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Case Series

Haemophagocytic Lymphohistiocytosis Secondary to Communicable Diseases in Children Presenting in a Tertiary Care Centre - A Case Series

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I N F O

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A B S T R A C T

Primary Haemophagocytic Lymphohistiocytosis (HLH) is a rare disorder. However, secondary HLH is not so rare. Viral infections like Epstein–Barr Virus (EBV) can lead to HLH. Bacterial infections can occasionally lead to HLH. Here, we have reported 4 cases of HLH related to bacterial infections common in our setting. The first case had leptospirosis, the second had leptospirosis with scrub typhus, the third had enteric fever, and the fourth had enteric fever and leptospirosis. These patients presented in sick condition. An apparent non-response to standard antibiotic therapy prompted us to do further investigation, which confirmed HLH. Such patients can have a turbulent and fatal course if not promptly diagnosed and treated. Hence a prompt workup and management of HLH in the cases in which clinical response to antibiotics is inadequate helps in improving outcomes and preventing mortality.

Keywords: Secondary Haemophagocytic Lymphohistiocytosis (HLH), Leptospirosis, Enteric Fever, Scrub Typhus

Introduction

Haemophagocytic Lymphohistiocytosis (HLH) is a hyperinflammatory disorder that is characterised by disseminated lesions involving multi-organ systems with infiltration of the involved organ with activated phagocytic macrophages and lymphocytes with defective cytolytic pathways.[1]

The aetiology of HLH can be primary or secondary.[2] Primary HLH is due to underlying mutations. Secondary HLH is associated with various aetiologies including infections.

The diagnostic criteria of HLH are fever, hepatosplenomegaly, cytopaenia affecting at least two lineages, hyperferritinaemia above 500 mcg/L, decreased Natural Killer cell activity, elevated soluble CD25 level above 2,400 U/ml, fasting triglyceride exceeding 265 mg/dl or fibrinogen below 150 mg/dl, and haemophagocytosis in the bone marrow, spleen or lymph nodes without evidence of malignancy.[2] The diagnosis of HLH needs at least five of the above criteria.

Among infections, viral infections are a common cause of HLH. In our settings, bacterial infections are quite common. Although zoonotic diseases are one of the common causes of secondary HLH, there is a paucity of case reports of leptospirosis-associated HLH.[3–6] Leptospirosis is a common zoonosis caused by spirochetes of the genus Leptospira in tropical and subtropical areas. Transmission from primary sources either rodents, cattle, pigs, or dogs to humans can be either direct or indirect.[7] Direct transmission to humans can occur through direct contact with body fluids or tissues of infected animals. Indirect transmission occurs when humans come in contact with contaminated environments like soil or water.[8] The mode of entrance can be through abraded skin or mucosa or by ingestion of contaminated water.[9] Leptospiral infection can range from mild disease to severe life-threatening multiorgan dysfunction.[10]

We report a case series of four children presenting with secondary HLH with three different infective aetiologies namely leptospirosis, scrub typhus and Salmonella typhi infection.

Cases

Case 1

A 10-year-old male child presented in our emergency ward with the complaint of high-grade fever for 1 week with abdominal pain and vomiting. On examination, the child was found to have tachycardia with wide pulse pressure. He also had pallor with icterus, hepatosplenomegaly, and bilateral decreased air entry in the chest. The child was started on IV antibiotics, IV fluids, and inotropic support. Laboratory investigations (Table 1) revealed bi-cytopaenia (thrombocytopaenia with anaemia), and transaminitis with pre-renal acute kidney injury. Chest X-ray showed bilateral pleural effusion. Ultrasound abdomen revealed hepatomegaly with mild ascites with bilateral pleural effusion. In view of suspected leptospirosis, intravenous doxycycline was added. The shock was improved by day 4 but the child continued to have high-grade fever. Leptospiral IgM ELISA serology was weakly positive but fever was not responding to antibiotics and doxycycline. Blood and urinary cultures sent initially were sterile. Malarial antigens and the Widal test were also negative. Samples for serum ferritin, fibrinogen, triglycerides, D-dimer, and COVID antibody titers were also sent. Bone marrow aspiration and biopsy were planned but parents refused to give consent for same. COVID-neutralising antibody titers were weakly positive. Keeping post-COVID Multisystem inflammatory syndrome (MISC) in children as a differential diagnosis, IV immunoglobulin G (IVIG)was administered. However, the child had little clinical response with continued high-grade fever and increasing C-reactive protein (CRP), Serum ferritin and triglycerides were also elevated, and fibrinogen was low (Table 1). Five out of eight diagnostic criteria for HLH were fulfilled. To find the aetiology of HLH, we sent a repeat leptospiral IgM serology, which was positive this time in comparison to a weakly positive report earlier. By the time we got the repeat leptospiral serology report, methylprednisolone had already been started for suspected MISC and the patient responded on day 7 of steroids, became afebrile and cytopaenia improved. Ascites and pleural effusion also gradually resolved. CRP values started decreasing and became negative on discharge. The child was discharged on day 19 of admission with gradual tapering of steroids and was advised to follow up in our Paediatrics OPD.

Table 1.Laboratory Parameters of Case 1 during the Hospital Stay

Day of Admission	Day 1	Day 3	Day 5	Day 7	Day 9	Day 11	Day 14	Day 17
Haemoglobin (g/dl)	8.1	8.6	8.8	9.3	9.1	10.4	10.6	10.4
Total leucocyte count (/mm^3)	7500	8400	8700	8800	6800	9400	8100	7700
Platelet (/mm^3)	0.3	0.4	0.59	0.85	1.0	1.2 lakh	1.46 lakh	1.69 lakh
B. urea/ creatinine (mg/dl)	115/ 2.0	110/ 1.9	82/ 1.2	36/ 1.1	15/ 1.1	24/ 0.7	22/ 0.6	21/ 0.5
Na/ K (mEq/l)	134/ 3.5	133/ 5.4	133/ 3.6	140/ 3.6	132/ 3.4	138/ 4.5	136/ 3.9	-
S. bilirubin (mEq/l)	6.3	5.2	3.9	-	3.3	-	1.6	0.8
ALT/ AST/ ALP (U/l)	-	249/ 118/ 717	-	-	96/ 185/ 561	-	-	49/ 58/ 320
S. protein (g/dl)	-	5.4	-	-	5.9	-	-	6
Albumin (g/dl)	-	2.9	-	-	3.2	-	-	3.3
Prothrombin time (sec)	-	15.9	-	-	14.7	-	-	-

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PTTK (sec)	-	33.2	-	-	34.5	-	-	-
INR	-	1.18	-	-	1.12	-	-	-
CRP (mg/dl)	24	24	48	48	24	12	6	Negative
Triglycerides (mg/dl)	-	-	297	-	-	-	-	-
Ferritin (mcg/l)	-	-	654	-	-	454	-	397
Fibrinogen (mg/dl)	-	-	140	-	-	-	-	-

ALT: Alanine Transaminase, AST: Aspartate Transaminase, ALP: Alkaline Phosphatase, PTTK: Partial Thromboplastin Time with Kaolin, INR: International Normalised Ratio, CRP: C-reactive Protein

Case 2

Another 5-year-old female presented in our emergency ward with a complaint of high-grade fever, cough, and burning sensation on micturition for 2 weeks. She was passing high-coloured urine and also had a decreased appetite for the last 1 week. On examination, the child was found to have pallor with icterus and hepatomegaly. Laboratory investigations (Table 2) revealed bi-cytopaenia (thrombocytopaenia with anaemia), and an ultrasound of the abdomen revealed hepatomegaly. Cerebrospinal fluid analysis (CSF) was unremarkable. Blood and urinary cultures sent were sterile. Malarial antigens and the Widal test were also negative. IV fluids and antibiotics were started and later in view of suspected leptospirosis, oral doxycycline was added. The child continued to have high-grade fever despite IV antibiotics and oral doxycycline. Thereafter, serum ferritin, fibrinogen, triglycerides, D-dimer, and COVID antibody titers were sent. Bone marrow aspiration and biopsy were also planned. leptospirosis IgM along with scrub typhus IgM were found to be positive. Serum ferritin and triglycerides were also elevated. Five out of eight diagnostic criteria for HLH were fulfilled.

Keeping this in view, IVIG was administered and the child responded clinically. CRP values started decreasing and became negative on discharge. The child was discharged on day 15 of admission and was advised to follow up in the Paediatric OPD.

Table 2.Laboratory Parameters of Case 2 during Hospital Stay

Day of Admission	Day 1	Day 2	Day 3	Day 5	Day 7	Day 8	Day 10
Hb (g/dl)	11.4	12.2	11.4	10.1	10.8	10.5	9.4
TLC (/mm^3)	16600	13200	7500	5000	4700	5500	7000
Platelet (lakhs/mm^3)	2.18	2.24	1.96	1.14	1.01	1.10	1.05
B. urea/ creatinine (mg/dl)	-	18/ 0.6	25/ 0.5	-	-	-	-
Na/ K (mEq/l)	134/ 4.0	139/ 3.4	-	-	138/ 4.7	-	-
S. bilirubin (mg/dl)	0.2	-	0.3	-	0.2	-	-
ALT/ AST/ ALP (U/L)	-	33/ 61	-	-	195/ 212	-	-
S. protein (g/dl)	-	7.2	-	-	5.6	-	-
Albumin (g/dl)	-	4.2	-	-	3.3	-	-
PT (sec)	-	14.1	-	-	15.5	-	-
PTTK (sec)	-	40.1	-	-	43.1	-	-
INR	-	1.18	-	-	1.15	-	-
CRP (mg/dl)	-	-	-	-	-	-	-
Triglycerides (mg/dl)	-	-	-	-	232	417.6	-
Ferritin (mcg/l)	-	-	> 1000	-	-	-	-

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Fibrinogen (mg/dl)	-	-	140	-	-	-	-
Lactate dehydrogenase (U/L)	-	-	-	-	245	55	-
D-dimer (mcg/ml)	-	-	-	-	> 15	-	-
Leptospirosis serology	-	-	-	-	IgM positive	-	-
Scrub typhus serology	-	-	-	-	IgM positive	-	-

Hb: Haemoglobin, TLC: Total Leucocyte Count, ALT: Alanine Transaminase, AST: Aspartate Transaminase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, PTTK: Partial Thromboplastin Time with Kaolin, INR: International Normalised Ratio, CRP: C-reactive Protein

Case 3

A one-year-old girl presented with fever for about 1 month duration along with loose stools (6 days) and decreased oral acceptance of feeds. The child had hepatosplenomegaly and pancytopenia. Her Typhidot (IgM and IgG) was positive (Table 3). Peripheral smear for malaria along with Rapid malarial antigen test (RMAT) was negative. Dengue serology (IgM) and NS1 antigen were negative.

The child was started on IV fluids and ceftriaxone. However, the child did not respond with persistent fever for which her antibiotic coverage was changed to cefoperazone plus sulbactam and amikacin.

However, unlike the usual insidious deterioration of enteric fever, the patient started deteriorating rapidly with worsening cytopaenia and unstable haemodynamic status. Inotropic support (inj. dobutamine) was then added and a packed red blood cell transfusion (PRBC) was also given. Keeping in view the possibility of HLH secondary to Salmonella typhi infection, IVIG was started and was given for 2 days.

The patient responded clinically, and her condition improved. Her fever subsided, haemodynamics stabilised and cytopaenia improved. Ionotropic support was then tapered and stopped. Subsequently, she was discharged from the hospital with advice for follow-up.

Table 3.Laboratory Parameters of Case 3 during Hospital Stay

Day of Admission	Day 1	Day 2	Day 3	Day 4	Day 5
Hb (g/dl)	9.4	7.6	7.4	8.8	-
TLC (/mm^3)	4400	7900	9600	10400	-
Platelet (lakhs/mm^3)	1.24	1.1	1.61	2.18	-
B. urea/ creatinine (mg/dl)	-	13/ 0.5	8/ 0.6	-	-
Na/ K (mEq/l)	134/ 4.5	133/ 4.0	-	-	-
S. bilirubin (mg/dl)	-	-	0.3	-	0.2
ALT/ AST/ ALP (U/L)	-	-	35/ 21/ 226	-	34/ 14/ 258
S. protein (g/dl)	-	-	6.1	-	-
Albumin (g/dl)	-	-	2.7	-	-
PT (sec)	-	15.9	-	-	-
PTTK (sec)	-	33.2	-	-	-
INR	-	1.18	-	-	-
CRP (mg/dl)	-	-	-	-	-
Triglycerides (mg/dl)	-	-	-	-	249

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Ferritin (mcg/L)	737	-	-	-	-
Fibrinogen (mg/dl)	-	-	140	-	-
LDH (U/L)	-	-	811	960	-
Typhidot serology	-	-	-	Positive	-
Blood-c/s	Salmonella typhi +	-	-	-	-

Hb: Haemoglobin, TLC: Total Leucocyte Count, ALT: Alanine Transaminase, AST: Aspartate Transaminase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, PTTK: Partial Thromboplastin Time with Kaolin, INR: International Normalised Ratio, CRP: C-reactive Protein, LDH: Lactate Dehydrogenase

Case 4

A 3-year-old girl presented with fever, vomiting, loose stools, and cough for 4 days. She had a recent history of fever about 1 month back for which she had been investigated with Widal titers positive (> 1:160) and was given inj. ceftriaxone for 10 days. She had become afebrile thereafter. However, the patient fell sick again. This time, the patient had a fever, and hepatosplenomegaly with a rash over the legs. Her investigations revealed bi-cytopaenia. She was started on inj. ceftriaxone but the high-grade fever persisted despite 4 days of antibiotics. Her serum LDH (lactate dehydrogenase) (960 U/L), serum ferritin (737 mcg/l), were raised (Table 4). Repeat serum LDH after 3 days showed further rise. Blood culture and sensitivity revealed Salmonella typhi which was sensitive to ceftriaxone, azithromycin, and ampicillin. Her leptospiral IgM serology was also positive. Oral azithromycin was added and her fever subsided by day 7. Her counts improved i.e., bi-cytopaenia resolved and she was discharged on day 10 uneventfully. She had laboratory and clinical evidence of HLH, however, with the treatment of primary infection, secondary HLH eventually resolved.

Table 4.Laboratory Parameters of Case 4 during Hospital Stay

Day of Admission	Day 1	Day 2	Day 3	Day 4	Day 5
Hb (g/dl)	9.4	7.6	7.4	8.8	-
TLC (/mm^3)	4,400	7,900	9,600	10,400	-
Platelet (lakhs/mm^3)	1.24	1.1	1.61	2.18	-
B. urea/ creatinine (mg/dl)	-	13/ 0.5	8/ 0.6	-	-
Na/ K (mEq/l)	134/ 4.5	133/ 4.0	-	-	-
S. bilirubin (mg/dl)	-	-	0.3	-	0.2
ALT/ AST/ ALP (U/l)	-	-	35/ 21/ 226	-	34/ 14/ 258
S. protein (g/dl)	-	-	6.1	-	-
Albumin (g/dl)	-	-	2.7	-	-
PT (sec)	-	15.9	-	-	-
PTTK (sec)	-	33.2	-	-	-
INR	-	1.18	-	-	-
CRP (mg/dl)	-	-	-	-	-
Triglycerides (mg/dl)	-	-	-	-	249
Ferritin (mcg/l)	737	-	-	-	-
Fibrinogen (mg/dl)	-	-	140	-	-
LDH (U/l)	-	-	811	960	-
Typhidot	-	-	-	Positive	-
Blood culture	Salmonella typhi +	-	-	-	-
Leptospiral IgM serology	-	-	-	-	Positive

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Hb: Haemoglobin, TLC: Total Leucocyte Count, ALT: Alanine Transaminase, AST: Aspartate Transaminase, ALP: Alkaline Phosphatase, PT: Prothrombin Time, PTTK: Partial Thromboplastin Time with Kaolin, INR: International Normalised Ratio, CRP: C-reactive Protein, LDH: Lactate Dehydrogenase

Discussion

Although various viruses have been found to be associated with secondary HLH, especially Epstein-Barr virus (EBV), in the Indian subcontinent, various tropical infections like tuberculosis, malaria, leishmaniasis, and typhoid can act as a trigger for secondary HLH.[11] The production of cytokines by host lymphocytes and monocytes is believed to be an underlying pathophysiology. Our knowledge of the management of this entity has been restricted due to the rarity of disease and the paucity of RCTs for best therapy. However, supportive care and treatment of the inciting infectious trigger are associated with a 60%–70% chance of recovery.[12] The clinical spectrum of leptospirosis ranges from asymptomatic infection in most cases to severe disease with life-threatening multiorgan dysfunction. There are two phases of the disease – the septicaemia phase and the immune phase.[4] In severe cases, the immune phase is characterised by jaundice, renal failure, thrombocytopaenia, etc. Sometimes, this immune phase can have an exaggerated cytokine response progressing to secondary HLH, which if not recognised timely, can be fatal.

There are many causes of secondary HLH with zoonotic diseases being one of the most prominent causes, but there is a paucity of literature regarding the association of leptospirosis with HLH in children. We searched the literature and came across a few studies that demonstrated an association of leptospirosis with secondary HLH in children.

In Thailand, a study was published in 2005 where the aetiology of obscure fever in 25 children was discussed. The study identified the aetiology in 52% of cases. The diseases attributed were dengue (40%), leptospirosis (8%), and micrococcus septicaemia (4%). Here, it was reported that the case with leptospirosis had actually developed an infection associated with secondary HLH.[10]

In 2013, a study published by JIPMER, Pondicherry reported leptospirosis in association with the haemophagocytic syndrome as a rare presentation in a 4-year-old child.[2]

In 2018, the Turkish Journal of Paediatrics published a case report of a 13-year-old girl child with secondary HLH caused by leptospirosis infection and a favourable outcome with antibiotic and corticosteroid therapy.[6]

Our cases presented with high-grade fever spikes with polyserositis, hepatic and renal involvement, and shock. The clinical picture helped us to keep leptospirosis as an aetiology while apparent non-response to standard antibiotic therapy prompted us to do investigations that confirmed HLH. The patient did not respond to IVIG therapy but responded very well to corticosteroid therapy.

Our cases highlight that leptospirosis although a common disease can have a complicated course. Secondary HLH, though rare, should be kept in differential diagnosis when clinical response to antibiotics is inadequate.

A few case reports with typhoid fever (Salmonella typhi) as a cause of secondary HLH have been reported in the literature. Fame et al.[13] from the USA have reported a case of a 13-year-old girl who presented with 2 weeks of fever with hepatosplenomegaly, somnolence, anaemia, and thrombocytopaenia with deranged liver enzymes. She was initially treated with ampicillin for 10 days but had a relapsed course. She responded favourably to 5 days of treatment with cotrimoxazole.

Chien et al. from Taiwan[14] described a 13-year-old boy who had a fever for 7 days, hepatomegaly, psychosis, brain oedema, maculopapular rash, anaemia, and thrombocytopaenia. This patient responded favourably to ceftriaxone in 3 days.

Similarly, Caksen et al.[15] from Turkey reported a 6-year-old boy presenting with fever (10 days), abdominal pain, jaundice, anaemia, leucopaenia, thrombocytopaenia, and deranged liver function tests. The child recovered with chloramphenicol.

A 2018 case report[16] from Colombia described an 8-year-old girl with HLH secondary to Salmonella typhi infection which recovered with antibiotics and IVIG.

Coinfection with different pathogens does exist but Salmonella and leptospiral coinfection are rare and a case of a 30-year-old has been reported with these pathogens which presented as sub-acute intestinal obstruction by Negi et al.[17]

A previous case report describes a mixed infection with Leptospira and Salmonella typhi.[18] However, a cause of secondary HLH has not been reported yet to the best of our knowledge. Developing countries like India face several endemic diseases which has been a daunting task to tackle and eradicate. Lack of sanitation, overcrowding, water contamination, poverty, and poor living conditions further compound this problem. This is especially important because at times leptospirosis and typhoid can be complicated by secondary HLH, which though rare, has potentially fatal outcomes. Also, both infections can coexist making things more complicated. HLH can overlap with other clinical entities, especially malignant disease, and can be very challenging for diagnosis and management.

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Conclusion

This case series study exemplifies the importance of a high degree of suspicion for HLH in cases of persistent fever, organomegaly, and cytopaenias.

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