Case Report

Therapeutic plasma exchange in familial hemophagocytic lymphohistiocytosis

Alicia Edwards-Richards^{a,b}, Marissa Defreitas^{a,b}, Chryso Katsoufis^a, Asumthia Jeyapalan^c, Michael Nares^c and Carolyn L. Abitbol^{a,*}

^a*Department of Pediatrics, Division of Pediatric Nephrology, University of Miami, Holtz Children's Hospital at Jackson Health System, Miami, FL, USA*

^b*Department of Pediatrics, Pediatric Postgraduate Training Program, University of Miami, Holtz Children's Hospital at Jackson Health System, Miami, FL, USA*

^c*Department of Pediatrics, Critical Care Medicine, University of Miami, Holtz Children's Hospital at Jackson Health System, Miami, FL, USA*

Received 11 February 2014

Revised 21 April 2014

Accepted 28 April 2014

Abstract. Familial hemophagocytic lymphohistiocytosis is a rare, life-threatening disorder characterized by impaired cytotoxicity, hypercytokinemia and immune-mediated organ injury. We report a 7-week-old male of consanguineous parents who presented with fever, pancytopenia and multi-organ failure. Elevated inflammatory markers and hypercytokinemia led to the diagnosis of familial hemophagocytic lymphohistiocytosis, which was confirmed with genetic testing. With the fulminant multiorgan failure, therapeutic plasma exchange was instituted, using the Prismaflex[®] platform, followed by standard chemo-immunotherapy. There was dramatic reversal of the multi-organ failure and stabilization of the coagulopathy with this neo-adjuvant therapy. Thereafter, he was maintained in clinical remission with chemo-immunotherapy for 3 mo while awaiting stem cell transplantation.

Keywords: Therapeutic plasma exchange, hemophagocytic lymphohistiocytosis, multi-organ failure, continuous renal replacement therapy

1. Introduction

Familial hemophagocytic lymphohistiocytosis (FHL) was first described in 1952 by Farquhar and Clarheaux [1]. Twenty-six years later, Ladisch et al. [2] defined the key immune features of the disorder which included a defect in cellular immunity and mononuclear leukocyte function, with an accompanying

plasma suppressor factor that inhibited lymphocyte proliferation. This rare disorder of immune regulation is now understood to result from defects in the perforin-dependent cytotoxic pathway [3, 4]. The cytotoxic pathway plays an integral role in clearing infectious stimuli; hence, a defect in this pathway renders affected individuals incapable of terminating the immune activation and elaboration of inflammatory cytokines that ensue. Case definition is based on a constellation of clinical and molecular findings as outlined in the hemophagocytic lymphohistiocytosis (HLH) 2004 diagnostic criteria. The latter was revised in 2007 to include genetic mutations as a diagnostic criterion [5, 6].

*Corresponding author: Carolyn L. Abitbol, M.D., Division of Pediatric Nephrology, University of Miami/Holtz Children's Hospital, (R-714), P.O. Box: 016960, Miami, Florida 33101, USA. Tel.: +1 305 585 6726; Fax: +1 305 585 7025; E-mail: cabitbol@med.miami.edu.

FHL is a uniformly fatal disease with an estimated survival of less than 2 mo without treatment. Prompt diagnosis and management is, therefore, of paramount importance in order to improve survival, which averages 55% at 3.1 yr with treatment [7, 8]. The standard therapy incorporates immune-modulation and chemotherapy as a bridge to definitive treatment with hematopoietic stem cell transplant. We present a 7-week-old male who was diagnosed with FHL who received therapeutic plasma exchange (TPE) as an adjunct to standard treatment.

2. Case report

A previously healthy male infant born to consanguineous first cousins presented at 7 wk of life with a 2-d history of persistent fever of 39.4°C, irritability and decreased oral intake. He had a complete sepsis workup, including a lumbar puncture, and he was empirically started on cefotaxime, ampicillin and acyclovir. He was anemic (hemoglobin of 8.1 g/dL) and thrombocytopenic (40,000/mm³) on presentation. He quickly deteriorated over the first 48 h of hospitalization with worsening pancytopenia and the development of hepatosplenomegaly and prominent hepatic dysfunction (coagulopathy, hypofibrinogenemia, transaminitis and hyperbilirubinemia). His course was complicated by worsening ascites and respiratory failure necessitating mechanical ventilation on day 3.

He was also noted to have markedly elevated ferritin levels (>100,000 ng/mL) and hypofibrinogenemia

(<50 mg/dL) which raised the suspicion for HLH (Fig. 1). A liver biopsy revealed sub-massive hepatocellular necrosis with marked acute and chronic inflammation, ballooning of the hepatocytes as well as intracellular and canalicular cholestasis. There was also portal and lobular inflammation by mixed mononuclear infiltration. Immunohistochemical analysis revealed positive staining for CD68 and S-100 proteins, a finding, which was better appreciated for the S-100 protein and these findings were consistent with mild hemophagocytosis. A bone marrow biopsy showed normocellular marrow without evidence of hemophagocytosis; however, there was increased activation of CD3 positive cells. He demonstrated absent NK cell activity and had markedly elevated soluble interleukin-2 receptor (sIL-2R) levels (Fig. 2). In light of the constellation of symptoms and biochemical findings, he was diagnosed with FHL pending genetic typing. The most likely trigger was cytomegalovirus (CMV) infection with plasma CMV DNA of 120,000 copies/mL.

He, therefore, was started on dexamethasone on day 10 as per HLH 2004 treatment guidelines [5]. His multiorgan failure progressed to include acute kidney injury with oliguria, proteinuria and worsening fluid overload. Consequently, continuous renal replacement therapy was initiated using an M-60 filter with the Prismaflex® system (Gambro, Lakewood, CO, USA). A priming volume of reconstituted red cells was infused via the return access at the beginning of

Fig. 1. Relationship between clinical markers of hepatic dysfunction, inflammation and immunomodulatory therapies. T Bili = Total bilirubin; AST = Aspartate aminotransferase; TPE = Therapeutic plasma exchange.

Fig. 2. Effect of therapeutic plasma exchange (TPE) on serum cytokine levels assessed prior to initiating TPE and again 24 h after the third TPE session. Interleukin-6 is elaborated by activated lymphocytes, which are abundant in hemophagocytic lymphohistiocytosis. Soluble interleukin-2 receptor is the alpha subunit of the interleukin-2 receptor is also produced by lymphocytes and is a sensitive marker of activated lymphocytes. sIL-2R = Soluble interleukin-2 receptor; IL-6 = Interleukin-6; TPE = Therapeutic plasma exchange.

the treatment. Therapy was continued without difficulty. However, despite use of steroids and intravenous immunoglobulins and ganciclovir (as treatment for CMV infection), he remained critically ill requiring frequent transfusions of blood products and significant respiratory support. In this setting, TPE was introduced to achieve a 1.5 volume exchange using a TPE 2,000 filter with the same Prismaflex[®] system on hospital day 13. Treatment was initiated with a priming volume of packed red cells, as described previously, for a total of three sessions. Pretreatment levels of interleukin 6 (IL-6), Tumor necrosis factor- α (TNF- α), a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS 13) and sIL-2R were obtained. Repeat levels of IL-6 and sIL-2R were obtained 24 h following the third session (Fig. 2). Liver enzymes, bilirubin and ferritin were followed daily.

The IL-6 and TNF- α levels were markedly elevated at 45.76 pg/mL and 63 pg/mL respectively. His ADAMTS 13 activity was low at 25% while his ferritin and sIL-2R levels were elevated at 50,554 ng/mL and 32,061 U/mL, respectively. He had dramatic decline in his bilirubin and transaminases as well as his blood product requirement following the first session of TPE. Repeat cytokine (IL-6) and inflammatory markers (ferritin and sIL-2R) following the third session of TPE showed 2 to 4 fold decrease (Figs. 1 and 2). Continuous venous-venous hemofiltration and mechanical ventilation were discontinued on day 21.

He was maintained in clinical remission for 3 mo with etoposide and corticosteroids while awaiting hematopoietic stem cell transplantation. He was later confirmed to have a homozygous mutation of the perforin gene (PRF1). Unfortunately, he suffered a relapse associated with infection and irreversible brain edema. With no hope of recovery, the family requested withdrawal of life support and the patient succumbed to his illness.

3. Discussion

In addition to the primary immune defects seen with FHL, the exaggerated inflammatory response and hypercytokinemia contribute to the organ injury that may cause the rapid demise of the patient [9]. Repeated plasma exchange has been shown to produce clinical improvement in patients with FHL in whom the therapeutic benefit was attributed to the lowering of the putative plasma suppressor factor described by Ladisch

et al. [10]. Increasingly, cytokines and chemokines are being shown to cause many of the observed clinical and biochemical features of FHL. These features include fever, organ dysfunction (hepatic and respiratory failure) and hypofibrinogenemia [11]. Cytokines such as interferon- γ (INF- γ), TNF- α and IL-6 are directly toxic to hematopoietic stem cells. Also, these cytokines down regulate the CD47 receptor on hematopoietic stem cells, which makes them more vulnerable to phagocytosis within the bone marrow, thus resulting in the pancytopenia seen in 80% of patients [12].

With this case of FHL in a critically ill infant, we demonstrate effective reversal of his clinical deterioration by TPE. The proposed mechanism is the acute reduction in the cytokine or inflammatory load. This theory is supported by the rapid decline in serologic markers of inflammation (ferritin and sIL-2R) and the candidate cytokine mediator (IL-6) following three sessions of TPE. Although the clinical and serological response was observed prior to initiation of etoposide, the response was sustained with continued use of this agent along with corticosteroids. TPE also confers the added benefit of restoring endogenous components of the clotting cascade (i.e. ADAMTS13) consumed during the consumption coagulopathy resulting in a decreased requirement for blood products. This is an important function since an estimated 95% of patients with FHL will develop disseminated intravascular coagulation [13].

FHL carries a high risk of mortality with rates of 36.4–75%, regardless of the age at the time of diagnosis [13]. Although the data on the outcomes of patients enrolled in the HLH 2004 treatment protocol are not yet available, results from the first trial -HLH94- described six patients dying within the first mo and six patients dying in the second mo of treatment. These deaths were attributed to HLH-related complications. Etoposide has been proved to be ineffective in the mouse model of HLH when the cytokine interferon- γ was infused simultaneously, emphasizing the need to control cytokine levels in the stabilization of these critically ill patients [7, 13–15]. The hope is that, once clinical stability is maintained, allogeneic hematopoietic stem cell transplantation may be potentially curative [16].

In conclusion, the fulminant and often fatal presentation of FHL underscores the need for prompt diagnosis and targeted therapy to attenuate the immune-mediated organ injury. The ability of TPE to lower cytokine lev-

els presents an important neo-adjunctive therapy in the early management of the disease.

Acknowledgments

We thank our Pediatric Nephrology colleagues Dr. Jayanthi Chandar, Dr. Michael Freundlich, Dr. Wacharee Seeherunvong and Dr. Gaston Zilleruelo for advice in treating this patient and their review of the manuscript. We also thank the Pediatric Dialysis and Critical Care nurses for their professionalism and devotion to patient care.

References

- [1] Farquhar JW, Claireaux AE. Familial haemophagocytic reticulosis. *Arch Dis Child* 1952;27(136):519-25.
- [2] Ladisch S, Poplack DG, Holiman B, Blaese RM. Immunodeficiency in familial erythrophagocytic lymphohistiocytosis. *Lancet* 1978;1(8064):581-3.
- [3] Egeler RM, Shapiro R, Loecheil B, Filipovich A. Characteristic immune abnormalities in hemophagocytic lymphohistiocytosis. *J Pediatr Hematol Oncol* 1996;18(4):340-5.
- [4] Lykens JE, Terrell CE, Zoller EE, Risma K, Jordan MB. Perforin is a critical physiologic regulator of T-cell activation. *Blood* 2011;118(3):618-26.
- [5] Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48(2):124-31.
- [6] Filipovich A, McClain K, Grom A. Histiocytic disorders: Recent insights into pathophysiology and practical guidelines. *Biol Blood Marrow Transplant* 2010;16(1 Suppl): S82-9.
- [7] Rosado FG, Kim AS. Hemophagocytic lymphohistiocytosis: An update on diagnosis and pathogenesis. *Am J Clin Pathol* 2013;139(6):713-27.
- [8] Henter JI, Samuelsson-Horne A, Aricó M, Egeler RM, Elinder G, Filipovich AH, et al; Histocyte Society. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002;100(7):2367-73.
- [9] Henter JI, Elinder G, Söder O, Hansson M, Andersson B, Andersson U. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood* 1991;78(11):2918-22.
- [10] Ladisch S, Ho W, Matheson D, Pilkington R, Hartman G. Immunologic and clinical effects of repeated blood exchange in familial erythrophagocytic lymphohistiocytosis. *Blood* 1982;60(4):814-21.
- [11] Janka GE, Lehmbert K. Hemophagocytic lymphohistiocytosis: Pathogenesis and treatment. *Hematology Am Soc Hematol Educ Program* 2013;2013:605-11.
- [12] Kuriyama T, Takenaka K, Kohno K, Yamauchi T, Daitoku S, Yoshimoto G, et al. Engulfment of hematopoietic stem cells caused by down-regulation of CD47 is critical in the pathogenesis of hemophagocytic lymphohistiocytosis. *Blood* 2012;120(19):4058-67.
- [13] Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood* 2011;118(15):4041-52.
- [14] Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome in children: An important diagnostic consideration in fever of unknown origin. *Clin Infect Dis* 2003;36(3):306-12.
- [15] Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA, Jordan MB. Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. *J Immunol* 2014;192(1):84-91.
- [16] Marsh RA, Vaughn G, Kim MO, Li D, Jodele S, Joshi S, et al. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. *Blood* 2010;116(26):5824-31.