Elmer Press

Case Report

J Hematol • 2013;2(2):76-78

Hepatitis C Virus Associated Hemophagocytic Lymphohistiocytosis: Case Report and Literature Review

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Abstract

A 46-year-old male presented with 10 days of fatigue, jaundice, and bloody sputum. Past medical history was significant for chronic hepatitis C virus (HCV) infection, with viral load > 10 million copies by PCR. Lab work showed severe derangements of multiple organ systems including cytopenias, renal failure, and transaminitis; a bone marrow biopsy revealed hemophagocytosis. On hospital day three he was started on definitive treatment for hemophagocytic lymphohistiocytosis (HLH) consisting of etoposide and dexamethasone, with marked improvement in condition. An exhaustive workup for infectious, rheumatologic, and malignant secondary etiologies was negative. In addition, genetic testing did not reveal a primary defect. We therefore postulate his HLH to be associated with chronic untreated HCV infection, a previously unreported clinical scenario in the literature.

Keywords: Hemophagocytic lymphohistiocytosis; Hepatitis C virus; Hematologic malignancy

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening illness from profound dysregulation and hyperactivity of the immune system, often leading to multi-organ failure and death without prompt treatment. The underlying pathology involves the inability to extinguish an antigen-stimulated response driven by the interaction of macrophages, $CD4^+$ helper/$CD8^+$ cytotoxic T cells, and NK cells [1, 2]. The condition is divided into cases with primary genetic defects in cell-mediated cytotoxicity and cases with secondary factors inciting the excessive immune response. Secondary causes are most commonly infectious, especially viral, and less often malignant or rheumatologic.

Case Report

A 46-year-old African-American male presented to clinic with 10 days of fatigue, jaundice, and bloody sputum. Past medical history was significant for chronic untreated hepatitis C virus (HCV) infection, genotype 1a, with viral load > 10 million IU/mL. On exam he appeared acutely ill, with conjunctival pallor, scleral icterus, and tachycardia. No hepatosplenomegaly was present. Lab work revealed multiple derangements including severe thrombocytopenia (platelet count 3000 mm^3), anemia (Hb 7.4 g/dL), acute renal failure (Cr 10.8 mg/dL), transaminitis (AST 214, ALT 178 IU/L), and direct hyperbilirubinemia (22 mg/dL).

The patient was admitted to the intensive care unit for

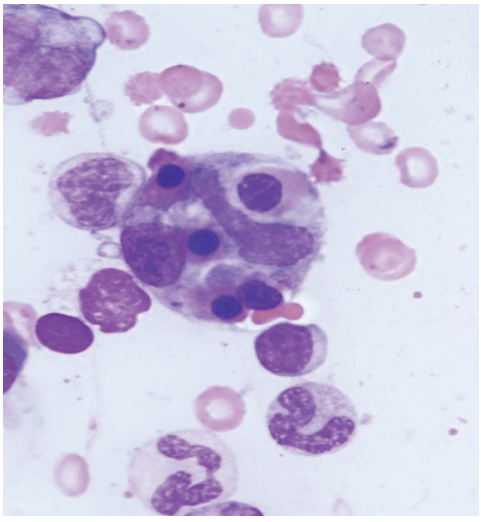

Figure 1. Bone marrow aspirate from the patient demonstrating numerous lymphocytes engulfed by a macrophage.

Manuscript accepted for publication August 15, 2013

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doi: http://dx.doi.org/10.4021/jh82w

Table 1. Literature Review of HLH Cases Associated With HCV.

Author	Patient	Hepatitis virus(es)	Clinical Scenario	Treatment	Outcome
Wu et al [7]	23 M	A, C	Acute hepatitis A with chronic hepatitis C	Parenteral steroids	Deceased due to DIC
Faurschou et al [6]	28 M	B, C	Acute hepatitis C with chronic hepatitis B	Methylprednisolone, cyclosporine, G-CSF, IVIG, anti-thymocyte globulin	Deceased on HD 27 from MOF
Tierney et al [8]	60 F	C	Undergoing treatment for HCV with interferon-alpha and ribavirin	Dexamethasone/IVIG, followed by etoposide	Death on HD 37 due to sepsis
Akamatsu et al [9]	48 F	C	Liver transplant patient for HCV-induced cirrhosis, s/p treatment for acute rejection, with persistent HCV viremia, HLH diagnosed on POD 50	Interferon-α and ribavirin, G-CSF	Remission of HLH, then deceased on POD 88 from graft failure
Pease and Mathew (this report)	46 M	C	No simultaneous co-infections or treatment-related immunomodulation	Etoposide/ dexamethasone	Remission

DIC, disseminated intravascular coagulation; G-CSF, granulocyte-colony stimulating factor; IVIG, intravenous immunoglobulin; HD, hospital day; MOF, multi-organ failure; POD, post-operative day

initiation of emergent hemodialysis. After no source of infection was identified, a suspicion for a malignant hematologic process led to a bone marrow biopsy on hospital day two, remarkable for hemophagocytosis (Fig. 1). Together with bicytopenia, hypertriglyceridemia (388 mg/dL), and hyperferritinemia (3914 ng/mL), this supported a preliminary diagnosis of HLH. On day three, definitive treatment was started with etoposide and dexamethasone, per the HLH-94 treatment protocol [3], with marked clinical and laboratory improvement over the proceeding 48 hours. Several days later, soluble CD25 levels returned elevated (> 6,500 U/mL), satisfying 5 of the 8 HLH-2004 diagnostic criteria [2].

An exhaustive workup for infectious, malignant, and rheumatologic secondary causes proved unrevealing. In addition, PCR-based testing for the five mutations accounting for nearly 100% of primary cases in North America (PRF1, MUNC13-4, STXBP2, STX11, and RAB27A) returned negative [2]. HCV infection remained as the only potential causative factor. The patient remains in remission 2 years post-treatment.

Discussion

The pathophysiology of HLH requires a potent stimulus of the immune system, followed by an inability to extinguish the consequent response. This is most commonly accomplished by viruses, with EBV and CMV the frequent culprits [1]. The association of hepatitis viruses with HLH also has precedence in the literature. While the context of HLH due to infection with hepatitis A or hepatitis B has been established [4, 5], the relationship with hepatitis C is more complex (Table 1). Several reports document co-infection with a separate strain of hepatitis virus in addition to hepatitis C [6, 7], while others detail a clinical picture of concurrent immune therapy and HCV as leading to HLH [8, 9]. However, we believe this is the first reported case of chronic HCV, without simultaneous co-infection or immunomodulatory therapy, as the lone inciting factor for HLH.

The hypothesized relationship of chronic HCV and subsequent HLH holds several implications. The U.S has a large population of patients with chronic hepatitis C, estimated at 2.7 - 3.9 million, many undiagnosed [10]. With most untreated and harboring high viral loads as potential antigenic stimuli, we may recognize HLH caused by HCV more frequently. Patients with acute multi-organ dysfunction of unknown cause need evaluation for hepatitis C and increased suspicion for the inclusion of HLH in the differential diagnosis should testing prove positive.

When considering many autoimmune conditions, in-

cluding cryoglobulinemia, thyroiditis, MPGN, and lymphomas, HCV is included in the differential as a possible inciting factor [11]. The proposed mechanism is presentation of both foreign HCV antigens and self-antigens to local dendritic cells, thus causing cross-reactivity and autoimmune disease. The accepted pathophysiology of HLH, a hyper-stimulated immune system, could be set in motion by such a reaction. Perhaps HLH needs to be added to the list of HCV-induced autoimmune conditions.

In addition, the risks and benefits of HCV treatment in this scenario become very complex. Interferon is the mainstay of treatment regimens outside of experimental contexts, and indeed interferon is one of several immunomodulating agents implicated in the "cytokine storm" of HLH [2]. Consequently, treatment of HCV in such a patient requires clarification, in view of the potential for immune stimulation from interferon therapy leading to relapse of HLH. That continued chronic immune system activation from the untreated hepatitis C viremia may itself lead to HLH relapse lends urgency to the issue. Our patient has yet to be treated for HCV due to the aforementioned risk of interferon therapy, but the discussion certainly would be revisited were his HLH to relapse.

Regardless of the decision to treat HCV, this is the first documented case of successful use of the HLH-94 treatment protocol in the context of HCV. The literature review reveals a variety of treatments in the four previously documented cases; unfortunately none of those patients survived. Our experience may be of guidance should similar cases arise in the future.

Declaration

The authors have no funding sources or conflicts of interest to report related to the manuscript.

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