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CASE REPORT

Acute hepatitis E virus infection causing acute liver failure requiring living-donor liver transplantation in a non-pregnant immunocompetent woman

Wai Sum Li [1] and Kenneth Chok[2]

[1]Queen Mary Hospital, Hong Kong, China

[2]Department of Surgery, The University of Hong Kong, Hong Kong, China

Correspondence:

Wai Sum Li

Queen Mary Hospital

Hong Kong, China

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Email: irisli.irisli.irisli@gmail.com

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Abstract:

We report a rare case of acute liver failure from acute hepatitis E virus (HEV) in a non-pregnant woman without comorbidities who survived after liver transplantation. The source was likely consumption of partially cooked pig liver. HEV genotype 3 is the second most common genotype causing acute hepatitis E in developed countries. Fulminant hepatitis E rarely occurs without a risk factor, as in our patient. Vigilant monitoring for chronic hepatitis E in post-transplant immunocompromised patients is needed.

KEYWORDS:

acute liver failure, fulminant hepatitis, hepatitis E, liver transplant

1 INTRODUCTION

Hepatitis E virus (HEV) is a small, 27-34 nm in diameter, non-enveloped single-stranded RNA virus, and the only member of the genus *Orthohepevirus*, in the family Hepeviridae. The genome size is about 7.2-kilobases.[1,2] Human HEV belongs to the mammalian HEV

species, with one serotype but four phylogenetically distinct genotypes. Genotype 1 includes strains from Asia and Africa, and genotypes 3 and 4 include human and swine HEV strains from industrialized countries and Asia, especially China.[3,4]

Human HEV infection clinically causes acute hepatitis E, and chronic hepatitis E in immunocompromised patients. The transmission route is primarily fecal-oral, most commonly water-borne in highly endemic areas of the Indian subcontinent, China, Southeast and Central Asia, the Middle East, and northern and western parts of Africa, where outbreak and sporadic cases of hepatitis E have been related to HEV genotypes 1 or 2.[3-5] Zoonotic transmission of HEV genotypes 3 and 4 in low endemic areas from animal reservoirs was suggested based on detection of HEV genomic material in sera, feces, and liver meat from mammalian animals, especially pigs and deer, and the phylogenetically close relationship among HEV of animal and human cases. [3-5] Other reported transmission routes include blood-borne through contaminated blood and blood products, maternal-to-child vertical transmission, and direct contact with HEV-infected animals.[6]

2 CASE REPORT

A 46-year-old woman presented to a regional hospital of Hong Kong (HK) for 2-day epigastric pain, yellowish skin discoloration, tea-colored urine, and unremarkable medical, allergic, travel, and drug history. She had consumed partially cooked pig liver in congee within 2 weeks prior to admission. She did not smoke or drink.

Physical examination revealed temperature 37.4°C, jaundice, and hepatomegaly without stigmata of chronic liver disease or hemodynamic instability. Initial laboratory investigations are shown in Table 1. Empirical intravenous antibiotics were given as treatment for biliary sepsis.

She subsequently developed hepatic encephalopathy and flapping tremor. She was transferred to the intensive care unit of a tertiary hospital with the only liver transplantation (LT) center in HK, for management of acute liver failure (ALF) and LT workup (Tables 1 and 2). The ammonium and lactate peaked at 229 μmol/L and >24 mmol/L respectively. Ultrasonography and computed tomography of abdomen were unremarkable.

Her liver function test results deteriorated further (Table 2), and she underwent total hepatectomy and living-donor right lobe LT for life saving. Her serum was tested in the regional reference laboratory and was positive for anti-HEV immunoglobulin-G (IgG) (MP Diagnostics HEV IgG ELISA) and immunoglobulin-M (IgM) (MP Diagnostics HEV IgM ELISA), and reverse-transcription polymerase chain reaction targeting ORF2 region, and sequencing and phylogenetic analysis revealed HEV-genotype 3. Post LT, she received mycophenolate mofetil and tacrolimus, and her liver function tests gradually improved (Table 2).

3 DISCUSSION

This is the first case report, to our knowledge, of HEV genotype 3-associated ALF in an immunocompetent patient, successfully treated with living-donor LT in HK, where endemicity is low for HEV. Hepatitis E in immunocompetent patients is generally self-limiting, especially for those without risk factors for ALF including chronic drinking history, chronic liver disease, and pregnancy, and is managed supportively.[4,7] The likely source of her infection was consumption of partially cooked pig liver in congee. HEV genotypes 3 and 4 have been recovered from humans, pigs, and deer.[3,4] Genotype 3 is the second most common genotype for hepatitis E in HK, following genotype 4, which constitutes >94%.[3,4,7,8]

Our patient's obtunded mental state pre-LT was related to hepatic encephalopathy rather than neurological extrahepatic manifestation of hepatitis E (Table 3).[4] The reason for her ALF was not precisely known. Immune response, rather than viral damage to hepatocytes, was suggested clinically for her hepatitis E including ALF.[9] For host factors, her initial total lymphocyte count of 1300 cells/μL might predict CD4 lymphocyte count to 350 cells/μL.[10-12] This finding might be part of HEV clinical manifestation, as 7.5% of autochthonous hepatitis E patients had lymphopenia.[13] The peripheral lymphocytes recruitment to liver, with the characteristic lymphocytic inflammatory infiltration, predominantly CD8, CD3, and CD4 lymphocytes, in expanded portal tract in acute hepatitis E patients, might explain her peripheral lymphopenia.[6,14] Her subsequent elevated total lymphocyte count likely resulted from host cellular

immune response. The speculated expanded natural killer cell population may produce elevated levels of interferon-γ and contribute to hepatocyte death.[9] CD8 lymphocyte proportion was higher in deceased liver of HEV-associated ALF than other hepatotropic viruses.[9] Her human immunodeficiency virus (HIV) test was negative and profiles of immunoglobulin levels were within range, with no known immunodeficiency, and no information on human leukocyte antigen typing, which was a required workup for bone marrow transplantation, but not for LT, and without any conditioning therapy pre-LT.

For virus factors, patients infected with HEV genotype 3 or 4 with isolated synonymous substitution of U at nucleotide (nt) 3148 (U3148) in HEV RNA helicase domain or with co-occurrence of substitution of C at nt 5907 (C5907) within ORF2, were associated with ALF.[15,16] The lower value of lowest prothrombin activity was significantly lower, and total bilirubin and alanine aminotransferase (ALT) higher, in these patients.[15,16]

The lack of viral load (VL) quantitation and full genome sequencing in our patient are limitations of our report. This was technically limited by their unavailability at hospital service and reference laboratories. Our patient's initial calculated prothrombin activity (37.3%) [17] was even lower, while total bilirubin and ALT levels were even higher than those with U3148 ± C5907 in HEV.[15,16] Consistently, her prothrombin times were lower and her total bilirubin was higher than those resulting from HEV with nonsynonymous mutation identified in RNA-dependent RNA polymerase region causing an amino acid change from cysteine to tryptophan at position 1483 (C1483W), or

asparagine to threonine at 1530 (N1530T) respectively, which was significantly associated with abnormal prothrombin time, high VL, and mortality.[18]

Chronic HEV infections have developed in HEV-infected immunocompromised patients and were of genotype 3, in up to 60% in infected solid organ transplant recipients, less common in HIV or hematological malignancies patients,[4,19] and very low-risk in stem cell transplant recipients. [19] No HEV reactivation has occurred in our patient so far at 4 years post LT (at the time of this report submission). Unlike those reported who developed hepatitis E infection during post-transplant and/or with immunocompromised status, [4,20,21] our patient developed acute hepatitis E pre-LT, and had LT in 4 days. Even though HEV persists in human liver or in macrophages [19,21,22] or extrahepatic sites as in animal models, [21] her liver, with HEV in hepatocytes and Kupffer cells, had been removed by total hepatectomy, which reduced her HEV VL before receipt of donor liver and immunosuppression. Replication of HEV in peripheral blood mononuclear cells of infected patients was found to be unlikely.[19] Her post-LT immunosuppressant, mycophenolate mofetil, which is a prodrug of mycophenolic acid that in-vitro inhibits HEV replication, may be associated with HEV clearance,[21] despite the fact that tacrolimus concomitantly stimulates HEV replication in vitro, and was the main predictor for chronic hepatitis E in solid organ transplant recipients.[20-22]

Dose reduction of immunosuppressants remains the initial management of chronic hepatitis E in immunocompromised patients for clearance of HEV viremia, followed by antivirals for those non-responders with persistent viremia.[21,23] A 3-month

course of ribavirin (RBV) or pegylated interferon-α-2a, either monotherapy or in combination, has been reported as effective treatment for severe HEV infection in non-immunocompromised or immunocompromised patient.[21,23-27] In all, 78% of infected transplant recipients achieved sustained virological response after RBV monotherapy.[25-27] A second prolonged course was needed for treating recurrence of HEV viremia.[27] Sofosbuvir inhibits HEV genotype 3 replication in vitro, and with additive inhibitory effect when combined with RBV.[21,28] Further clinical studies are needed to investigate RBV and sofosbuvir combination for treating chronic hepatitis E and HEV superinfection in immunocompromised patients, and on different genotypes.

Further follow-up for surveillance and detection of chronic hepatitis E symptoms and signs, virologically and radiologically, are needed for prompt diagnosis of chronic hepatitis E in our patient status post LT. [4] The hospital laboratory should develop new tests to cope with patient service needs accordingly. Further research may answer the differential transmission mode and virulence among genotypes, and genetic relatedness between human and swine HEV.[3] This is an unusual autochthonous case of HEV genotype 3-associated ALF in an immunocompetent woman. LT is a life-saving option for patients with ALF caused by HEV who fulfill transplantation criteria.

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TABLE 1 Hematological and biochemical results of our patient with acute hepatitis E

	Admission to regional hospital	Reference range	Admission to tertiary hospital	Day of transplantation	1 month post transplantation	Day of hospital discharge	2 months post transplantation on follow up	Reference range
Complete blood picture								
White blood cells (WBC, $x10^9$/L)	7.8	3.7-9.3	25.85	28.87	8.58	6.33	5.27	3.89-9.93
Neutrophil ($x10^9$/L)	5.1	1.8-6.2	20.68	22.92	6.85	4.87	4.24	2.01-7.42
Lymphocyte (x 10^9/L)	1.3	1.0-3.2	2.33	5.06	0.77	0.75	0.57	1.06-3.61
Monocyte ($x10^9$/L)	0.9	0.2-0.7	1.29	2.97	0.65	0.51	0.35	0.18-0.65
Hemoglobin (Hb, g/dL)	10.3	11.5-15.4	8.7	5.6	8.9	8.8	9.6	11.5-14.8
Platelet (Plt, $x10^9$/L)	100	8.1-11.5	114	82	342	257	323	162-341
Clotting profile								
PT (sec)	18.3	10.1-12.4		37.8	19.1	18.7	12.9	
INR	1.6			3.3	1.8	1.7	1.2	
APTT (sec)	51.9	25.1-35.5		49.0	34.4	33.7	29.4	
Renal function								

test							
Sodium (mmol/L)	139	136-145	137	137	137	140	136-148
Potassium (K, mmol/L)	3.8	3.5-5.1	4.1	4.2	4.2	4.7	3.6-5.0
Urea (mmol/L)	4.2	<8.3	12.7	14.5	7.0	4.1	2.8-6.7
Creatinine (umol/L)	48	44-80	99	103	102	110	49-82
Ammonia (μmol/L)	ND	ND	139	229	<9	ND	<33
Liver function test							
Total protein (g/L)	61	64-83	75	77	62	61	67-87
Albumin (g/L)	29	35-52	26	30	32	30	39-50
Globulin (g/L)	32		49	47	30	31	26-40
Bilirubin, total (μmol/L)	331	<17	780	854	30	12	4-23
Alkaline phosphatase (U/L)	159	35-104	152	138	134	177	32-93
Alanine transaminase (U/L)	3306	<33	>3000	>3000	68	111	7-36
Aspartate transaminase (U/L)			>3000	>3000	40	56	14-30

ND, not done; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time.

TABLE 2 Results of investigation performed for acute liver failure and transplant workup in our patient.

Tests performed	**Results (reference range)**
HBsAg	Negative
Anti-HBs	<10
Anti-HBc (Total)	Negative
Hepatitis B DNA viral load	<10 IU/mL
Anti-HAV Ab (total)	Positive
Anti-HAV IgM	Negative
Anti-HEV (total)	Positive
Anti-HEV IgM	Positive
Anti-HIV-1	Negative
Antibody titer	
CMV IgG	Positive
EBV-VCA polyvalent	640
HSV	Anti-complementary reaction
Hantavirus polyvalent	<40
Widal test (TO, TH, AH, BH, CH)	< 1:50
Leptospira IgM	Negative
Bacterial culture	
Blood, sputum & urine	No growth
Immunoglobulin levels	
IgG	21.80 (7.00-16.00) g/L
IgA	5.15 (0.70-4.00) g/L
IgM	2.82 (0.40- 2.30) g/L

Autoimmune markers	
C3	46 (76-150) mg/dL
C4	14 (9-35) mg/dL
ANA titer	Negative
Anti-ENA screen	Negative
Anti-smooth muscle Ab	Negative
Anti-mitochondrial Ab	Negative
Tumor markers	
Alpha-fetoprotein	1.0 (≤ 5.8) IU/mL
CA19-9	8.2 (<37) U/mL
Carcinoembroyonic antigen	1.1 (<5) ng/mL
CA15.3	20 (<23) U/mL
Copper	16 (11.0-25.0) µmol/L
Ceruloplasmin	0.47 (0.19-0.40) g/L

HBsAg, hepatitis B surface antigen; HBs, hepatitis B surface; HBc, hepatitis B core; HAV Ab, hepatitis A virus antibody; IgM, immunoglobulin M; HEV, hepatitis E virus; HIV, human immunodeficiency virus; CMV, cytomegalovirus; IgG, immunoglobulin G; EBV-VCA, Epstein-Barr virus viral capsid antigen; HSV, herpes simplex virus; IgA, immunoglobulin A; ANA, anti-nuclear antibody; ENA, extractable nuclear antigens.

TABLE 3 Extrahepatic manifestations of hepatitis E

Acute pancreatitis
Hematological manifestations
Thrombocytopenia
Hemolysis
Hemolysis secondary to G6PD deficiency
Immune hemolysis
Autoimmune phenomena
Membranous glomerulonephritis
Henoch-Schönlein purpura
Neurological syndromes
Guillian-Barré syndrome
Meningoencephalitis
Pseudotumor cerebri
Nerve palsies: oculomotor nerve, facial nerve
Bilateral pyramidal syndrome
Peripheral neuropathy