Case Report

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Effectiveness of therapeutic plasma exchange in a critically ill child with secondary hemophagocytic lymphohistiocytosis

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Abstract:

Currently, the ASFA has not included TPE in the management of HLH but many cases reports have reported successful role of TPE in HLH. Here we are presenting a case in which HLH was managed successfully with TPE. Diagnosis of HLH is based on the HLH 2004 diagnostic criteria proposed by HLH society. TPE was done using COM.TEC (Fresenius Kabi, Germany). Patient required three sessions of TPE. After three sessions of TPE patient's clinical condition improved remarkably and he was switched to IV Dexamethasone as maintenance treatment. One standard TPE procedure was 1.5 plasma volume exchanges. In view of deranged coagulation profile fresh frozen plasma was used as a replacement fluid. During follow up after one month of discharge, patient was absolutely normal. In developing countries like India, where infections are still a prime concern to the physicians, making an accurate diagnosis of HLH is a great concern. High suspicion, timely diagnosis and early start of TPE can be life saving in such patients.

Keywords:

Hemophagocytic lymphohistiocytosis, criteria 2004, therapeutic plasma exchange

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of pathologic hyperactive inflammation due to unchecked immune activation. HLH is a life-threatening clinical syndrome that occurs in all age groups, primarily recognized in pediatric age group patients.[1] In developing countries, it remains relatively underdiagnosed owing to lack of awareness in medical fraternity and a wide spectrum of clinical presentations in patients. The spectrum of clinical presentation may range from a simple fever to severe inflammation.[2-4] Diagnosis of HLH is based on the HLH 2004 diagnostic criteria proposed by the HLH society. This criterion requires fulfillment of five of eight clinical tools.[5] These criteria include following clinical features: (1) fever, (2) splenomegaly, (3) cytopenia, (4) hypertriglyceridemia, (5) hemophagocytosis in the bone marrow, spleen, lymph nodes, or liver, (6) low or absent natural killer (NK) cells activity, (7) ferritin >500 ng/ml, and (8) elevated serum CD 25.

Early diagnosis is important in the successful management of such cases; otherwise, it may result to severe multiorgan damage and even death.[6,7] Currently, the American Society for Apheresis (ASFA) has not included therapeutic plasma exchange (TPE) in the management of HLH, but some case reports have reported successful role of TPE in HLH.[8,9] Here, we present a case in which HLH was managed successfully with TPE.

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Case Report

A 19-year-old male patient was absolutely well 1 week ago. He presented to our hospital with the chief complaints of persistent fever, body ache, throat pain, and decreased oral intake for the last 1 week. Vitals were persistently low (systolic/diastolic 90/40 mmHg) even after infusing 1500 ml of normal saline (0.9%). The patient was then shifted to the medical intensive care unit for further treatment and a broad-spectrum antibiotic and inotropic support (noradrenaline) was started. Detailed investigations of dengue, typhoid, malaria, and leptospira demonstrated negative test results. Kidney function tests (KFTs) and liver function tests (LFTs) were highly deranged both at the time of admission and before the start of TPE [Table 1].

Clinical hematology consultation was obtained in view of pancytopenia, coagulation disturbance, and organomegaly (hepatospenomegaly). Based on the clinical history, laboratory findings, and systemic examination results, HLH was suspected and further investigations were done in that direction. Before the start of TPE, patient's hematological parameters, coagulation parameters, serum triglyceride, serum fibrinogen level, serum Ferritin were sent to the laboratory. KFT and LFT were repeated again. Bone marrow biopsy sample was taken and sent for histopathology. Due to progressive deterioration of clinical conditions, he was intubated and started on intravenous (IV) methylprednisolone pulse and TPE. The laboratory results obtained showed convincing results in favor of HLH (lactate dehydrogenase [LDH] - 2860 IU/L, fibrinogen - 50 mg/dl, ferritin - 3210 ng/ml, fasting triglyceride - 619 mg/dl). LFT, KFT, and coagulation profile were grossly deranged [Table 1]. Bone marrow biopsy demonstrated presence of hemophagocytosis in the bone marrow. After three sessions of TPE, his clinical condition improved remarkably and he was switched to IV dexamethasone as maintenance treatment. TPE procedures were done aggressively on 3 consecutive days. TPE was done using COM.TEC (Fresenius Kabi, Germany). Before the start of TPE, written consent was taken from the father and benefits and risks of TPE were explained to him in detail. One standard TPE procedure was 1.5 plasma volume exchanges. In view of deranged coagulation profile, fresh frozen plasma (FFP) was used as a replacement fluid. Peripheral femoral line was used for TPE. All aseptic precautions were taken during the plasma exchange procedures. After three sessions of TPE, his organ function improved and he was extubated. Table 1 demonstrates laboratory features 3 days after the completion of TPE (Hb% - 11.6, absolute neutrophil count - 3.62, platelet count - 98, prothrombin time/international normalized ratio (PT/INR) - 13.5, fibrinogen - 152, fasting triglyceride - 245, and serum ferritin - 250).

During hospital stay, the patient required blood transfusion of 2 units of packed red cells, 18 units of FFP (used during plasma exchange), 4 units of single donor platelet concentrates, and 24 units of cryoprecipitate. He was discharged after 16 days of hospital admission and 7 days after the completion of the last TPE procedure. At the time of discharge, hematological, biochemical, and coagulation parameters were within normal range. Complete blood count such as hemoglobin, platelet count, and total leukocyte/absolute neutrophil count was done using XN 1000 (SYSMEX, USA). Biochemical parameters such as serum ferritin, fibrinogen, fasting triglycerides, LDH, and LFT, KFT were done with Vitros 5600 (Ortho Clinical Diagnostics, USA). Coagulation parameters (PT/

Table 1: Laboratory parameters before and after the therapeutic plasma exchange procedure

Laboratory parameters	Before TPE	After TPE	Follow up after 1 month	Normal range
Hb (g/dl)	9.8	11.6	13.8	13-17
Platelet count ($\times 10^9$/L)	22	98	211	150-450
Absolute neutrophil count ($\times 10^9$/L)	0.9	3.62	4.5	2-7
Fibrinogen (mg/dl)	50	152	207	200-400
PT/INR (s)	24.1/1.7	14.5/1.1	14.1/1.0	12.8-15.1/1
APTT (s)	40.3	26.2	25.9	23.7-35.4
Serum creatinine (mg/dl)	1.9	1.2	1.1	0.66-1.25
Serum ferritin (ng/ml)	3210	250	118	20-250
Fasting triglyceride (mg/dl)	619	245	185	<200
SGOT (μ/L)	723	38	22	17-59
SGPT (μ/L)	343	85	61	21-72
Total bilirubin (mg/dl)	9.78	1.92	1.1	0.2-1.3
Direct bilirubin (mg/dl)	8.77	1.81	1.0	0.0-0.4
Indirect bilirubin (mg/dl)	1.01	0.11	0.1	0.0-1.1
Alkaline phosphatise (u/L)	323	211	99	48-261
LDH (U/L)	2836	542	234	120-246

TPE = Therapeutic plasma exchange, Hb = Hemoglobin, PT = Prothrombin time, INR = International normalized ratio, aPTT = Activated partial thromboplastin time, SGPT = Serum glutamic pyruvic transaminase, SGOT = Serum glutamic oxaloacetic transaminase, LDH = Lactate dehydrogenase

INR and activated partial thromboplastin time) were measured on Destiny Plus (Tcoag, Stago). Bone marrow biopsy was done to detect hemophagocytosis and rule out lymphoid malignancy and aplasia. Diagnosis was made based on the HLH 2004 criteria.[5]

Discussion

HLH is a clinical condition resulting from extensive inflammation due to unchecked abnormal activation of immune cells. In HLH, there is lack of downregulation of activated macrophages. Primary HLH results from gene mutation in, and it affects both the genders.[1,2] Primary HLH is autosomal recessive in nature and results from the genetic mutations in the perforin gene which is responsible for the formation of perforin. Perforin is normally secreted from the NK cells and the cytotoxic T-lymphocytes and acts to trigger cell death. The incidence of HLH is reported to be as high as 1 in 3000 in pediatric hospital admissions. Secondary HLH is an acquired pathologic hyperactive inflammation primarily due to an Epstein–Barr virus infection. Other associated conditions that trigger HLH are viral, bacterial, and fungal infections and malignancy.[1-3,10] In developed countries where infection rate is low, diagnosis of HLH is not difficult; however, in a developing country like India where there is a huge burden of infections, making diagnosis of HLH is a challenge. Timely diagnosis of HLH is vital for the patient as delay in diagnosis may prove fatal to patients. Small case series published in literature have also shown beneficial effect of TPE in primary and secondary HLH. The most plausible explanations which have been given for its beneficial effects are "calming of hypercytotokinemia" and providing "hematological support" to the patient. In our case also, we just required three sessions of TPE which resulted in extubation of the patient and normalization of clinical, hematological, and biochemical parameters. Till now, the ASFA has not included this rare entity into its list of indications. Further research is required to establish TPE as a modality of HLH treatment. The most common limitation of this study was that we could not do NK cell activity and soluble CD25 estimation study in making the diagnosis of HLH.

Conclusion

In developing countries like India, where infections are still a prime concern to the physicians, making an accurate diagnosis of HLH is a great concern. High suspicion, timely diagnosis, and early start of TPE can be life-saving in such patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the boy's father has given his consent for his images and other clinical information to be reported in the journal. The boy's father understands that his name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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