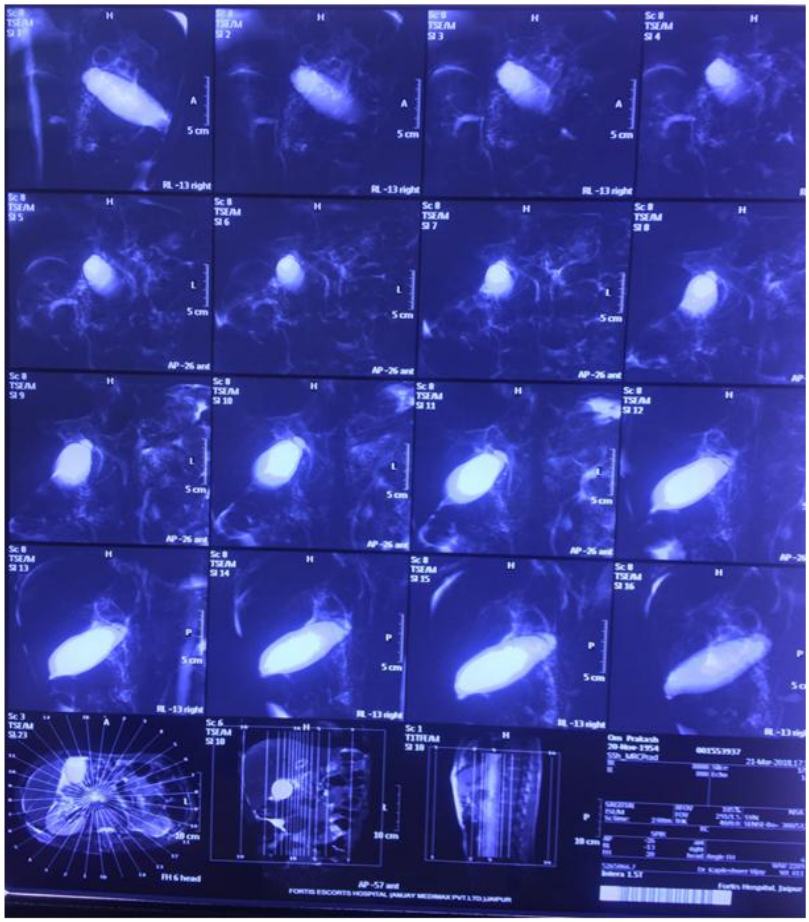


Fig. 2. MRCP dated 21.03.2018

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH may be established by: **
A. A molecular diagnosis consistent with HLH: Pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4
OR
B.Five out of the eight criteria listed below are fulfilled:
1. Fever ≥38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood):
Hemoglobin <9 g/dl (in infants <4 weeks: hemoglobin <10 g/dl)
Platelets <100X103/ml
Neutrophils <1X103/ml
4. Hypertriglyceridemia (fasting, > 265 mg/dl) and/or hypofibrinogenemia (<150 mg/dl)
5. Hemophagocytosis in bone marrow or spleen or lymph nodes or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/ml***
8. Elevated Soluble CD25 (alpha chain of soluble IL-2 receptor)****

* adapted from Henter et al [3].

** Additionally, in the case of familial HLH, no evidence of malignancy should be apparent.

***While the HLH-2004 protocol uses ferritin>500 ng/ml, we generally view ferritin>3000 ng/ml as concerning for HLH, and ferritin>10,000 as highly suspicious. [23].

****Elevations above age-adjusted, laboratory-specific normal levels (defined as >2 SDfrom the mean) appear more meaningful than the original designation of '>2,400 U/ml, because of variations between laboratories [24].

Table 2. Complete Blood counts and inflammatory markers

Date/ Normal range	Hb gm/dl (13-17)	TLC x 103 cells /cmm (4-10)	DLC(%)	PC x103 cells/cmm (150-400)	ESR mm !st hour (0-15)	CRP mg/L (0-5)
05.03.2018	8.5	3.7	P45 L50	42		
07.03.2018	8.3	3.8	P52 L42	33		
10.03.2018	9.2	2.3	P40 L57	49		
15.03.2018	6.4	5.0	P40 L58	18		
18.03.2018	9.5	7.0	P45 L47	46		
20.03.2018	8.9	7.44	P89 L08	65		
24.03.2018	8.6	9.5	P74 L20	40	35	98
27.03.2018	8.7	7.4	P89 L8	65		
28.03.2018	8.8	5.9	P85 L12	105		
30.04.2018	7.0	1.7		50		
31.03.2018	7.3	0.7	P44 L50	25	25	100.6

Hb: Hemoglobin; TLC: total leukocyte count; DLC: differential leukocyte count; PC: Platelet count; ESR: Erythrocyte sedimentation rate; CRP: C reactive protein

pathognomonic for the diagnosis of HLH. The clinical manifestations of HLH are due to: (1) Hyper activation of CD 8 + T lymphocytes and macrophages; (2) Proliferation, ectopic migration, and infiltration of these cells into various organs; and (3) Hypercytokinemia with persistently elevated levels of multiple pro-Inflammatory cytokines, resulting in progressive organ dysfunction. The mortality is from hemorrhage, multi-system organ failure or infection. Survival from HLH requires prompt recognition of syndrome, correction of its underlying cause and HLA specific therapies [11,12].

While we agree that earlier diagnosis of HLH is a challenge due to nonspecific features mimicking SIRS, nevertheless clinicians should suspect it in any case of fever, cytopenia, transaminitis and send serum ferritin test which is available at almost all tertiary care centers. Liver injury with mild elevation of transaminases is seen in 85% patients with HLH and about half have hyperbilirubinemia. Florid liver failure is rare, and post hepatic form of injury mimicking cholangitis has rarely been reported so far [13].

Table 3. Serum biochemisty

Date/Normal range	Bilirubin total/direct mg/dl (0-1.3)/ (up to 0.3)	SGOT (AST) IU/L (15-37)	SGPT (ALT) IU/L (30-65)	ALP U/L (82-169)	Total Proteins/ albumin gm/dl (6.4-8.6)/(3.8/5.6)	LDH U/L (110-210)	PT- INR (1.2 ratio)	Ferritin ng/ml (30-400)	Triglycerides mg/dl(<150)	Procalcitonin ng/ml (< 0.5)
05.03.2018	0.8/0.4	389	189	483	5.2/2.3					
07.03.2018	1.1/0.5	290	113	360	6.6/3.5					
10.03.2018	2.1/0.9	562	142	850	4.4/2.1					
15.03.2018	4.0/2.0	398	104	595	4.2/2.3					
18.03.2018	7.0/4.0	480	210	680	4.9/2.4					
20.03.2018	14.2/11.2	416	215	786	5.9/2.2	648				
22.03.2018							1.20	>16500	211	0.902
24.03.2018	21.5/18.6	440	218	602	5.0/1.5	1114				
25.03.2018								>80,000	294	
27.03.2018	14.2/11.2	157	113	447	5.9/2.2	648				
28.03.2018	12.7/10.4	133	113	428	5.8/2.2	541				
31.03.2018	13.0/10.7	80	98	261	4.4/1.6	343	1.32	8310.4		56.840

SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; ALP: Alkaline phosphatase; PT: prothrombin time; LDH: lactate dehydrogenase

Table 4. Other relevant investigations and imaging results

Date	Test	Result
05.03.2018	NCCT Chest	Few tiny centrilobular nodules in lateral basal segment of left lower lobe seen? bronchiolitis.
06.03.2018	Upper GI endoscopy	Few erosions seen in stomach.
07.03.2018	CECT Whole abdomen	Cholelithiasis with minimal Gall Bladder wall thickening and mild pericholecystic fluid collection. Bilateral pleural effusion present.
	NCCT Brain	Bilateral chronic infarcts in posterior cerebral artery territory involving parieto-occipital lobe on right side and temporal-parieto-occipital lobes on left side. Chronic infarcts are also seen in bilateral basal ganglion and thalami.
		Positive.
21.03.2018	MRCP	Mild hepatomegaly with altered intensity, distended gall bladder filled with sludge showing minimal edematous wall thickening without peri cholecyctic collection. Few tiny gall stone at GB neck region are seen. Mild ascites.
23.03.2018	Auto immune hepatitis panel	ANA,Anti smooth muscle antibodies,Anti mitochondrial antibodies, Liver Kidney micro antibodies and P ANCA, Anti soluble Liver antigen :Negative
	Natural killer (NK) Cell Panel (Flowcytoimetry)	73.4 (60-85%)
	CD3	6.8 (5-28%) #
	CD(16+56)	99 (0-99%)
	CD45	
24.03.2018	DNA detection in blood	Syndrome evaluation system detects DNA of Gram positive bacteria, Gram negative bacteria, Mycobacterium tuberculosis, leptospira, fungi, Toxoplasma gondii and viruses. Epstein-Barr Virus DNA was detected positive.
	Ultrasonography Abdomen	Mild fatty hepatomegaly, cholelithiasis, mild ascites, mild right pleural effusion with basal atelectasis.
	Serum Fibrinogen	233 mg/dl (200-400 mg/dl)
26.03.2018	Lipid Profile	Triglycerides:294 mg/dl Total Chlesterol:103 mg/dl HDL:03 mg/dl Direct LDL:06 mg/dl VLDL:58.8 mg/dl
		73.90 U/ml (< 20)
27.03.2018	EBV IgG	< 10.0 U/ml(<20)
	EBV IgM	Positive; Organism: Acinetobacter Baumannii. Sensitive to
02.04.2018	Blood Culture	colisitn (MIC </= 0.5).
		Sterile.
	Urine culture	

#Diagnostic criteria is < 10% activity by flow cytometric assays

NCCT:Non contrast computerized tomography; CECT-Contrast enhanced computerized tomography;MRCP:Magnetic resonance cholangeopancreatography;EBV: Epstein barr virus; GB:Gall Bladder;HDL:High density lipoprotein;LDL:Low density lipoprotein;VLDL:Very low density lipoprotein;MIC:Minimum inhibitory concentration

The case presented had a delayed diagnosis and was initially labeled as cholangitis with sepsis followed by obstructive jaundice and then autoimmune hepatitis. Despite persistent fever, rising serum bilirubin, transaminases and cytopenias, HLH was not thought of. However, bone marrow biopsy was done but it did not show any evidence of Hemophagocytosis. Had it been present, it would have been thought of earlier. Prevalence of Hemophagocytosis in association with HLH diagnosis ranges from 25 to 100% [14]. Despite the nomenclature of HLH, diagnosis should never be made or excluded solely on the presence or absence of Hemophagocytosis because it may be induced by more common events including blood transfusions, infection, autoimmune disease and other forms of bone marrow failure or causes of red blood cell destruction [15].

After shifting to our facility patient was promptly evaluated and obstructive jaundice in view of cholelithiasis was ruled out. As authors had past experience of diagnosing and treating such patients which have been reported, his serum ferritin, lipid profile, fibrinogen and NK cell panel

were done and he was diagnosed to have sHLHS [11,16,17]. DNA PCR test done on blood were positive for EBV and serum EBV IgG antibodies were high suggesting that probably he had reactivation of latent EBV infection. EBV is the most frequent infection associated with HLH. EBV-associated HLH varies widely from inflammation that resolves spontaneously to unrelenting disease requiring HCT. It has been associated with acute infections not only in B cells, but also in T cells and NK cells [15,18,19]. Survival is improved if Etoposide containing therapy is initiated promptly upon diagnosis [20]. As Rituximab can eliminate EBV-infected B cells, it may be a beneficial addition to other therapies in patients with progressive EBV-HLH [21].

The HLH-2004 protocol for treatment includes Dexamethasone and Etoposide, an antimonocytic and antihistiocytic agent. Monocytes and histiocytes are thought to control antigen load via elimination of infected antigen-presenting cells [22]. Cyclosporine A which suppresses cytotoxic T lymphocyte and macrophage activity has also been recommended. Intrathecal methotrexate is used for central nervous system involvement.

Our patient was initiated on Etoposide, Dexamethasone as per HLH-2004 protocol and Cyclosporine was started upfront. We gave reduced dose of Etoposide initially in view of severe hyperbilirubinemia. The first dose was 100 mg, second 150 mg and third 200 mg respectively. He initially showed good recovery, became afebrile; transaminases, hyperbilirubinemia and ferritin started settling down and cytopenias improved. He was discharged on twice weekly Etoposide, daily oral Dexamethasone, Cyclosporine, oral Cefuroxime axetil, and supportive treatment. However, he was readmitted after 36 hours with recurrence of fever, severe bicytopenia, cough and hypotension. He had left side lobar pneumonia. Rituximab 500 mg was given in view of progressive EBV-HLH. Secondary bacterial infection was treated with appropriate antibiotics.

Prognosis of adult HLH is very poor, with mortality of 41-75%. Authors reported a mortality of 57% in their small case series [11]. Early diagnosis and timely treatment with the HLH-2004 protocol has been shown to improve survival in adult patients with HLH. Delay in diagnosis, high ferritin levels, low albumin and multiorgan involvement are associated with poor prognosis as in this case [22]. We did not conduct genetic studies to rule out a mutation in our patient because of non availability of these tests.

4. CONCLUSION

HLH is a rare and under-diagnosed clinical syndrome and is rapidly fatal if not diagnosed and managed timely. It can present in heterogeneous ways. Unexplained liver failure with concurrent cytopenias and elevated inflammatory indices should suggest HLH, while a diagnosis of HLH with normal liver indices should be considered very unusual. Ferritin levels above 10,000 microg/L appear to be specific and sensitive for HLH. The diagnosis of HLH should be evaluated in patients without a significant medical history who has a new onset of febrile illness with highly elevated ferritin levels. Therapy should not be delayed in the absence of histological confirmation if there is high suspicion of HLH on the basis of clinical presentation.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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