CLINICAL VIGNETTE

Hepatitis E

Sittiporn Bencharit, MD and Michael G. Quon, MD

Case Presentation

A 54-year-old female visiting from India was brought to the emergency room for weakness, fever and emesis. Prior to coming to the United States, an abdominal ultrasound in India had gallstones, and she was prescribed ursodiol 300 mg twice a day.

Evaluation in the emergency room revealed stable vital signs, with no abdominal tenderness. Medications include: metformin, ursodiol, levothyroxine, and acetaminophen. Repeat ultrasound revealed cholelithiasis with gallbladder wall thickening and a 4mm common bile duct. Her liver function test, LFT, was as follow: total Bilirubin 1.7, AST 556, ALT 539, and Alkaline Phosphatase 153. Her INR was 1.4. Hepatitis A IGM Ab, Hep Bs Antigen, Hep Bcore Ab, Hep C Ab were all negative. She was discharged from the emergency room with advice for follow up as outpatient.

One week later she returned to the hospital for low grade fever, and fatigue. She had no abdominal pain, but was complaining of malaise. Her LFT now were markedly elevated with Total Bilirubin of 3.8, AST1050, ALT 820, and Alk Phos 158, Total Protein 6.9, and Globulin 3.3. Her INR is 1.8, WBC 5.0 and Platelet Count of 186. She was admitted to the hospital, MRCP revealed cholelithiasis, gallbladder wall thickening, and pericholecystic fluid without choledocholithiasis.

She was presumed to have acute hepatitis, as her symptoms were not consistent with biliary cholangitis. She denied taking any herbal supplement, nor any new drug except for ursodiol which was started prior to her travel to the United States. During her hospitalization, her LFT had deteriorated, Total Bilirubin 6.7, AST 887, ALT 785, and INR 2.0. Her ANA 1:160, Anti-mitochondrial AB, and Smooth Muscle antibody were negative. Hepatitis E antibody was drawn when she was admitted to the hospital, but the result was not available for 2 weeks.

She requested to fly back to India. As we still had no diagnosis of her transaminitis, a liver biopsy was performed. The report was: marked portal, interface, and lobular hepatitis with bridging necrosis. Differential diagnosis: viral hepatitis, autoimmune hepatitis. As clinically she appeared to be stable, she was discharged from the hospital. One week after discharge, her Hepatitis E IGM antibody confirmed a diagnosis of hepatitis E infection.

Discussion

Hepatitis E infection is one of the most common causes of acute hepatitis in the world, yet it is often not recognized.[1] The World Health Organization (WHO) estimates that hepatitis E (HEV) causes 20 million new cases of infection annually, with more than 55,000 deaths.[2] In the United States and developed countries, the prevalence of Hepatitis E is lower than in developing countries. Population-based surveys from 1988 to 1994 reported 21% of US adults had anti-HEV antibody, higher than hepatitis B (5.7%) or hepatitis C (2%).[3] The disease was originally identified in 1980 as "epidemic, non-A, non-B hepatitis". Mikhail Balayan identified hepatitis E (HEV) using immune electron microscopy to examine his own stool samples, after he ingested pooled stool extracts from 9 patients.[4]

Hepatitis E (HEV) is a small nonenveloped single strand RNA that is 24-37nm in diameter. There are 5 genotypes with 4 known to be associated with human infection.[5] Genotype 1 and 2 appear to be confined to humans and have been identified as causing epidemic hepatitis, associated with waterborne and fecal-oral transmission. Genotype 3 and 4 are found in animals but can infect humans.[6]

Transmission of HEV can occur through contaminated food and water, blood transfusions, and mother to child transmission. Zoonotic transmission usually occurs with ingested infected and uncooked meat. Swine are most commonly implicated but wild game, organ meats, and raw shellfishes can lead to infection.

Acute hepatitis E has an incubation period of 3-8 weeks, a short prodromal phase, and a period of symptoms or jaundice lasting days to several weeks.[7] Generally it is a self-limited disease, although acute hepatic failure can develop in a small group of patients. The vast majority of patients are asymptomatic, or mildly symptomatic.[8] Jaundice is usually accompanied by malaise, anorexia, nausea, vomiting, fever, and abdominal pain.[9] Rarely, extrahepatic manifestations renal, hematologic, neurologic, and pancreatic complications. Acute pancreatitis, thrombocytopenia, aplastic anemia, autoimmune thyroiditis, myositis, cryoglobulinemia, Bell's palsy, peripheral neuropathy, and Guillian Barre syndrome have been reported.[10]

The majority of patients clear the virus spontaneously, but a few develop acute hepatic failure, cholestatic hepatitis and chronic hepatitis E. Risk factors for developing complication include

pregnancy, preexisting liver disease, malnutrition, solid organ transplant recipients, HIV or immunosuppression..

Acute HEV hepatitis should be considered when patients present with acute hepatitis of unknown causes, including drug induced liver injury. There is no standard diagnostic test for acute HEV, although there are many commercially available assays. The sensitivity and specificity varies widely between these tests.[11]

The initial diagnostic test is anti-HEV IGM assay. Anti-HEV IGM appears during the early phase of the disease and disappears rapidly over 4 to 5 months.[12] Anti – HEV IGG appears shortly after anti-HEV IGM, with titer increases throughout the acute phase into the convalescent phase. HEV RNA can be detected in the stool one week before, with persistence two weeks after the onset of illness. HEV viremia can be detected 2-6 weeks after infection, but may persists for years in those who developed chronic HEV infection.

Treatment of acute HEV hepatitis is supportive care, as most will clear their viremia. In immunocompromised patients, chronic HEV may occur and are identified by presence of HEV RNA. Patients on immunosuppression with reduction of immunosuppression therapy, 30% of the patients cleared the virus. For those with solid organ transplant, initial tacrolimus reduction is recommended.[13]

Ribavirin 600 mg daily has been used to treat chronic HEV in non pregnant patients, in those whose HEV RNA persists after reduction in immunosuppressive therapy, and/or in solid organ transplant.[14] Ninety-five percent of solid organ transplant recipients cleared the virus. Checking HEV RNA in stool and in blood after 12 weeks of therapy assesses response to therapy. Therapy is stopped if HEV RNA is not detectable. If HEV RNA persists, the treatment is extended for another 12 weeks.

Prevention and control of HEV when traveling to endemic area, includes voiding contaminated water and undercooked meat or shellfish. HEV vaccine has been effective in preventing hepatitis but is only available in China.

Summary

Hepatitis E is a global disease that is not well-known to most clinicians in this country. Some cases of acute HEV hepatitis may be misdiagnosed as drug induced injury. This patient came from an HIV endemic area, but underwent work up to exclude other causes of acute hepatitis. The anti HEV IGM was a sent to a reference lab and did not return until after the patient was discharged. Increasing awareness and a faster turn around time for the anti HEV IGM could have spared costly tests in this patient.

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