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Case Report

Intravenous Immunoglobulin Responsive Secondary Hemophagocytic Lymphohistiocytosis Following Incomplete Infantile Kawasaki Disease

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Abstract

An eleven-month-old boy presented with fever, maculopapular erythematous rash, non-purulent bulbar conjunctivitis and progressive hepatosplenomegaly. There was progressive fall of hemoglobin and platelet count. Echocardiography revealed coronary aneurysms thereby confirming Kawasaki disease. Child had biochemical and histopathological evidence of hemophagocytic lymphohistiocytosis (HLH). He became afebrile 36 hours after intravenous immunoglobulin (IVIG) transfusion. Secondary HLH resolved with treatment of the primary disease. Resolution of coronary aneurysms occurred 6 months after treatment with aspirin and clopidogrel.

Keywords: *Secondary Hemophagocytic Lymphohistiocytosis; Incomplete Kawasaki Disease; Intravenous Immunoglobulin; HLH 2009 Criteria*

Introduction

Kawasaki disease (KD) is an acute febrile illness of unknown aetiology, having mean age of onset of 3 years, and characterized by vasculitis with predilection for the coronaries. In addition to persistent fever for 5 days, the 5 principal clinical criteria of KD are bilateral non-purulent bulbar conjunctival injection, extremity changes (erythema of palms and soles and edema of hands and feet in acute phase, periungual desquamation of fingers and toes in subacute phase), >1.5 cm cervical lymphadenopathy (usually unilateral), lip and oral cavity changes (pharyngeal and oral mucosal injection, lip cracking, strawberry tongue) and polymorphous exanthem. Classical KD patients have ≥ 4 principal criteria. Incomplete KD patients have < 4 principal criteria [1]. Histiocyte syndromes of childhood result from a prominent proliferation of cells of monocyte-macrophage lineage of bone marrow origin [2]. Class II histiocytosis comprises of 2 variants:

1. Familial hemophagocytic lymphohistiocytosis (FHLH)-5 subtypes of autosomal recessive inherited form of histiocytosis are each associated with a specific gene [3]:
    - FHL1:HPLH1
    - FHL2: PRF1 (Perforin)
    - FHL3: UNC13D (Munc 13-4)

- FHL4: STX11 (syntaxin 11)
- FHL5: STXBP2 (syntaxin binding protein 2)/UNC18-2.

2. Infection associated hemophagocytic syndrome occurring secondary to viral, bacterial, protozoal, mycobacterial and fungal infections [2].

Autoimmune associated hemophagocytic syndrome (AAHS)/macrophage activation syndrome (MAS) may occur following rheumatologic disorders like systemic juvenile idiopathic arthritis, adult onset Still's disease, Kawasaki disease, rheumatoid arthritis, polymyositis, dermatomyositis, systemic sclerosis, systemic lupus erythematosus [4]. Unfortunately acute KD shares many clinical and biochemical findings including fever, rash and raised liver enzymes with HLH/MAS, hence it is difficult to distinguish between the two processes. 1.9% of children with acute Kawasaki disease develop overt MAS. Kawasaki disease complicated with MAS is also labelled as Kawasaki shock syndrome [5]. Pathophysiology seems to be the inability of natural killer cells and cytotoxic T lymphocytes to remove the source of antigenic stimulation leading to persistent antigen driven activation and proliferation of T cells associated with persistent production of cytokines which further stimulate macrophages [6].

Case Report

An 11-month-old boy was admitted with high- grade continuous fever for 3 days. He had developed generalized maculopapular erythematous blanching rash on 2nd day of fever sparing the palms and soles (Figure 1) and bilateral non-purulent bulbar conjunctivitis developed on the 3rd day of fever. He had firm, non-tender hepatomegaly with sharp margin, smooth surface and span of 8 centimetres. Firm, non- tender spleen was palpable 1 cm below the left costal margin. There was no free-fluid in the abdomen. Cardiovascular, respiratory and neurological systems were normal on examination. Hemogram and liver function test (LFT) on day of admission are given in tables 1 and 2 below. C-reactive protein (CRP)- 96 mg/l (reference value- < 6 mg/l). Dengue-NS1 and blood smear examination and dual antigen test for malarial parasites were negative. Microscopic examination of urine revealed 6 - 8 pus cells/cubic mm. Chest radiograph was normal. Blood and urine cultures were sterile. Renal function test was normal. Echocardiogram was normal except for a thin-film of pericardial effusion. We treated the child with maintenance fluids, paracetamol as antipyretic and started injection ceftriaxone empirically. The child remained toxic with continuous high- grade fever and progressive increase in liver span to 10 cm and spleen to 4 cm and appearance of icterus and few petechial spots on the 6th day of fever. Hemogram and LFT worsened (shown in tables 1 and 2). The child was given 15 ml/kg of packed erythrocyte transfusion and 1 unit of platelet transfusion. Widal test, chikungunya IgM, dengue IgM, Epstein-Barr viral capsid antigen (VCA) IgM, human parvovirus B 19 and adenovirus serology, real-time polymerase chain reaction for coxsackie A and B viruses, rapid antigen detection tests for circulating influenza virus strains (H1N1 and H3N2) and respiratory syncytial virus and TORCH titres were negative and CRP-120 mg/l on the 7th day of fever. On the 7th day of fever he developed shock with low pulse volume, capillary refill time of 4 seconds, cold clammy extremities and thus we started dobutamine infusion @10 µg/kg/min as an inotrope. Arterial blood gas revealed pH- 7.0, pO_2- 80.0 mm Hg, pCO2-35.0 mm Hg, base deficit-12.0 meq/l, HCO3-14.0 meq/l, sodium 115.0 meq/l, potassium-3.6 meq/l. An emergent repeat echocardiogram revealed left anterior descending artery (LAD) and right coronary artery (RCA) aneurysm of 5 mm and 6 mm respectively. There was mitral regurgitation, mild pericardial effusion and left ventricular systolic dysfunction with ejection fraction 45%. Hence, we confirmed the diagnosis of incomplete Kawasaki disease since the child had < 4 principal clinical criteria. Since the child had thrombocytopenia instead of usual thrombocytosis seen in Kawasaki disease, along with elevated liver enzymes, we decided to investigate for secondary HLH. Serum ferritin was 600 ng/ml, triglyceride-300 mg/dl, fibrinogen-120 mg/dl and bone marrow aspirate revealed hemophagocytosis by macrophages (Figure 2). Hence, it was a case of hemophagocytic lymphohistiocytosis secondary to Kawasaki disease. We confirmed the cytokine profile of the child with ELISA method before and after IVIG transfusion (Table 3).

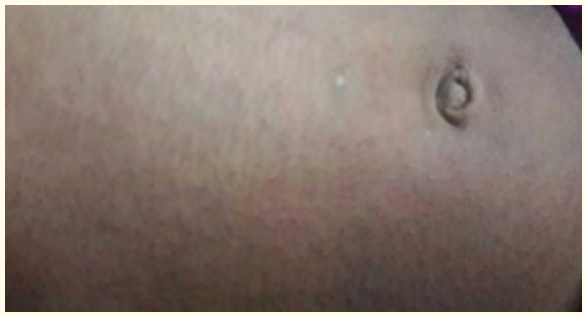

Figure 1: *The picture shows the maculopapular erythematous blanching rash that appeared on the 2nd day of fever.*

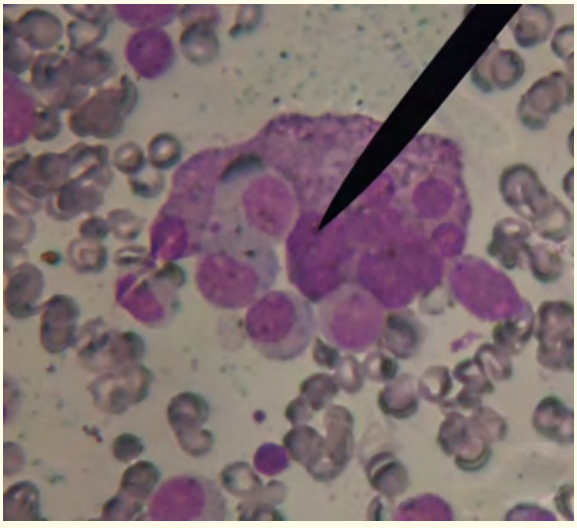

Figure 2: *The bone marrow aspirate shows a hemophagocytic macrophage (marked by the pointer).*

2 gm/kg IVIG was given on the day 7 of fever. The child became afebrile 36 hours after IVIG transfusion. Hemogram and LFT showed sequential improvement (Tables 1 and 2). On day 10, CRP < 6 mg/litre. Progressive reduction of liver and spleen size occurred and were completely regressed by day 12. Aspirin (@80 mg/kg) was started from day 11, when the platelet count had normalized. High dose aspirin was given for 4 days after which inflammatory markers (ESR, CRP) normalized. Thereafter, aspirin was continued @5 mg/kg/day. 1 week after IVIG transfusion echocardiogram revealed resolution of LAD aneurysm, mitral regurgitation, pericardial effusion and LVEF was 60%. However, a 4 mm aneurysm of RCA persisted. 6 weeks later echocardiogram revealed a 4 mm RCA aneurysm. We started 1 mg/kg clopidogrel tablet. Serial monthly echocardiogram revealed sequential reduction of aneurysm size, 3 mm at the end of 4 months and completely resolved at the end of 6 months. The child achieved age appropriate growth and developmental milestones on 1 year follow- up.

Items	Reference values	Day 3 of fever	Day 6	Day 9	Day 11	Day 15
Hemoglobin concentrations (g/dl)	11.0-14.0	8.0	5.0	8.0	9.0	9.1
Total leucocyte counts (/µl)	4,000-11,000	7,000	5,000	7,600	8,100	10,000
Differential leucocyte percentage (%)		N-45, L-50, M-2, E-3, B-O	N-30, L-62, M-6, E-2, B-O	N-40, L-56, M-3, E-1, B-O	N-42, L- 54, M-3, E-1, B-O	N-45, L-51, M-2, E-2, B-O
Platelet counts ($\times 10^9$/l)	(150 - 450) $\times 10^9$	150×10^9	30×10^9	90×10^9	150×10^9	170×10^9
Erythrocyte sedimentation rate (mm/h)	<30	110	130	100	50	15

Table 1: *Showing sequential hemograms.*

[N: Neutrophil; L: Lymphocyte; M: Monocyte; E: Eosinophil; B: Basophil].

Items	Reference values	Day 3 of fever	Day 6	Day 9	Day 11	Day 15
Direct/Indirect (mg/dl)	0.1-0.2/0.2-0.6	0.6/0.4	2.5/0.9	1.9/0.6	1.2/0.5	0.8/0.5
ALT (IU/L)	10-35	100	200	150	90	40
AST (IU/L)	10-35	120	350	200	110	45
Albumin (g/dl)	3.5-5.5	3.0	2.0	2.8	2.9	3.5
Globulin (g/dl)	2.2-3.4	3.5	4.2	4.0	3.9	3.6
PT/APTT (sec)	PT- 11.5, APTT- 22.6-35		16.8/39		12.5/34	

Table 2: *Showing sequential LFT.*

[ALT: Alanine Transaminase; AST: Aspartate Transaminase; PT: Prothrombin Time; APTT: Activate Partial Thromboplastin Time].

Items	Laboratory reference values	Pre- IVIG	Post- IVIG
IL-6	0.31 - 5 pg/ml	18.2	11.1
IL-10	1.2 - 7.8 pg/ml	9.5	7
TNF-α	5 - 27.2 pg/ml	20.1	6.6
IFN-γ	< 2.2 IU/ml	3.5	1.6

Table 3: *Showing pre and post IVIG cytokine profile.*

[IL: Interleukin; TNF: Tumour Necrosis Factor; IFN: Interferon].

Discussion

In the past 5 years (2011-2015), there were 4 case series and 6 case reports of KD complicated with HLH/MAS (Table 4).

Serial no.	Author	Year	No. of patients	Age	Sex	Treatment	Outcome
1	Servel., *et al*. [7]	2012	1	14 yrs	M	IVIG, steroid, infliximab	Recovered
2	Nasir., *et al*. [8]	2012	3	3wks 2wks 2wks	F F M	IVIG, aspirin	Recovered
3	Kang., *et al*. [5]	2013	12	6.5 yrs (median age)	8M, 4F	10 patients required chemotherapy under HLH protocol, 2 patients given only IVIG	9 recovered, 2 died, 1 lost to follow up.
4	Mukherjee., *et al*. [6]	2014	1	4 yrs	M	IVIG, pulse methyl prednisolone and tapering oral prednisolone	Recovered
5	Shafferman., *et al*. [9]	2014	1	11 wks	F	IVIG, methyl prednisolone, aspirin, anakinra (9 mg/kg/day), infliximab	Recovered
6	Ogawa., *et al*. [10]	2015	1	9 yrs	F	IVIG, flurbiprofen	Recovered
7	Bose., *et al*. [11]	2015	1	5.5 yrs	F	IVIG, dexamethasone	Recovered
8	Forti., *et al*. [12]	2015	1	4 yrs	M	IVIG, dexamethasone	Recovered
9	Jun., *et al*. [13]	2015	2	3 yrs 11 months	M M	IVIG, HLH protocol	Recovered
10	Wang., *et al*. [14]	2015	11	81.3 ± 4.4 months (median age)	All males	7 patients got chemotherapy under HLH protocol, 4 patients given only IVIG.	10 recovered, 1 died.

Table 4

[M: Male; F: Female].

The most important distinguishing factor between recurrent KD and KD complicated by MAS is the time course of signs and symptoms. The onset of MAS following KD occurs after 13.3 days (range 3 - 22 days). However, recurrent KD typically occurred later at a mean of 17.9 months (range 1 - 60 months) [5]. In majority of the published cases, secondary HLH manifested itself late after a prolonged and recurrent course of KD [15]. Kang., *et al*. [5] described that a diagnosis of HLH should be considered when symptoms like recurrent KD develop within 1 month of the 1st episode of KD. However, Mukherjee., *et al.* [6] and Latino., *et al*. [16] reported the occurrence of MAS during acute phase of KD. Ogawa., *et al*. [10] even reported HLH prior to the diagnosis of KD. In our case the features of HLH like hepatosplenomegaly, cytopenias and deranged liver function were evident early in the course of the disease but the diagnosis of KD was delayed because the child had only 2 of the principal clinical criteria and the first echocardiogram did not show pathognomonic findings. Chen., *et al*. [17] described such a unique feature of HLH at the initiation of KD in an18-months-old child, who died.

Kim., *et al*. [18] compared 2 groups of patients: Group 1(HLH patients following KD), Group2 (HLH following other diseases). Patients in group 1 was older than the average age of most KD patients, had a lower survival rate ($p = 0.001$), higher AST ($p = 0.031$) and ferritin ($p = 0.005$) and frequent hyponatremia ($p = 0.000$) when compared to group 2 patients. Although our patient had high AST, ferritin and grossly low sodium level, he was only 11 months of age. KD complicated with HLH in infancy was reported by Shafferman., *et al*. [5], Nasir., *et al*. [8], Jun., *et al*. [13] (Table 4) and also by Titze., *et al*. [15] in a 7-week-old baby (Table 4).

HLH 2009 criteria have low sensitivity and specificity for the diagnosis of MAS complicating KD; since in the series of Wang., *et al*. 8 patients fulfilled Ravelli's criteria and only 3 fulfilled 2009 HLH criteria [14]. Our case met the 2009 HLH criteria since the patient had fever > 38.50 centigrade lasting >7 days, splenomegaly > 3 cm, bicytopenias (haemoglobin < 9 gm%, platelet count < 1,00,000/mm3), hyperferritinemia ≥ 500 ng/ml, presence of hemophagocytosis in bone marrow without evidence of marrow hyperplasia or malignant neoplasm, and other results supportive of HLH diagnosis-hypertriglyceridemia > 265 mg/dl, hypofibrinogenemia < 150 mg/dl, and hyponatremia.

Cytokine storm is characteristic of HLH. Serum IL-6 concentrations are significantly elevated in KD patients with HLH [19]. Pre IVIG level of IL-10 > 8 pg/ml, and post IVIG levels of IL-6 > 10 pg/ml and IL-10 > 6 pg/ml are associated with coronary artery lesions [20]. Similar findings were found in our case.

The Histiocyte Society has established the HLH-2004 protocol as standard immunosuppressive therapy consisting of steroids, cyclosporin A, etoposide and intrathecal methotrexate in certain cases of cerebrospinal involvement [15]. In majority of the published reports, patients presented with fever refractory to IVIG therapy when complicated with HLH. In the case series of Latino., *et al.* [16], out of 638 KD patients between January 2001 and March 2008, 12 had developed MAS. 11 patients needed treatment beyond the standard KD protocol, but 1 patient responded to IVIG alone. All the patients eventually recovered with no long-term sequelae. Al-Eid., *et al.* [21] used steroid, etoposide and granulocyte colony stimulating factor (G-CSF) in a 6-year-old boy. Treatment beyond the initial IVIG transfusion was also described by Kang., *et al.* [5], Mukherjee., *et al.* [6], Shafferman., *et al.* [9], Bose., *et al.* [11], Forti., *et al.* [12] and Jun., *et al.* [13] (Table 4). Early use of anakinra in conjunction with standard immunosuppression is very effective in pediatric rheumatic disease-related MAS [9,22]. The most remarkable feature of our patient was the dramatic response to IVIG. Fever did not recur beyond 36 hours, organomegaly rapidly regressed and blood counts improved after IVIG therapy. Inone., *et al.* [23] described a 13 month old child with forme-fruste HLH who responded to IVIG. Western blot and flow cytometry demonstrated that high dose IVIG inhibits TNF α induced activation of nuclear-factor kappa β and blocks FcgammaRIII on the membranes of monocytes/macrophages, which can play an important role in patients of autoimmune diseases [24,25]. Moreover, treating the primary disease often resolute the secondary hemophagocytic syndrome [2]. The frontline management of AAHS usually involves corticosteroids with/without IVIG [26]. However, Hui., *et al.* [27] have described the use of IVIG alone in milder grades of HLH. There are very few published case reports about children with HLH responding to IVIG [27].

Thus, this case report emphasizes that MAS/HLH is an often under recognized complication of KD and the understanding of the clinical features, diagnostic criteria and treatment is still in progress.

Conflict of Interest

None.

Funding

None.

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