Hepatitis A Virus Infection-Associated Hemophagocytic Lymphohistiocytosis in Two Children

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by high fever, maculopapular rash, neurological symptoms, abnormal liver functions and coagulopathy. Primary HLH is due to an underlying genetic abnormality. Secondary HLH are due to an underlying infection, autoimmune disease or malignancy. Secondary HLH due to viral infections are commonly due to the herpes group commonest of which is the Epstein Barr virus (EBV). We describe two children with virus associated hemophagocytic lymphohistiocytosis (VAHLH) secondary to hepatitis A infection.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome characterized by high fever, maculopapular rash, neurological symptoms, abnormal liver functions and coagulopathy. It is caused by uncontrolled activation of cytotoxic T cells and antigen presenting cells [1]. Secondary HLH are due to an underlying infection, autoimmune disease or malignancy and primary HLH is due to an underlying genetic abnormality. Secondary HLH due to viral infections are commonly due to the herpes group commonest of which is the Epstein Barr virus (EBV) [2]. We describe two children with HLH secondary to hepatitis A infection.

Case 1

A 3 years 6 months old boy was brought with fever and passing dark yellow color urine for 4 days. He had an episode of generalized tonic-clonic seizures on the first day of fever. There was no history of altered sleep pattern or bleeding manifestations. On examination he was febrile, icteric, irritable and pale. Liver was palpable 5 cm below the right costal margin and spleen was palpable 3 cm below the left costal margin. No family history of familial HLH. Investigations revealed hemoglobin of 10.0 gm %, white blood cell count of 3,500 cu.mm with differential count of neutrophils 18 % lymphocytes 75 % and monocytes 7 %. His platelet count was 79,000 cu.mm. Liver function tests were suggestive of cholestatic jaundice with raised liver enzymes (Table 1). Serology for hepatitis B virus (HBV) surface antigen—HbsAg was negative. Blood culture was sterile. ELISA test was positive for anti-hepatitis A virus immunoglobulin M (anti-HAV IgM). The sensitivity of detection of anti-HAV IgM antibodies for the diagnosis of hepatitis A is approximately 99–100 % with a positive predictive value of 88 %. False-positive test results may be due to presence of cross-reactive antibodies from other viral infections or underlying illnesses like rheumatoid arthritis. Positive results should therefore be correlated with the patient's clinical history and exposure.

In view of pancytopenia, HLH workup was done. His serum triglycerides level was 400 mg %, fibrinogen 90.3 mg/dl, ferritin was 5,914. Bone marrows aspirate and trephine biopsy showed hypercellular marrow with trilineage hematopoiesis and with marked increase in reticulo-endothelial activity and macrophages displaying hemophagocytosis. He was started on treatment with oral dexamethasone and cyclosporine as per HLH 2004 protocol.

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Table 1 Clinical and laboratory features of two children with Hepatitis A induced HLH

Features (Normal values)	Patient 1		Patient 2	
	Presentation	At last follow up	Presentation	At last follow up
Fever	+	–	+	–
Hepatosplenomegaly	+	–	+	–
Haemoglobin(g/dl)	10.0	10.2	6.6	14.3
Total white cell count (5,000 to 11,000/CUMM)	3,500	7,300	20,300	12,200
Differential count	N18 %, L75 %, M7 %	N18 %, L75 %, M7 %	N 82 %, L12 % M6 %	N57 %,L34 % M9 %
Platelet count(150,000 to 400,000/CUMM)	79,000	288,000	210,000	325,000
Prothrombin time (10–12.5 s)/INR	16.2/1.49	11/1.1	14.8/1.35	11.2/1.0
aPTT(25–34.8 s)	48.2	32	26.0	26.0
Total Bilirubin (0.1–1 mg/dl)	4.4	0.5	25.6	0.4
Direct Bilirubin	3.8	0.1	21.2	0.2
Total protein (6.0–8.5 g %)	6.0	7.5	6.5	7.7
Albumin (3.5–5.0 g %)	3.3	4.6	2.4	4.7
SGOT (8–40U/L)	1,528	28	578	50
SGPT (5–35U/L)	656	24	439	44
Alkaline phosphatase (100–320 U/L)	272	124	273	255
Triglycerides (<150 mg %)	400	73	452	112
Ferritin (10–140 ng/ml)	5,914	6.2	30,898	90.5
Fibrinogen (160400 mg/dl)–	90.3	245.3	206	274
Bone marrow hemophagocytosis	+		Not done	

His fever settled and counts increased with decrease in ferritin and triglycerides. He was afebrile and stable at discharge. At follow up at 6 months, he was doing well with no fever and hepatosplenomegaly.

Case 2

9 year old girl presented with fever for 2 months associated with jaundice for the last one month. She was diagnosed to have systemic onset juvenile idiopathic arthritis (SoJIA) 5 years back and treated with naproxen and methotrexate. She was on Tab. Methotrexate 7.5 mg once a week at the time of presentation. No bleeding or encephalopathy symptoms. On examination she was febrile, No rash or lymphadenopathy were noted. Her liver was palpable 5 cm below the right costal margin and spleen was palpable 1 cm below the left costal margin. Other systems were normal. No family history of familial HLH. Investigations revealed

hemoglobin of 6.6gm/dl with total white cell count of 20,300 cu.mm, platelet count 2,10,000 cu.mm. Liver functions test was suggestive of cholestatic jaundice with raised liver enzymes (Table 1). ELISA test was positive for HAV IgM (Hepatitis A virus immunoglobulin M). Serology for HBV—HBsAg was negative. Blood culture was sterile. In view of underlying SoJIA and jaundice, secondary HLH was considered and further workup for HLH was done. Her triglycerides were 537 mg %, fibrinogen 200 mg/dl and ferritin 30,898. Bone marrow aspiration was not done due to coagulopathy and clear evidence of HLH. In children with systemic JIA, decrease in total count, platelet count and hemoglobin should raise the suspicion of infection or macrophage activation syndrome and further work up to be done accordingly. She was started on Inj. Dexamethasone and T. cyclosporine as per HLH 2004 protocol. Her fever and jaundice settled. She was afebrile and well at discharge with tapering doses of dexamethasone and cyclosporine. At follow up at 6 months, she is doing well and her SoJIA is under control.

Discussion

Hemophagocytic lymphohistiocytosis is a potentially fatal condition. It is caused secondary to dysfunction of cytotoxic T cells and NK cells which causes uncontrolled immune damage. This leads to cellular damage, multiorgan failure along with activation of benign macrophages and hemophagocytosis in the reticuloendothelial system. Clinically this leads to pancytopenia, hepatosplenomegaly and lymphadenopathy [3].

Diagnosis of hemophagocytic syndrome is based on clinical, laboratory and histopathological findings. There are guidelines to diagnose primary HLH which are proposed by the Histiocyte society in 1991 [4]. This was later updated in 2004 [5]. It is imperative to start treatment early as it is lifesaving, especially because some of the clinical criteria occur later during the disease. The clinical features that are most prominent are fever and splenomegaly. Other findings like jaundice, lymphadenopathy, and rash are also common. Cytopenia is almost always associated with histiocytosis. Marked liver dysfunction and elevated ferritin levels are characteristic [6]. Increased plasma concentration of alpha chain of interleukin-2 receptor (sCD25) and impaired NK-cell activity are diagnostic [7]. Histopathologic findings are hemophagocytosis which can be seen in any organ specifically in the bone marrow.

Hemophagocytic lymphohistiocytosis is fatal if left untreated. As HLH is an uncommon disease there are no randomized control trials in the treatment of HLH. Chemotherapy using dexamethasone, cyclosporine and etoposide were proposed by the Histiocyte society in 1994 [8]. Intravenous immunoglobulin if used early has chances of success [9] however its role is clearly not understood.

Viral hepatitis A is a self limiting disease in childhood. The hematological complications that are recognized are aplastic anemia, post infectious thrombocytopenic purpura and virus associated hemophagocytic lymphohistiocytosis (VAHLH) [10]. EBV is the most common agent causing VAHLH(2). Other common viruses that are associated with VAHLH are cytomegalovirus, human herpes virus 6 (HHV-6) and HHV-8 [11]. Although the hepatitis A virus is a rare cause for VAHLH, it is the more commonly associated with the same than the other hepatitis virus. [12, 13].

Both our patients had jaundice and had fever which did not respond to conventional treatment. Both of them satisfied five of the eight criteria proposed by the HLH-2004 guidelines. Both of them responded to treatment with dexamethasone and cyclosporine. Although there is significant number of case reports of hepatitis A induced HLH in adults there are only two such reports in the pediatric population [14, 15]. Russo et al. [14] described two pediatric patients who were known cases of systemic juvenile

idiopathic arthritis with hepatitis A induced macrophage activation syndrome, similar to our second patient. Bay et al. [15] reported two cases with HLH secondary to hepatitis A infection. Both their patients were treated with intravenous immunoglobulin. Both patients attained initial remission and were well during follow up. Both children were treated according to the HLH-2004 protocol. Both children attained initial remission. However one patient reportedly had recurrent cytopenia following the initial remission [10, 14].

In the light of the two patients and the previous publications it is concluded that the possibility of hepatitis A infection is to be considered if the child has evidence of hemophagocytic syndrome associated with jaundice. The treatment of the condition is to be started early as most of the findings are not present early in the course of the illness.

Conflict of interest None.

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