Case Report: Fulminant Hepatitis E in a Woman Taking Oral Contraceptive Medication

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Abstract. We describe a fulminant autochthonous hepatic failure caused by hepatitis E (HEV) in a patient admitted in our hospital for liver-transplant evaluation. The only risk factor recorded for this severe course was the use of oral contraceptives that are known to mimic a hormonal status similar to pregnancy. The diagnosis was based on the presence of IgG and IgM anti-HEV in the serum of the patient and confirmed by the isolation of a strain of HEV genotype 3f from a blood sample obtained the fourth day after hospital admission. HEV genotype 3 is present in human and swine populations in Spain. The patient began to recover while waiting for a liver transplant. To our knowledge, this is the first report of fulminant hepatitis E in a non-pregnant European patient on oral contraceptives.

INTRODUCTION

Fulminant hepatic failure (FHF) refers to the rapid development of severe acute liver injury with encephalopathy in a person who previously had a normal liver. It can result from a variety of causes, but the etiology is unknown in most cases. Recently, several cases of FHF caused by hepatitis E virus (HEV) have been reported.¹ Large waterborne epidemics of acute hepatitis have occurred in tropical and underdeveloped countries where drinking water is focally contaminated. In industrialized countries, cases of autochthonous HEV have been recognized recently in persons with no evidence of travel to endemic areas; this has been suggested to be a distinct clinico-epidemiological entity, and the name of hepatitis E indigenous to economically developed countries (IDC HE) has been proposed.²

HEV has been isolated from sewage in Spain³ where it is a zoonotic illness in which the most probable reservoir for the human population is swine.^{4,5} It has been the cause of sporadic acute HEV in Spain^{6,7} and is considered to be an occupational disease.^{8,9} Phylogenetic analysis has shown that all the HEV isolates identified in our country are clustered into genotype 3. This genotype, prevalent in sporadic cases of hepatitis E reported in industrialized countries, is also prevalent in pigs in many countries throughout the world.¹⁰

HEV is the cause of severe clinical FHF in pregnant women and is associated with high mortality, particularly in the third trimester.¹¹ Jaiswal and others¹² reported a high rate of infection with HEV (57.5%) causing acute hepatitis in pregnant women in India. Patra and others¹³ also reported a great difference in mortality rate between pregnant and non-pregnant women suffering acute hepatitis E. FHF was present in 55% (mortality = 41%) of pregnant women in contrast to 2% (mortality = 0.6%) of non-pregnant women. This difference was not observed when the infecting agent was hepatitis B virus. Likewise, Jilani and others,¹⁴ also in India, have confirmed the different evolution of hepatitis E in pregnant and non-pregnant women, reporting a higher maternal and fetal

mortality rate in pregnant women (65.8%; 25/38) than in non-pregnant women (23.5%; 4/15).

In this paper, we report a case of FHF caused by HEV in a non-pregnant woman who was on oral-contraceptive treatment. This risk factor could have enhanced the severity of the clinical disease because of the fact that contraceptive treatment mimics the hormonal status of pregnant women.

CASE REPORT

A 37-year-old female office worker, living in a small village near Madrid, with no history of alcohol consumption and no close contact with animals was admitted in La Paz Hospital (Madrid, Spain) with asthenia, epigastralgia, nausea, and fever (38.5°C) of 5-day evolution. On physical examination, the patient was slightly jaundiced (total bilirubin = 4.3 mg/dL). Biochemical parameters on admission were as follows: aspartate aminotransferase (AST) = 4,522 U/L (reference value < 19 U/L); alanine aminotransferase (ALT) = 3,751 U/L (reference value < 23 U/L); and lactate dehydrogenase (LDH) = 3,359 U/L (reference value < 140 U/L). Liver synthetic function, as defined by international normalized ratio (INR) estimation, was slightly impaired the first day after admission (INR = 1.8) and increased to 3.7 the second day in spite of vitamin K treatment. Bilirubin value was 7.3 mg/dL, and after 25 days in the hospital, it peaked at 29 mg/dL. Four days after admission, the patient was transferred to a Transplantation Center (Hospital Ramón y Cajal, Madrid, Spain) for liver-transplantation evaluation.

On admission at our hospital, coagulation factor V was 20 u/dL (36, 36%) and coagulation factor VII was 10 u/dL (18, 18%). Both coagulation factors showed slight improvement 24 hours later (26 u/dL, 47.2% and 12 u/dL, 21.8%, respectively). Transaminase values peaked at 24 hours after admission (AST = 5300 U/L and ALT = 4025 U/L) and then decreased slowly. Enzymatic values of cholestasis, gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase were not elevated during the course of the disease. During the first days at the hospital, the patient suffered hypoglycemia (45 mg/dL) that were treated with a glucose-based solution. Bradypsychia corresponding to encephalopathy grade I was observed. Renal function was normal along the hospitalization period.

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Tests were done to rule out autoimmune liver disease, including antinuclear antibody, antismooth muscle antibody, and anti-LKM. All were negative. Serological markers of hepatitis A, hepatitis B, and hepatitis C were negative. Antibodies to human immunodeficiency virus, Epstein–Barr virus, cytomegalovirus, and herpes virus were also negative or clinically not significant.

Finally, the diagnosis of FHF caused by HEV was made when IgG and IgM anti-HEV were detected by a commercial ELISA (Bioelisa HEV IgG and Bioelisa IgM, Biokit, Barcelona, Spain) and were confirmed by Western Blot analysis (RecomBlot HEV IgG/IgM, Mikrogen, Martinsried, Germany). In addition, HEV RNA was amplified by RT-nested-PCR¹⁵ in two serum samples taken at the moment of admission to the hospital and 3 days later, respectively. Stool samples were not taken.

The identified strain belonged to genotype 3, subtype 3f. The partial sequence of the HEV strain isolated from this patient was obtained and compared with other known human and swine strains of HEV. Phylogenetic analysis of a 260-bp long fragment belonging to the ORF2 revealed that this HEV isolate showed a high percentage of homology (91.9–97.3%) with some Spanish human strains followed by other Spanish swine HEV strains (86.9–94.2%). When compared with other human European strains, the closest homology of this strain was observed with some British HEV strains (83.4–91.9% nucleotide identity). On comparing with other European swine strains, the highest homology was recorded for Dutch strains (81.9–93.0%) followed by British strains (85.7–86.5%). Most of the nucleotide mutations were found to be silent and did not result in significant differences at the amino acid level. The HEV strain identified in this work showed a 100% amino acid sequence homology compared with other human and swine HEV strains from genotype 3, subtype 3f. A phylogenetic analysis of these sequences is illustrated in Figure 1. The HEV sequence identified in this work was deposited in the Genbank database with accession number 1160736.

Regarding the investigation of toxin- and drug-related causes of FHF, the only outstanding feature in the patient's history was the oral anti-conception treatment she had been receiving since 16 years of age. In the last 2 years, she had been orally taking 250 µg of norgestral and 35 µg of ethinyl estradiol that were suspended by her general practitioner because of nausea and vomiting 48 hours before hospital admission. The serum concentration of estradiol and progesterone were measured in a banked blood specimen drawn the second day after admission (fourth day after suspension of the contraceptive treatment). The levels of these hormones were 224 pg/mL and 0.2 ng/mL, respectively, which are considered normal values in a luteal and follicular phase.

Abdominal ultrasonography revealed a lesion of around 2 cm in segment V of the liver. Hepatic magnetic resonance imaging showed a second lesion of 2.3 cm in segment VII. These two lesions were suggestive of hepatic adenomas. The patient recovered within 28 days after admission to the hospital. She was treated with routine antiencephalopathy treatment, vitamin K, acetylcysteine, and prophylactic antibiotics.

DISCUSSION

To our knowledge, this is the first report of FHF caused by autochthonous hepatitis in a non-pregnant European patient

FIGURE 1. Phylogenetic tree based on nucleotide sequences of a 260-bp region within the ORF2 gene of HEV; 628-HRC is the case described in this paper, and it is shown in bold letter. Bootstrap values were determined on 1,000 resamplings of the data sets. The sequence reported in this work was compared with 64 selected sequences from the genotype 3 available in the GenBank database, including strains from human (□) and swine (●) origin.

with the risk factor of oral-contraceptive medication. Two cases of FHF caused by HEV in non-pregnant young women taking oral contraceptives have been previously recorded. However, in both cases, a travel to rural endemic areas in India was considered as a risk factor.¹⁶ An exhaustive epidemiological questionnaire was performed, but the transmission

route could not be found. There was no family history of hepatitis, and the patient had not been abroad and had not received a transfusion in the last year. She did not recall eating undercooked pork products nor did she have any close contact with animals during the 2 months preceding the onset of acute hepatitis.

FHF was diagnosed because of the presence of IgG and IgM anti-HEV in blood. Isolation and genotyping of HEV in samples took place at the moment of admission to the hospital and at the appearance of fulminant hepatitis. The sequence identified in this patient clustered into genotype 3, subtype 3f, following the classification by Lu and others.¹⁷ The strain located in the cluster was very close to the VH2 strain of human origin isolated in a patient suffering from acute hepatitis E in Spain, but it was not so close to swine strains. Therefore, it was unlike some human strains isolated from acute hepatitis E related with swine, like the strain 77HU isolated in Spain from a slaughterhouse worker with an acute hepatitis E.⁸ Genotype 3 HEV has been found all over the world and is prevalent in autochthonous hepatitis E in many developed countries in Europe, the United States, and Japan.¹¹ Some cases caused by this genotype 3 have been reported in humans and in pig populations in Spain.^{5,7,8}

HEV can present as an asymptomatic infection, acute hepatitis, chronic hepatitis in liver-transplant recipients,¹⁸ and severe or fulminant hepatitis E requiring liver transplant.¹⁹ In our patient, all risk factors for being infected by HEV were investigated, and the only risk factor she showed seemed to be the contraceptive medication taken for more than 20 years.

It is well known that the mortality rate can be as high as 41%¹³ in pregnant women. It has been confirmed that estrogens and gestagens in pregnancy can increase viral replication by a direct effect or by causing a decrease in cellular immunity because of a decrease in CD4 levels and an increase in CD8 levels.¹² Unfortunately, CD4 levels could not be measured because of insufficient volume of banked samples. Other studies have also shown that the increase of estrogens may produce a decrease in bone-marrow B-cell production, mainly pre-B and immature (fractions B-D) bone-marrow B-cells.²⁰ In the patient studied, serum levels of estrogens and progesterone were normal, because the measurements were performed 4 days after their suspension. Unfortunately, no blood sample was available from the time that the patient was taking the oral contraceptives, but interestingly, two hepatic adenomas were detected, which are liver-cell tumors related to the use of oral contraceptive medication and elevated estrogens levels in blood. The suspension of the contraceptive treatment could have influenced the favorable outcome of the FHF in this patient in contrast to the fatal outcome of acute hepatitis E in pregnant women. In conclusion, the severe outcome of this case indicates the relevance of testing for hepatitis E in all patients with unexplained FHF and specially, in women receiving gestagens and estrogens like contraceptive treatment, because these hormones may be a risk factor for developing FHF in case of suffering acute hepatitis E. We recommend investigating the use of contraceptives in all cases of HEV-infected non-pregnant women. If it is confirmed that the contraceptive treatment helps the development of FHF in VHE-infected women, vaccination of women on oral contraceptive is indicated when HEV vaccine is available. Unfortunately, FHF

during pregnancy in HEV-infected women in developing countries continues to be an unsolved mystery. The study of similar clinical cases in industrialized countries can contribute to discovering the reasons for the severity of this disease.

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