Reactive Hemophagocytic Lymphohistiocytosis After Hepatitis A Infection

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a clinical condition which result in cytotoxic Tcell and antigen presenting cell overproduction and also their cytokines. Hepatitis A Virus associated HLH is very rare condition among other viruses. This condition is often difficult to diagnose, so treatment is often delayed. Here we present a case of adolescent boy with secondary virus associated HLH diagnosis with Hepatitis A infection and successfull treatment by short course of intravenous immunoglobulin and steroid.

Keywords Hepatitis A virus · Hemophagocytic lymphohistiocytosis · Children

Indroduction

Hemophagocytic lymphohistiocytosis is a disease composed of two different conditions that may be difficult to distinguish from one another: a primary and a secondary form and mostly it has major diagnostic and therapeutic difficulties [1]. Primary HLH, also known as familial hemophagocytic lymphohistiocytosis (FHL) is a heterogeneous autosomal recessive disorder found to be more prevalent with parental consanguinity. FHL is a fatal disorder that has four types (FHL1, 2, 3, 4) due to mutations in certain genes and FHL2 (20–50 % of FHL cases), which is particularly common in Turkey, consists of mutations in the perforin gene in which resultant imperfect perforin production [2].

FHL onset is typically during infancy or early childhood and if untreated FHL median survival is less than 2 months after diagnosis [1]. FHL may be triggered by viral, bacterial or fungal infections. Secondary HLH may be seen by immunological activation of the immune system and it has been described in immunocompromised patients as well as immunocompetent ones after viral infections, malignancies and rheumatological diseases [3].

In this paper, we report a rare pediatric case of hemophagocytosis associated with Hepatitis A infection.

Case

Ten years old boy was brought to pediatric emergency clinic for his complaints as nausea, vomiting, fever, fatigue and jaundice. At physical examination scleral icterus was prominent without other physical finding. His laboratory evaluations revealed elevated liver transaminases above 1,000 IU/L and total bilirubin 1.3 mg/dL. The Laboratory findings of the patient is given in Table 1. He was hospitalized and by serologic investigations diagnosis of acute Hepatitis A infection was made.

At the third day of his follow up, fever, pancytopenia and hepatosplenomegaly were detected and no fever focus was found. Because of refractory fever and ongoing liver and splenic enlargement (~3 cm below the costal margin in both) bone marrow examination was planned. Its evaluation revealed hemophagocytosis without any other hematological malignancy (Fig. 1). Because 3 days intravenous immunoglobulin treatment for 1 g/kg/day have not resulted in clinical improvement, 10 mg/m²/day dexamethasone treatment was given to patient for a week. All the physical and laboratory findings were regressed beside fever. The patient was discharged at the 12th day of

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Table 1 Laboratory parameters of the patient while his follow up

	1 day	3 day	10 day	14 day	1 month	2 month
Hemoglobin (g/dl)	6.6	7.4	10.9	12.5	12	11.2
Leukocyte (1/mm ³)	2,200	2,400	5,000	4,300	4,055	5,450
Platelet (×10 ⁴ /mm ³)	10.9	13.8	22.8	30.1	25.3	30.4
ALT (IU/L)	140	200	82	49	275	67
AST(IU/l)	326	498	81	42	244	58
Total bilirubin (mg/dl)	0.1	1.3	0.4	0.3	0.7	0.7
LDH(IU/L)	1,423		1131	466	709	416
Ferritin (ng/ml)	4,190		2,000	2,000	672	430
Triglyceride (mg/dl)	343			425	109	126

Fig. 1 Haemophagocytosis in the bone marrow smear of the patient hospitalization. The patient is followed up for 9 months after hospitalization without any disease sign or other complications.

Discussion

Hemophagocytic Lymphocytosis is a clinical syndrome seen as a result in macrophage and T cell activation with

overproduction of their cytokines. It can be familial or secondary to other disease like malignancies or viral infections as virus associated HLH. Among the viruses HAV is one of the rare causes of reactive hemophagocytosis [4]. Despite the term familial, family history is often negative and this disorder is very rare in adults [5].

In the clinical picture fever, hepatosplenomegaly, hypofibrinogenemia, pancytopenia, hypertriglyceridemia, may be seen. Histopathologically it is characterised by histiocytic infiltration of reticuloendothelial system with phagocytosis of hematopoietic cells by macrophages [1]. HLH secondary to infection is mostly related to viruses although some bacterial, fungal and parasitic infections may also cause the disease. The most common virus associated with HLH is Epstein Barr Viruses. Hepatitis A virus is a rare cause of HLH [4].

In pediatric population HAV associated HLH reported with case reports only [4, 6]. In two case reports from Japan the patients with hepatitis A infection had recovered without any treatment [7]. The authors recommend bone marrow investigation for the hepatitis A virus infections causing thrombocytopenia. Also other case report from same journal revealed hepatitis A and C virus infections causing hemophagocytosis [8].

On searching the literature there are two cases of Hepatitis A associated HLH reported from Turkey, which were treated with intravenous immunoglobulin [6]. Our case did not responded to intravenous Immunoglobulin treatment and after a weekly dexamethasone treatment clinical and laboratory improvement has been achieved. In the literature it has been discussed but why some only respond to IVIG and others require further therapies like steroid, is not known exactly [4, 7, 8].

As a result, physicians may be facing this rare complication in common infections like Hepatitis A virus infection and early recognition and management of this disorder can be lifesaving.

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