Case Report

Infectious Mononucleosis Causing Acute Liver Failure and Hemolytic Anemia in a Patient with Underlying Hereditary Hemochromatosis

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Keywords

Infectious mononucleosis · Hereditary hemochromatosis · Auto-immune hemolytic anemia

Abstract

Infectious mononucleosis is a largely benign disease process that occurs secondary to infection with the Epstein-Barr virus. However, it can also present with more serious complications, including auto-immune hemolytic anemia and acute liver failure. Hereditary hemochromatosis is a genetic disorder that leads to organ damage via increased iron uptake and deposition. This case report describes a 25-year-old man who presented with acute liver failure and severe hemolytic anemia. Workup revealed that not only did he have a rare presentation of Epstein-Barr virus-induced acute liver failure and C_3-positive IgG-negative hemolytic anemia, he also had previously undiagnosed hereditary hemochromatosis. This combined presentation of these pathologies presents a unique opportunity to study their interaction and possible synergistic pathophysiology. Furthermore, the evolving understanding of the disease mechanisms behind these disease processes is described.

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Introduction

Infectious mononucleosis (IM) is a disease caused by the Epstein-Barr virus (EBV). EBV is a member of the *Gammaherpesvirinae* subfamily of herpes viruses [1]. More than 90% of the world's population carry EBV in its latent form within their B cells [1]. The classic presentation of IM is a self-limited infection with fever, oropharyngitis, and bilateral lymphadenitis. In the acute phase, elevated transaminases are found in 80% of patients, while jaundice is noted in only about 5% [2]. IM involves a severe cytotoxic T-lymphocyte response to EBV;

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this can lead to hepatic injury [2], though the exact pathophysiology is still under debate. Acute liver failure is rare in IM, as is hemolytic anemia [3]. The majority of cases of hemolytic anemia are IgG-mediated warm autoimmune hemolytic anemia (AIHA). Of the remainder, IgM-mediated cold agglutinins and Donath-Landsteiner make up the majority. Occasionally, C_3 can accompany IgG in warm hemolytic anemia, but IgG-negative, cold agglutinin-negative hemolytic anemia is rarer [4].

Epidemiological data regarding the risk factors associated with these more virulent responses is sparse. However, it stands to reason that comorbid liver injuring disease processes would potentiate liver damage. Hemochromatosis is one such pathology with hepatic injury via iron deposition [5]. Due to the chronic nature of the disease and lack of screening, the majority of diagnoses are made incidentally [6].

Here, we report a case of EBV-induced hepatitis with acute liver failure and IgG-negative warm hemolytic anemia in the setting of previously undiagnosed hereditary hemochromatosis in a 25-year-old man.

Case Report

A 25-year-old Caucasian male presented as a transfer from an outside hospital due to concern for acute liver failure. The patient had been suffering from fatigue, malaise, dark urine, and a sore throat for 6 days. The symptoms began mildly and quickly escalated over 2 days. The patient had never experienced similar symptoms. He denied fevers, hematemesis, hematochezia, melena, abdominal pains, diarrhea, nausea, vomiting, dysuria, myalgia, or urinary frequency. Due to concerns of acute liver failure, he was immediately transferred to our hospital.

The patient's only medical history was a prior rotator cuff surgery with a benign hospital course. The patient was in excellent physical shape. As part of his workout routine he was taking several supplements, including creatinine and GAT Nitraflex. He was also taking the selective estrogen modulator clomiphene, the testosterone modulator ligandrol, and a growth hormone analog MK-677. He denied recent travel or sick contacts. The patient reported that he had unprotected sexual encounters, most recently 1 month prior to admission. He denied a history of smoking or intravenous drug use and had moderate alcohol consumption on weekends.

Upon presentation, he was afebrile with a blood pressure of 113/68 mm Hg, pulse of 92 bpm, respiratory rate of 18, and oxygen saturation of 99% on room air. Physical examination showed a moderately jaundiced and ill appearing man. The patient had icteric sclera. He had no focal neurological deficits, and his heart and lung exams were benign. The abdomen was nontender with no masses and normal bowel sounds, but was remarkable for moderate hepatomegaly and splenomegaly (Fig. 1). The extremities had full range of motion with no cyanosis, clubbing, or edema. He had no signs of asterixis and was alert and fully oriented. Initial laboratory tests were significant for AST/ALT 1,611/3,529 U/L, alkaline phosphatase 114 U/L, and an elevated total bilirubin to 15.2 mg/dL with a direct bilirubin of 12.3 mg/dL. He had a normocytic anemic of 8.3 g/dL, elevated ferritin of 5,731 ng/dL, and INR 1.3. He was immediately started on N-acetylcysteine and a broad workup was ordered.

In the first 12 h, the patient's AST/ALT improved to approximately 900/2,500 U/L, but his malaise continued to worsen. During the admission, his hemoglobin dropped to 6.2 g/dL, and consequently, he received a total of 3 matched packed red blood cell (RBC) transfusions. His first 2 transfusions did not improve his anemia; however, the third was transfused warmed and there was an improved response raising his hemoglobin to 7.8 g/dL.

Laboratory results included negative blood and urine cultures and no exposure to any hepatitis viruses. Further workup revealed that the patient was EBV positive by PCR with a viral load of 52,000 (log 4.716) copies/mL. The patient had mild fevers throughout his hospital
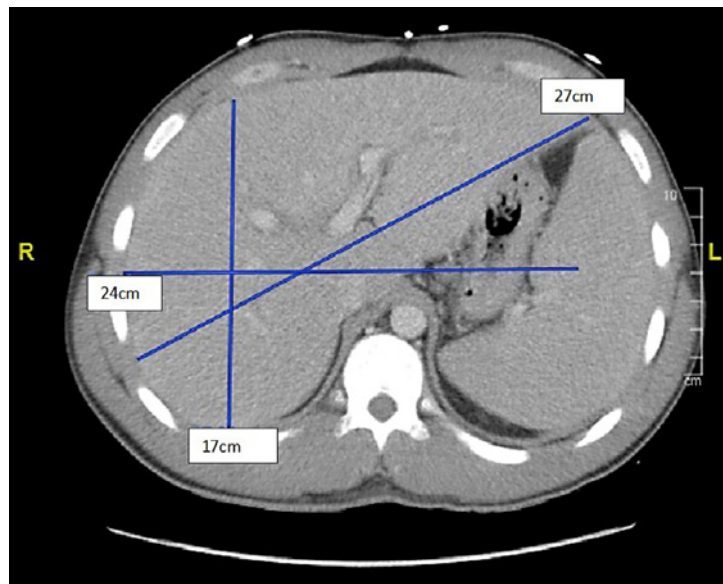
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Fig. 1. Liver enlargement measured in maximum, craniocaudal, and ventrodorsal dimensions.

Table 1. A time course of ferritin biomarker levels and anemia in relation to the initiation of steroid treatment

Date	Ferritin level, ng/dL	Hemoglobin level, g/dL	
February 19, 2019	5,731 (H)	7.3 (L)	Hospital stay
February 21, 2019		6.5 (L)	Steroids begun
February 25, 2019		8.2	Repeat laboratory tests
June 3, 2019	1,313 (H)	12.2 (L)	First outpatient visit
April 17, 2019	544 (H)	15.1	Phlebotomy started
May 15, 2019	360	15.4	
May 31, 2019	396	15.2	
June 20, 2019	261	14.9	

H, high; L, low.

stay. A direct Coombs test was negative for IgG, but a follow-up C_3b/d test was positive with cold agglutinin titers and Donath-Landsteiner test both negative.

Due to the ongoing liver failure, a liver biopsy was undertaken. The initial results were consistent with EBV-induced viral hepatitis with no evidence of auto-immune hepatitis. The patient was recovering well and received 2 more warmed units of blood prior to discharge. Repeat outpatient laboratory workup showed improving liver function tests but worsening anemia to 6.8 g/dL. At this time, he was started on prednisone 1 mg/kg, resulting in marked improvement in hemoglobin to a level of 12.2 g/dL 2 weeks later. Ferritin also trended down to 544 ng/dL at a follow-up 2 months later (Table 1).

Lactate dehydrogenase and ferritin continued to trend downwards. The final liver pathology showed a marked mixed portal and lobular inflammatory infiltrate (Fig. 2). Marked cholestasis and apoptotic hepatocytes were present. EBV immunostaining was positive throughout the liver. Further immunostaining showed an inflammatory infiltrate predominantly of T lymphocytes that were positive for CD3, CD8, CD5, perforin, Granzyme B, and TIA1. CD10 and Cyclin D1 were negative. Trichrome and reticulin stains showed no increased fibrosis. PAS and PAS-D stains show no accumulation of PAS-positive intracytoplasmic globules. Iron stains including Prussian blue stain showed significant iron deposition in the
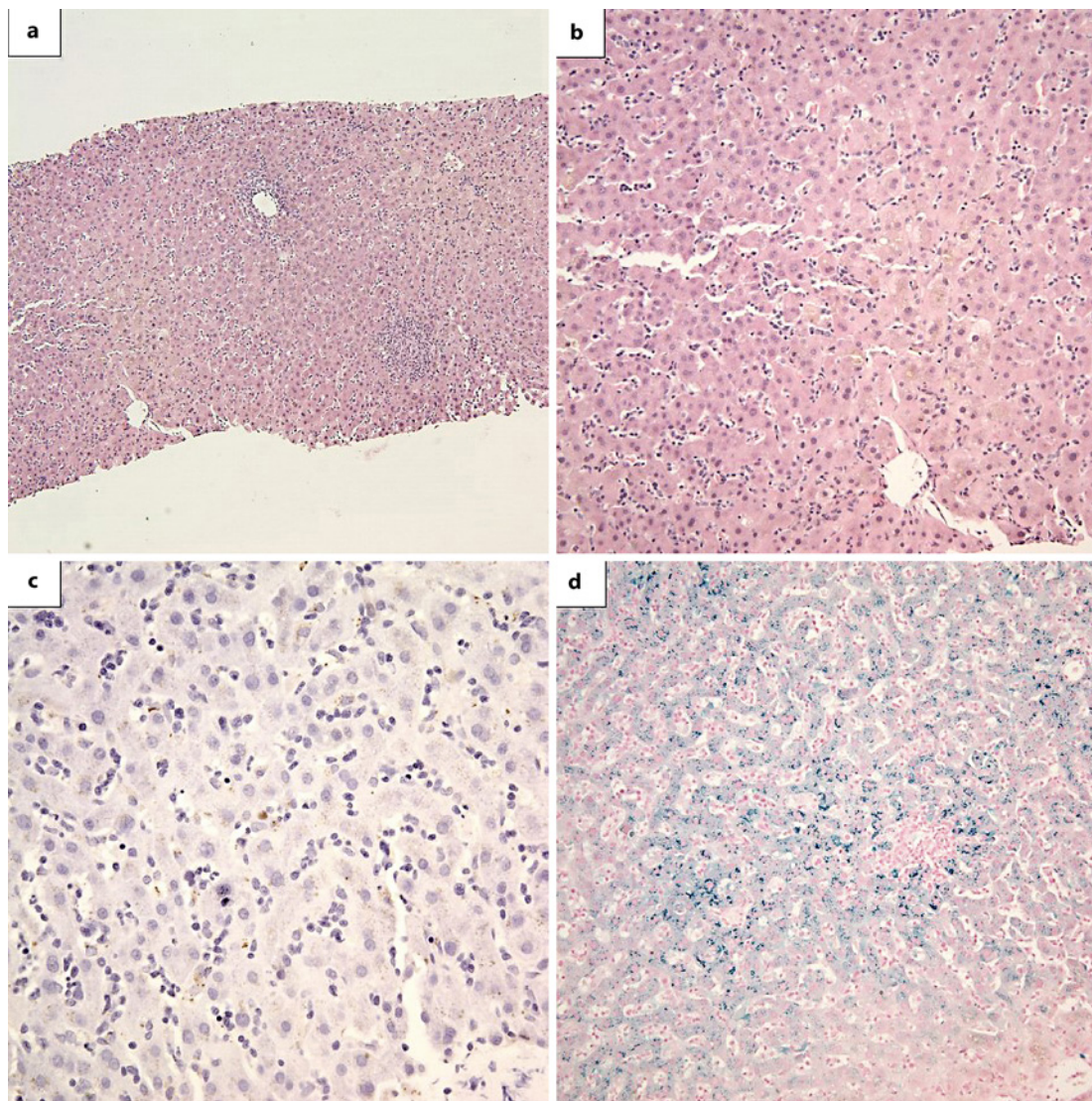
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Fig. 2. Histological slides taken from the liver biopsy showing inflammatory cells (**a**) and numerous sinusoidal lymphocytes (**b**). **c** EBV stain with rare nuclear staining of lymphocytes (center). **d** Iron stain with blue iron deposits in the hepatocytes.

hepatocytes. Further blood testing revealed that the patient was *HFE* gene C282Y homozygous despite no known family history of hemochromatosis and no previous symptoms or laboratory abnormalities. The patient was successfully tapered off steroids, and he was then started on routine phlebotomy sessions for his hereditary hemochromatosis.

Discussion

Transaminitis is common in IM, typically with a 3- to 5-fold increase in LFTs [2]. Our patient had acute liver injury with extremely elevated LFTs and ferritin, representing less than 1% of all cases [3]. Also, rare in our case was the patient's hemolytic anemia [4]. The patient was anemic, with elevated ferritin, lactate dehydrogenase, and indirect bilirubin. He required multiple blood transfusions that responded better to warmed blood; eventually, he

required steroids for his anemia. The patient had no exposure to heparin and no disturbances in their PT, PTT, or platelet levels. Given these facts, we concluded that the patient suffered from intravascular hemolysis. While warm AIHA is most common, the DAT test was negative for IgG but positive for complement fixation. Cold agglutinin titers were also negative, making our patient's hemolysis likely complement mediated related to the underling EBV infection.

RBCs express important cell markers that interact with the complement cascade. CD35 binds to C_3b, CD55 binds decay accelerating factor, and CD59 inhibits C_9 from forming the membrane attack complex unless present in sufficient concentrations [6]. When complement is activated, it leads to the formation of membrane attack complex and cell lysis. In a majority of cases, IgG autoantibodies to RBC markers lead to the activation of C_3 causing a warm-type hemolytic anemia. Warm AIHA accounts for 60–70% of adult cases and 50% of pediatric cases [6]. In 20–25% of cases, cold agglutinins (often IgM) activate C_3[7]. In 40% of pediatric cases, paroxysmal cold hemoglobinuria forms secondary to Donath-Landsteiner antibodies [8]. In 6–10% of warm-type AIHA, there are no IgG antibodies [7]. The mechanism is unclear; some hypotheses include antibody-antigen complexes that later dissociate, transitory IgG or IgM levels, or complement activated by non-RBCs targeting IgG antibody that then deposits on RBCs [7]. C_3-only warm AIHA has a typically mild presentation. Complement complexes can be seen on RBCs under physiologic conditions with no signs of hemolysis [9]. This has led to a diversity of mechanisms proposed for the extreme presentations. Our patient, who required multiple transfusions and a prolonged steroid tapper, is an example of an extreme presentation. The reason for this extreme reaction may involve the patient's other comorbidities.

Hemochromatosis is a disorder of iron deposition in the major organs, particularly in the liver. Hemochromatosis is most commonly an autosomal recessive disorder of the *HFE* gene on chromosome 6 [10], which encodes a transmembrane protein responsible for regulating the transferrin/transferrin receptor interaction [11]. The disease is most common in Caucasians, with a prevalence of 1 in 250–300 people [10]. Hemochromatosis was historically diagnosed after end organ damage was detected, but this trend is beginning to change with improvements in laboratory tests and clinical follow-up. Features of early diagnosis are often vague with mildly abnormal liver function tests [12]. Our patient had no family history yet was found to be C282Y homozygous with extremely elevated ferritin levels, an important biomarker for diseases severity [12]. Due to early detection and ongoing phlebotomy, ferritin levels have normalized with no signs of long-term organ damage.

The exact pathogenesis of IM hepatitis is not fully characterized, but the most widely accepted model for liver injury is through activation of the immune system as opposed to direct viral invasion of the hepatocytes. It has been shown that CD8+ T cells are activated and that they sequester in the liver via intracellular adhesion molecule 1. In IM hepatitis, EBV-infected CD8+ T cells, presumably activated T cells, accumulate in the liver [2, 13]. This leads to numerous cytokine cascades involving interferon, tumor necrosis factor α, and Fas ligand, among others [13]. EBV cytotoxicity has been implicated in a number of cancers including hepatocellular carcinoma [13]. Hepatocellular carcinoma accounts for as many as 45% of all deaths in patients afflicted with primary hemochromatosis as well [14]. In hemochromatosis, iron deposition leads to free radical formation that produce cytotoxic by-products when metabolized by lipid peroxidation, which leads to cellular, protein, mRNA, and DNA damage and hence oncogenesis [15]. However, recent research has shown that these depositions also lead to immunologic abnormalities and can serve as foci for enhanced DNA synthesis and immune cell activity [15]. The generation of these free radicals and cytokines may also help to explain the severe C_3-only-positive AIHA our patient presented with. In most cases, complement activation alone is insufficient to lead to large-scale hemolysis. The proinflammatory pathology may have led to a more extreme hemolytic anemia.

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Conclusion

The comorbid presentation of EBV-induced C_3-only-positive warm AHIA and hepatitis with hemochromatosis is a rare confluence of events. Our understanding of both of these disease processes is rapidly evolving, and emergent research reveals potential overlap in the biochemical cascades involved in both disease pathologies. Given the hepatotoxicity and immunologic effects of both pathologies, their similarity may lead to biochemical synergy. The increased inflammatory state may have both sensitized the liver to acute failure and helped trigger the hemolysis seen in this patient. This case helps explore potential synergies between hereditary hemochromatosis and associated complications of IM.

Statement of Ethics

The subject of this case report gave his informed consent to publish their case including the publication of images. No institutional review board or other approvals were required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Joshua Kra was the senior hematologist/oncologist responsible for the patient's care in the inpatient and outpatient setting and was responsible for selection, revision, and final approval of the case report. Mark Forsberg was the medical resident responsible for the acquisition and interpretation of data, research, and the drafting of this case report. Mark Galan was the senior pathologist responsible for the acquisition and interpretation of the pathological data found within Figure 2 and for reviewing and approving the case report.

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