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Case Report:

Malaria associated Hemophagocytic Lymphohistiocytosis

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ABSTRACT

Malaria associated HLH is well known but under diagnosed. We report an 18 month child with falciparum malaria who after completion of treatment with antimalarials and parasite clearance did not show clinical improvement. She was subsequently diagnosed with HLH and started on dexamethasone, cyclosporine and etoposide. Within a week child showed dramatic improvement.Hence,malaria associated HLH should be suspected and treated promptly.

Keywords :

Malaria, Hemophagocyticlymphohistiocytosis

INTRODUCTION

HemophagocyticLymphohistiocysis (HLH) is a rare disorder.The incidence of familial HLH in children has been reported as 1.2 per million [1] but that of infection associated HLH is still uncertain.Thoughmalaria as a cause of secondary HLH is well known, it has been under-reported. To the best of our knowledge only12 cases of malaria associated HLH have been reported worldwide. [2,3,4,5,9,13,14,15,16,17,18,19] Of this only 5 cases have been documented in children and none of them required specific treatment for HLH.[2,3,4,5,9]In spiteIndia being an endemic country for malaria, HLH still remains under diagnosed.Hencehere we highlight an uncommon aspect "HLH" of a very common disease "malaria" and report a case of 18 month old child with P.falciparum malaria associated HLH who improved only after treatment as per HLH 2004 protocol. [1]

CASE:

18 month old girl presented with high grade fever and vomiting of 5 days duration. She had no medical or surgical illness in the past. On examination she was febrile (temperature-39.5 0C) and irritable. She had pallor,firm palpable liver and spleen of 4cm (span - 10 cm) and 5 cm respectively. There was no significant lymphadenopathy or icterus. On investigations the initial CBC showed pancytopenia (Hb - 7.9 g/dl, TLC- 3400/mm3, ANC-884, platelet - 40000/mm3), peripheral smear revealed trophozoites of Plasmodium falciparum with a parasitic index of 20% and elevated liver enzymes (AST - 240.8 and ALT - 115.8 IU/L).Her renal and metabolic parameters were normal. The child was started on injection artesunate and oral clindamycin. Three days later the peripheral smear was repeated which showed complete clearance of malarial parasite but the child continued to remain febrile and irritable. Hemoglobin further dropped to 5.5 g/dl with persisting leukopenia and thrombocytopenia. Blood culture, urine culture, Chest X-ray, USG abdomen, CT brain and lumbar puncture revealed no other focus of fever. Despite packed cell transfusion, the hemoglobin did not improve. Direct Coombs test, reticulocyte count and repeat peripheral smear were not suggestive of active hemolysis. In view of persisting high grade fever, splenomegaly and pancytopenia even after completion of 7 days IV antimalarials, HLH was suspected and work up sent accordingly revealed : Serum triglyceride- 310.9 mg/dl , ferritin- 3560 mcg/L , LDH- 4000 IU/L, bone marrow aspiration and biopsy showed marked increase in histiocytes

without obvious evidence of hemophagocytosis . The child fulfilled 5 of 8 HLH 2004 criteria viz. fever, splenomegaly, pancytopenia, hyperferritinemia and hypertriglyceridemia. She remained symptomatic even 5 days after completion of antimalarial treatment and ongoing supportive care, hence was started on treatment as per HLH 2004 protocol. On 3rd day of treatment fever subsided, child improved dramatically and lab parameters which were repeated on day 7 revealed significant improvements. She was discharged in the 2nd week of treatment on oral steroids and cyclosporine. Unfortunately, she presented to the casualty 3 days later with foreign body aspiration and succumbed in spite of all resuscitative efforts.

TABLE I

INVESTIGATION	DAY 1	DAY 3	DAY 5	DAY 8	DAY 18**
Haemoglobin (gm/dl)	7.9	7.2	5.5	5.7	9.2
TLC (per mm3)	3400	3800	6400	7200	9800
ANC	884	760	640	1080	6270
Platelet (per mm3)	40000	71000	87000	98000	1.58
Peripheral Smear	Ring and trophozoites of P.falciparum	-	No malarial parasites.No features of active hemolysis		
ESR (mm/hr)	25				
Blood Culture	Sterile			Sterile	
Serum Bilirubin (mg/dl)		4.59 (D - 3.2)	2.42 (D - 1.9)		
AST (IU/L)		175	95		64
ALT (IU/L)		115	60		42
CSF			Protein-10.2 Sugar- 42 Cells - 3 (lymphocytes)		
USG Abdomen	Hepatosplen omegaly				
CT Brain			Normal study		
Direct Coomb's Test			Negative		
Serum Triglyceride (mg/dl)				310.9	194
LDH (IU/L)				4900	
Serum Ferritin (mcg/L)				3560	480
Bone Marrow Biopsy				Marked increase in histiocytosis with erythroid hyperplasia, no hemophagocytosis	
Typhi Dot M	Negative				
Paul Bunnel			Negative		
Weil Felix			Negative		

**** HLH 2004 treatment protocol started on day 11 of admission**

DISCUSSION:

Infection associated HLH in children is a rare entity.The largestpaediatric case series of 122 patients studied over 6 yearsacross 11 countries reported by the International Registry for HLH, Histiocyte Society, showed only 40% of HLH in children being associated with infections.[20]There is paucity of data about HLH from India.Largest Indian case series of 43 patients studied over 2 years showed Infectious etiologyin 14 (42%) children, with viruses accounting for the majority.[12]

Similar observations have been made in other case series across the world in Thailand(52 cases)[10], Vietnam(33 cases)[6], Iran(7 cases)[8],Taiwan(18 cases)[11],India(7 cases).[7]None of these case series have reported malaria accounting for HLH.

Till date to the best of our knowledge only 5isolated cases of Malaria associated secondary HLH in children have been reported worldwide,[2,3,4,5,9]of which only two have been from India, in spiteof being an endemic country.[5,9]

TABLE II
Malaria associated with HLH cases reported in children till date:

Cases SL.No./year	Age(mo= months,yrs)	Fever	Splenome	Cytopenia	Triglyceridemia/ hypofibrinogenemia	Hemopha	Hyperferri	Mutationa	NK cell activity	Soluble	Peripheral	Treatment	Outcome
Index case 2013)	18mo/F	+	+	+	+/+	–	+	Not done	Not done	Not done	PF*	Antimalarials +HLH-2004	Improved
1.[5] (2011)	11mo/M	+	+	+	+/+	+	+	Not done	Not done	Not done	PF*	Antimalarials	Improved
2.[9] (2011)	12yrs/F	+	+	+	+/+	_	+	Not done	Not done	Not done	PF*	Antimalarials	Improved
3.[3] (2004)	3yrs/M	+	+	+	+/+	+	+	Not done	Not done	Not done	PF*	Antimalarials	Improved
4.[4] (2002)	11yrs/F	+	+	+	+/+	+	+	Not done	Normal	Not done	PV# & PF*	Antimalarials	Improved
5.[2] (2000)	2yrs/M	+	+	+	+/+	_	+	Not done	Not done	Not done	PF*	Antimalarials + Steroids	Improved

***Pf- Plasmodium falciparum #Pv-Plasmodium vivax**

Our case fulfilled criteria of fever, splenomegaly, pancytopenia, hyperferritinemia and hypertriglyceridemia (5 out of 8) in accordance with the current HLH guidelines [1] but bone marrow aspiration and biopsy showed only presence of histiocytes without hemophagocytosis. Due to financial and resource constraints we could not demonstrate hemophagocytosis in liver or lymph nodes.Amongst reported cases 3 of them had obvious evidence of hemophagocytosis in bone marrow [3,4,5] and only two were labelled as HLH in absence of it.[2,9] In Aericoet al'ssurvey nearly 20 percent of cases required more

than one bone marrow specimen to demonstrate hemophagocytosis.[8] Hence we emphasize that HLH can be diagnosed if theother criteria are met even if there is no evidence of hemophagocytosis.

In spite of treatment with antimalarials(7 day course of inj. Artesunate and oral clindamycin)and repeat peripheral smear showing clearance of parasite, she continued to remain febrile with persistence of splenomegaly and bicytopenia. Unlike the other 4reported cases which responded to antimalarials and supportive care[3,4,5,9] and only1patient requiringsteroids[2],our case improved dramaticallyafter 3 days of receiving etoposide, cyclosporine and dexamethasone as per the HLH 2004 protocol. This is the first paediatric case of P.falciparum malaria with HLH to be put on HLH 2004 protocol based treatment that did not show clinical improvement with antimalarials and supportive care. Hence we highlight the need of treatment for secondary HLH with full protocol if not improving with specific and supportive treatment. Unfortunately we could not complete the planned protocol for the child because of her accidental death due to foreign body aspiration.

CONCLUSION: HLH which is a fatal but treatable condition should be suspected as a complication of malaria in patients who do not show clinical improvement even after parasitic clearance. Histopathological evidence of hemphagocytosis need not be chased for labelling and treating the diagnosis of HLH if the other criteria are met. Whenever required steroid, etoposide and cyclosoprine should be incorporated for treating secondary HLH due to malaria not responding to specific and supportive treatment.

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