Acute Hepatitis E: A Rare Cause of Acute Liver Failure in a Patient With Acute Myeloid Leukemia

Zachary Field 1 , Michelle Russin 1 , Rodrigo M. Murillo Alvarez 2 , Mario Madruga 1 , Steve Carlan 3

1. Internal Medicine, Orlando Regional Medical Center, Orlando, USA 2. Pathology, Orlando Regional Medical Center, Orlando, USA 3. Obstetrics and Gynecology, Orlando Regional Medical Center, Orlando, USA

Corresponding author: Steve Carlan, stevecarlan@gmail.com

Abstract
Immunocompromised patients are particularly at risk to develop hepatitis E virus (HEV) infection and its related complications. We present a rare case of HEV infection in a 35-year-old Hispanic female with concomitant acute myeloid leukemia (AML). The patient presented with acute liver failure within a few weeks after receiving a blood transfusion.

Our case likely represented an acute de novo HEV infection after chemotherapy in a patient with concurrent AML, evidenced by the presence of anti-HEV IgM antibodies as well as histological findings, and with a previous history of recent transfusions being one of the strongest risk factors for transmission. Liver failure from an acute de novo hepatitis E infection with concurrent AML can be catastrophic in the immunosuppressed patient. Our case is particularly unique due to the uncommon presentation of acute hepatitis E in a non-pregnant reproductive aged Hispanic female with recently diagnosed AML. Clinicians should maintain a low threshold to test serum HEV-RNA if a patient presents with signs and symptoms suggestive of acute hepatitis.

Categories: Internal Medicine, Infectious Disease, Hematology
Keywords: hepatitis e virus, liver function, acute myeloid leukemia (aml)

Introduction
Hepatitis E viral (HEV) infection has a worldwide distribution and usually has a self-limited clinical course [1-3]. In most patients, an estimated recovery occurs within four to six weeks, but immunocompromised patients are at risk of developing symptomatic acute hepatitis or even chronic infection [4,5]. Fecal contamination is the most common mechanism of transmission in developing countries due to poor sanitary conditions [1], while in developed countries animal reservoir transmission and transfusion-related transmission have been reported [6].

Case Presentation
A 35-year-old Hispanic female with a past medical history significant only for acute myeloid leukemia (AML), who had previously undergone chemotherapy and consolidation therapy, presented for evaluation of progressively worsening jaundice over the past seven days. She also reported clay-colored stools that developed the day prior to admission, as well as generalized symptoms of nausea, chills, and malaise. Regarding her AML, the patient was diagnosed five months prior to admission with cytogenetics revealing a t(8;21) translocation. She underwent induction chemotherapy with 7 + 3 regimen. She then had three cycles of consolidation therapy with high-dose cytosine arabinoside. The patient was originally from Mexico, but had been living in the United States for 16 years.

The physical exam was only significant for scleral icterus and jaundice. Laboratory values are seen in Table I and were notable for an aspartate aminotransferase (AST) of 3,846 U/L (13-39 U/L), alanine aminotransferase (ALT) of 3,346 U/L (7-52 U/L), alkaline phosphatase of 189 U/L (34-104 U/L), and total bilirubin of 13.3 mg/dL [0.3-1.0 mg/dL]. An acute hepatitis panel was ordered, which tested for hepatitis A, hepatitis B, and hepatitis C antibodies as well as hepatitis B surface antigen, and was negative.
### Basic Lab Results and Anticoagulation Studies

| Test                                      | Result | Flag | Units     | Reference Interval |
|-------------------------------------------|--------|------|-----------|--------------------|
| Sodium, serum                             | 134    | High | mmol/L    | 136-145            |
| Potassium, serum                          | 3.5    | Low  | mmol/L    | 3.6-5.1            |
| Chloride, serum                           | 103    | -    | mmol/L    | 98-107             |
| CO₂ content                               | 24     | -    | mmol/L    | 22-32              |
| Blood urea nitrogen (BUN)                 | 5      | Low  | mg/dL     | 8-20               |
| Creatinine, serum                         | 0.5    | -    | mg/dL     | 0.5-1.0            |
| BUN/creatinine ratio                      | 10     | -    | Ratio     | 7.3-21.7           |
| Glucose serum                             | 133    | High | mg/dL     | 65-100             |
| Anion gap                                 | 7      | -    | mmol/L    | 2-12               |
| Calcium, serum                            | 8.5    | Low  | mg/dL     | 8.6-10.3           |
| Aspartate aminotransferase                | 3,846  | High | IU/L      | 13-39              |
| Alanine aminotransferase                  | 3,346  | High | IU/L      | 7-52               |
| Alkaline phosphatase                      | 189    | High | IU/L      | 34-104             |
| Bilirubin, total                          | 13.3   | High | mg/dL     | 0.3-1.0            |
| Protein total, serum                      | 6.1    | Low  | g/dL      | 6.5-8.9            |
| Albumin, serum                            | 2.8    | Low  | g/dL      | 3.5-5.7            |
| Osmolality, calculated                    | 280    | -    | mOs/kg    | 280-300            |
| Bilirubin, direct                         | 8.1    | High | mg/dL     | 0.0-0.2            |
| White blood cell count                    | 4.8    | -    | x10⁹/μL   | 4.1-10.4           |
| Red blood cell count                      | 3.71   | Low  | x10⁶/μL   | 3.9-5.0            |
| Hemoglobin                                | 12.6   | -    | g/dL      | 11.8-15.1          |
| Hematocrit                                | 36.8   | -    | %         | 34.0-44.0          |
| Platelet count                            | 65     | Low  | x10⁵/μL   | 145-355            |

### TABLE 1: Laboratory values

Her liver function tests began to improve, but the etiology of her acute liver failure remained unclear. The patient underwent magnetic resonance cholangiopancreatography (MRCP), which showed some sludge and gallstones but no pericholecystic fluid or evidence of an impacted stone (Figure 1).
FIGURE 1: Magnetic resonance cholangiopancreatography (MRCP)

Stones (marked with arrow) and sludge within a contracted gallbladder. Gallbladder wall measuring 3 mm, the upper limit of normal. Diffuse signal changes of the liver consistent with iron overload. No focal liver lesions are seen.

Further workup including antinuclear antibody (ANA), anti-mitochondrial antibody, anti-smooth muscle antibody, HIV antigen, acetaminophen level, ceruloplasmin level, as well as cytomegalovirus polymerase chain reaction (PCR), Epstein-Barr antibodies, herpes-simplex PCR, and hemochromatosis gene (HFE) gene analysis were all negative or within normal limits.

Iron studies were ordered that revealed a ferritin of 88 ng/mL (10.0-291.0 ng/mL), serum iron of 240 µg/dL (28-170 µg/dL), total iron-binding capacity of 209 µg/dL (255-450 µg/dL), transferrin saturation of 115% (20%-50%), and transferrin of 149 mg/dL (192-382 mg/dL). The hematology and oncology service was consulted and did not believe that her presentation was related to chemotherapy toxicity. Gastroenterology was consulted who recommended that the patient undergo a liver biopsy, which showed extensive ballooning degeneration with lobular disarray and evidence of necrosis (Figure 2).
hepatocellular carcinoma, especially in an immunosuppressed patient, regeneration of growth factors and may evolve into cirrhosis, putting a patient at further risk for a protracted disease course. The hepatic damage produced by the HEV can result in the production and accumulation of cytokines, which can lead to liver fibrosis and cirrhosis.

If not feasible or unsuccessful, ribavirin should be prescribed in the event of HEV infection, reduction of immunosuppression has been reported as successful as treatment but must be accompanied by other antiviral agents. To avoid exposure to sources of HEV infection, such as raw or undercooked foods and animal exposure, cancer patients are a high-risk population who should be informed to practice good hygiene, especially with a background of malignancy, even without travel to endemic regions.

Due to the recently discovered rising number of hepatitis E cases in immunocompromised patients, clinicians should maintain a low threshold to test serum HEV-RNA if a patient presents with signs and symptoms suggestive of acute hepatitis. Cancer patients are a high-risk population who should be informed to avoid exposure to sources of HEV infection, such as raw or undercooked foods and animal exposure. In the event of HEV infection, reduction of immunosuppression has been reported successful as treatment but if not feasible or unsuccessful, ribavirin should be prescribed. While clearance is usually spontaneous in immune-competent individuals, these at-risk groups may develop a more complicated and protracted disease course. The hepatic damage produced by the HEV can result in the production and regeneration of growth factors and may evolve into cirrhosis, putting a patient at further risk for hepatocellular carcinoma, especially in an immunosuppressed patient.
The incubation period for HEV is two to six weeks [8]. Given that our patient’s symptoms developed 16 days after her last transfusion and she lacked other risk factors for contracting HEV, it is likely that she acquired the infection through a contaminated blood product transfusion. Blood product donors are not currently screened for HEV, yet there are increasing numbers of reported transmissions of acute and chronic infections in blood transfusion recipients. While knowing immunosuppressed patients are already at higher risk for acquiring viral infections, clinicians should be aware that the administration of transfused blood products may further increase the risk of HEV. Infection with HEV during the immunocompromised state can significantly alter the patient’s disease course [12]. Close follow-up with any immunocompromised patient for either spontaneous viral clearance or resolution of symptoms to determine the need for therapeutic intervention is therefore recommended.

Conclusions

Although the majority of HEV infections occur in developing countries, cases in the developed world do occur and several cases have been well documented, particularly in immunocompromised hosts unable to effectively clear the infection. In this group, a high index of suspicion of HEV infection is important, especially when clinical manifestations of acute hepatitis, abnormal liver function studies, or a medical history of a hematological malignancy is present. The diagnosis is usually achieved by the identification of HEV antibodies or HEV-RNA; however, a liver biopsy can be justified in order to assess severity and evolution of the disease and to rule out other causes. A close follow-up is required to determine the need for additional interventions until the infection is entirely cleared.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. IRB Orlando Regional Health issued approval Not Applicable. IRB considers case reports such as this submission ‘Not Research’. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Bai M-J, Zhou N, Dong W, Li G-X, Ceng W, Zhu X-Q: Seroprevalence and risk factors of hepatitis E virus infection in cancer patients in eastern China. Int J Infect Dis. 2018, 71:42-47. 10.1016/j.ijid.2018.04.003
2. Haboubi HNY, Diyar R, Benton A, Ch’Ng CL: A case of acute hepatitis E infection in a patient with non- Hodgkin lymphoma treated successfully with ribavirin. Case Rep Gastrointest Med. 2017, 2017:8941218. 10.1155/2017/8941218
3. Geng Y, Zhang H, Huang W, Harrison TJ, Geng K, Li Z, Wang Y: Persistent hepatitis E virus genotype 4 infection in a child with acute lymphoblastic leukemia. Hepat Mon. 2014, 14:e15618. 10.5812/hepatmon.15618
4. Alnuaimi K, Lavolé J, Lasroux-Combes C, Rogue Afonso A-M, Sogni P, Pol S, Mallet V: Chronic hepatitis E in patients with indolent lymphoma after treatment with rituximab and bendamustine. Hepatology. 2018, 67:2468-2470. 10.1002/hep.29697
5. Nicolini L, Zappulo E, Viscoli C, Mikulska M: Management of chronic viral hepatitis in the hematological patient., Expert Rev Anti Infect Ther. 2018, 16:227-241. 10.1080/14787210.2018.1438264
6. Fuse K, Matsuyama Y, Moriyma M, et al.: Late onset post-transfusion hepatitis E developing during chemotherapy for acute promyelocytic leukemia. Intern Med. 2015, 54:657-661. 10.2169/internalmedicine.54.2352
7. Khuroo MS, Khuroo NS: Hepatitis E: discovery, global impact, control and cure . World J Gastroenterol. 2016, 22:7030-7045. 10.3748/wjg.v22.i51.7030
8. Kamar N, Dalton HR, Abravanel F, Izopet J: Hepatitis E virus infection. Clin Microbiol Rev. 2014, 27:116-138. 10.1128/CMBR.00057-13
9. Horvatits T, zur Wiersch J5, Lüthgehetmann M, Lohse AW, Pischke S: The clinical perspective on hepatitis E. Viruses. 2019, 11:617-656. 10.3390/v11070617
10. Abravanel F, Mansuy J-M, Huynh A, et al.: Low risk of hepatitis E virus reactivation after haematopoietic stem cell transplantation. J Clin Virol. 2012, 54:152-155. 10.1016/j.jcv.2012.02.015
11. Von Felden J, Alric L, Pischke S, et al.: The burden of hepatitis E among patients with hematological malignancies: a retrospective European cohort study. J Hepatol. 2019, 71:465-472. 10.1016/j.jhep.2019.04.022
12. Dalton HR, Saunders M, Woolston KL: Hepatitis E virus in developed countries: one of the most successful zoonotic viral diseases in human history?, J Virus Erad. 2015, 1:23-29.