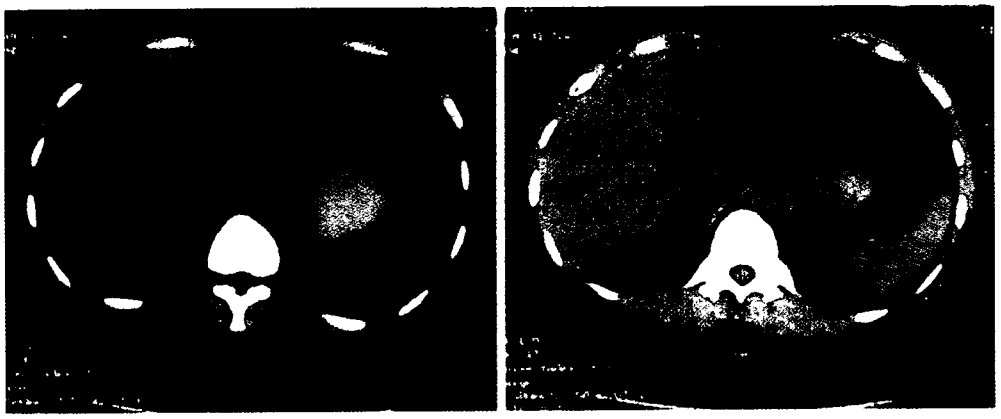

Figure 1. 入院時腹部CT：肝容積は1027m*l*で萎縮を認めない．腹水，脾腫など認めず．

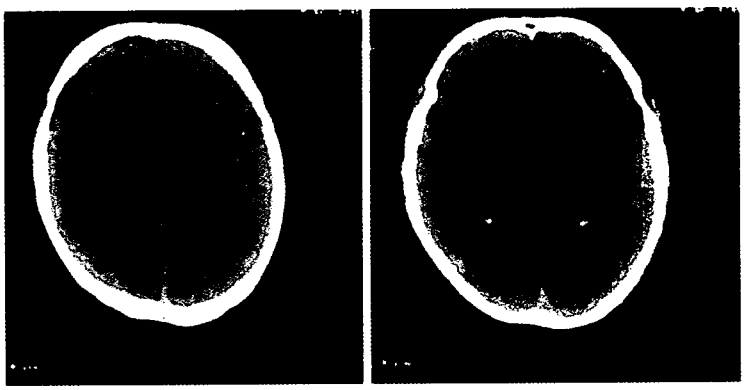

Figure 2. 脳症発症時頭部CT：脳浮腫の所見．占拠性病変は認めない．

III も42%と低下していた．生化学検査では，TB 12.7mg/d*l*，DB 9.1mg/d*l*（D/T比0.72）と直接型優位の黄疸を認め，AST 1307IU/*l*，ALT 3489 IU/*l*，γ-GTP 324IU/*l*とそれぞれ上昇していた．アンモニア値は正常範囲内であった．

血清学的検査（ELISA法）にてHEV-IgM抗体143（30以上陽性），HEV-IgG抗体124（13以上陽性）とそれぞれ陽性であり，その他の肝炎ウイルスマーカーが陰性であったことより，急性E型肝炎が疑われた．SRLによるHEV-RNA（RT-PCR）は陰性であったが，後日保存血清にて東芝病院研究部の三代先生にE型肝炎PCR検査[2)3)]を測定していただいた結果，中国型のGenotype IV型（JKS2-Tok04）が検出された．

また岩手医大第一内科および厚生労働省登録システムによる急性肝炎重症型劇症化予測式[2)]に基づき計算した入院時予測劇症化確率は37.4%であった．

腹部CT（Figure 1）：肝の萎縮，腹水，脾腫は認めず，volumeは1027m*l*であった．

頭部CT（Figure 2）：脳浮腫は認めなかった．

脳波：軽度の徐波化を認めるも，明らかな3相波は認めなかった．

臨床経過（Figure 3）：

転院時意識は清明であったが，PT%は18%と更に低下し，新鮮凍結血漿10単位を輸血した．翌日にはNH_3 115μmol/*l*と上昇したため，経過より劇症化が予想され，同日より血漿交換（PE）と持続的血液濾過透析（CHDF）を開始した．第3病日に意識混濁，羽ばたき振戦が出現，肝性昏睡

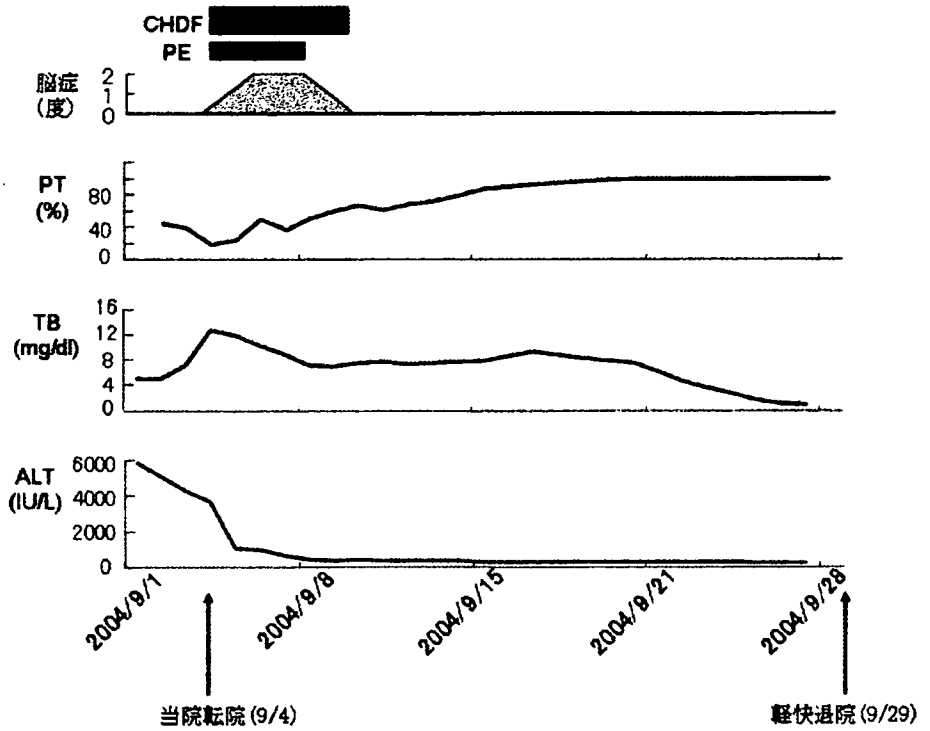

Figure 3. 臨床経過. PE：plasma exchange CHDF：continuous hemodiafiltration

II度と判定し劇症肝炎と診断した．なお，急性肝不全研究会による肝移植適応ガイドライン[4)5)]では，初回判定生存であり，人工肝補助による加療を継続した．PE，CHDF施行5日目には意識清明となり，羽ばたき振戦も消失した．人工肝補助療法としてPE計3回，CHDF計6回を行い，その後黄疸はやや遷延したものの，第31病日には，肝機能（TB 0.7mg/dl，AST 15IU/l，ALT 20IU/l，PT% 100%）は正常化し軽快退院した．退院後も自覚症状，肝炎の再燃は認めていない．

II 考 察

E型肝炎は経口感染で，潜伏期間は2～9週（平均6週）といわれ，東南アジア，赤道周辺，中南米などで多く発生し，最近人蓄共通感染症（zoonosis）であると考えられている[6)～10)]．初発症状は発熱，倦怠感，嘔気などで，家族内感染はA型肝炎と比べ低い．発症年齢は15～40歳前後で，一般に慢性化せず，死亡率は0.07～0.6%といわれている[10)]．GenotypeはI～IVに分かれ，Iは主にアジア・アフリカ型，IIはメキシコ型，IIIは欧米型で，IVは主に中国，台湾型である[11)12)]．また大部分が予後良好であるが，まれに劇症化（特に妊婦での感染[13)]）し予後不良となる．

本症例では現病歴，既往歴，家族歴，各種検査で遺伝性肝疾患，薬剤性，自己免疫性肝炎は否定的で，A，B，C型肝炎ウイルスマーカーは陰性であり，その他のウイルスマーカーも陰性であった．食物の同定はできていないが，頻繁な中国への渡航歴とgenotypeより中国渡航時にE型肝炎ウイルスに感染したものと考えられた．肝胆道系酵素は他院入院時がピークで，転院後は軽快傾向となった．入院時意識清明で予測劇症化確率は37%であったが，PT%が著明に低下したため人工肝補助療法を積極的に導入した．開始翌日に意識レベルが低下，羽ばたき振戦が出現して劇症肝炎と診断し，人工肝補助を継続し開始5日後には覚醒し，救命し得た．

本邦におけるE型劇症肝炎の報告例は，医学

Table 3. 本邦におけるE型劇症肝炎の報告例

症例	年齢/性	発症場所	海外渡航歴	人工肝補助	遺伝子型	転帰
1	61 M	岩手	なし	施行	III	死亡
2	60 M	岩手	なし	施行	IV	死亡
3	66 M	茨城	なし	不明	IV	死亡
4	34 F	北海道	なし	施行	III	移植後死亡
5	64 M	北海道	なし	施行	IV	死亡
6	58 M	北海道	なし	施行	IV	死亡
7	51 M	北海道	なし	施行	IV	生存
8	70 M	不明	なし	不明	IV	死亡
9	69 M	北海道	なし	不明	IV	死亡
10	34 M	千葉	不明	施行	不明	死亡
11	40 M	中国山東省	中国	施行	IV	生存

文献6)14)～21) 症例11は自験例

中央雑誌での検索にて12年間で15例の報告のみで非常にまれであり，そのうち自験例を含め詳細が明らかな11例をまとめた（Table 3）[6)14)~21)]．E型肝炎は妊婦で重篤化するといわれているが，わが国における報告例は中高年の男性が多く，女性は1例で妊婦症例は認めなかった．発症地域は北東日本が多いが，北日本ではブタ肝臓の生食習慣もあり関連が示唆される[21)]．また本邦での劇症化報告例は海外渡航歴のない国内型のみで，自験例のような海外で感染した症例においては，帰国後劇症化し加療した例の報告はなかった[21)~26)]．遺伝子型はgenotype IVが多く，自験例もgenotype IVであったが，重症化との関連性を示唆する報告もある[27)]．検索可能であった症例では全例人工肝補助療法を施行されているが，自験例を含め生存例は2例であり，劇症化すると予後不良である．E型肝炎と診断されるには，まず他の原因を鑑別した上で，改めて検査を提出し，その結果が出るまでも時間を要することから，治療開始時期などが後手に回る可能性があると思われる．自験例においては，当院転院時点では原因不明であったが，経過より脳症発現前日という比較的早い時期より人工肝補助療法を含めた集学的治療を開始した．このことが，脳症の進行などを抑え，比較的良好に全身状態を保ち救命に寄与したと思われる．

わが国の急性肝炎の30%は原因不明であるとされ，重症，劇症肝炎症例でも全体の約30%が原因不明である．熊谷ら[28)]の施設では，原因不明の急性肝炎の16%でHEV-RNAが陽性であった．また10年間の22例の非A～C型劇症肝炎症例中，保存血清のあった19例についてHEV-RNAを測定したところ，2例が陽性であり，これは同施設の劇症肝炎全体の6%になると報告した．これらのことより原因不明の重症，劇症肝炎症例では，E型肝炎を積極的に疑い，詳細な病歴とともに血清学的検査を施行することが望ましい．E型肝炎に対する特異的な治療は現時点ではなく，劇症化の際にはその他の原因による劇症肝炎の治療に準じて人工肝補助療法を施行するべきである．血清学的検査による確定診断には時間を要するのが現状であり，E型肝炎を疑い重症化さらに劇症化の兆候が見られる際には，検査結果が出る以前であっても，予測し早期からの人工肝補助療法の導入を検討すべきであると思われた．

結　語

海外渡航時のE型肝炎ウイルス感染による劇症肝炎の1例を経験した．本症例では，予測劇症化確率は高値ではなかったものの，経過から脳症発症前より積極的に人工肝補助療法を導入したことより救命し得たと考えられ，貴重な症例であり若干の文献的考察を加えて報告した．

なお，本論文の要旨は第31回日本急性肝不全研究会に

て報告した.

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A case of fulminant hepatitis E treated with artificial liver support

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A 40-year-old man, who had suffered from general malaise and brown urine during his stay in China, was addmitted with remarkable jaundice and hepatocellular disorders soon after he returned to Japan. Because his coagulation test results worsened, he was transferred to our hospital. No evidence of hepatitis A-D virus infection, autoimmune hepatitis, or metabolic disorders was noticed. His prothrombin time was extended (18%), grade II encephalopathy appeared on the second hospital day, and fulminant hepatitis was diagnosed. Artificial liver support was introduced, and his hepatic coma and coagulation parameters gradually recovered. Genotype IV hepatitis E virus RNA was detected in his early phase sera and also both IgG and IgM type anti-hepatitis E virus antibodies were detected. Fulminant hepatitis E resulting from infection in China was diagnosed.

V. 参考

NEJM の 2008 年 2 月號に掲載された
衝撃の「慢性 E 型肝炎」！
(Brief Report と Correspondence)

BRIEF REPORT

Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

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SUMMARY

Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD3, and CD4 T cells were significantly lower in patients in whom chronic disease developed.

ACUTE HEPATITIS CAUSED BY THE HEPATITIS E VIRUS (HEV) IS ENDEMIC IN developing countries and appears to be an emerging disease in industrialized countries.[1,2] Seroprevalence studies have reported anti-HEV IgG antibodies in 6 to 16% of renal-transplant recipients.[3,4] This hepatotropic RNA virus is often not fully considered or routinely sought in cases of acute hepatitis in recipients of solid-organ transplants. Only three cases of acute HEV infection have been reported in organ-transplant recipients.[5-7] Even though two cases of persistent HEV infection have been reported,[8,9] HEV is considered an agent responsible for acute hepatitis that does not become chronic.[10]

We report here 14 cases of acute hepatitis E infection in organ-transplant recipients. We suggest that HEV infection may evolve to chronic hepatitis in immunocompromised patients.

PATIENTS AND METHODS

Between January 1, 2004, and December 31, 2006, all recipients of liver, kidney, or kidney and pancreas transplants attending our outpatient and inpatient clinics who presented with unexplained short-term elevations of liver-enzyme levels were screened for HEV infection by serologic and molecular tools. Patients chronically infected with hepatitis B, C, or D viruses were excluded from the study. Biliary-tract complications were ruled out by abdominal ultrasonography. Toxin- and drug-related causes of abnormal liver-function test results were ruled out by patient history. Fourteen of 217 patients (6.5%) tested positive for serum HEV RNA.

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Anti-HEV status was determined by an enzyme immunoassay (HEV EIA, Abbott). HEV RNA in serum and stool was detected by real-time polymerase-chain-reaction (PCR) amplification (TaqMan, Applied Biosystems) of a 189-bp product located in the ORF2 region.[11] Strains were sequenced and compared with reference HEV strains (GenBank). The grades and stages of chronic hepatitis were assessed according to the Metavir classification.[12]

Proportions were compared by the chi-square test or Fisher's exact test. Quantitative variables were compared by the nonparametric Mann–Whitney, Friedman, and Wilcoxon tests. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

PREVALENCE OF ANTI-HEV IgG

All patients who received a kidney transplant (241 recipients) or a liver transplant (86 recipients) between January 1, 2004, and December 31, 2006, in the department of nephrology, dialysis, and multiorgan transplantation were screened for HEV infection at the time of transplantation. The prevalence of anti-HEV IgG was 13.5% for all recipients, 14.5% for kidney recipients, and 10.4% for liver recipients.

CLINICAL AND BIOLOGIC PRESENTATION

We identified 14 patients with a solid-organ transplant (3 liver recipients, 9 kidney recipients, and

Table 1. Demographic Features of Transplant Recipients at Diagnosis of Acute HEV Infection.*

Patient No.	Organ Transplanted	HEV Infection†	Donor‡	Years of Age	Sex	Mo since Transplantation	Initial Organ Disease	Induction Therapy	Immunosuppressive Therapy
1	Liver	Chronic	Cadaver	57	M	6	Alcoholic cirrhosis	None	Tacrolimus/mycophenolate mofetil/steroid
2	Liver	Chronic	Cadaver	67	M	53	Alcoholic cirrhosis	Basiliximab	Tacrolimus/mycophenolate mofetil/steroid
3	Liver	Chronic	Cadaver	28	F	10	Wilson's disease	None	Tacrolimus/mycophenolate mofetil/steroid
4	Kidney	Chronic	Cadaver	49	M	10	Thrombotic microangiopathy	Basiliximab	Mycophenolate mofetil/steroid
5	Kidney	Resolving	Cadaver	34	M	90	Malformative uropathy	Rabbit antithymocyte globulins	Everolimus/mycophenolate mofetil/steroid
6	Kidney	Resolving	Living	33	M	57	Interstitial nephropathy	Basiliximab	Sirolimus/mycophenolate sodium/steroid
7	Kidney	Chronic	Cadaver	52	M	63	IgA nephropathy	None	Sirolimus/steroid
8	Kidney	Resolving	Cadaver	42	M	168	Crescentic glomerulonephritis	Rabbit antithymocyte globulins	Cyclosporin A/mycophenolate mofetil
9	Kidney	Chronic	Cadaver	30	M	48	Alport's disease	Rabbit antithymocyte globulins	Sirolimus/steroid
10	Kidney	Resolving	Cadaver	51	M	67	Interstitial nephropathy	Rabbit antithymocyte globulins	Cyclosporin A/mycophenolate mofetil/steroid
11	Kidney	Resolving	Cadaver	62	F	108	Chronic glomerulonephritis	Rabbit antithymocyte globulins	Cyclosporin A/steroid
12	Kidney	Resolving	Cadaver	28	M	25	IgA nephropathy	Rabbit antithymocyte globulins	Tacrolimus/mycophenolate mofetil/steroid
13	Kidney and pancreas	Chronic	Cadaver	55	F	60	Diabetes mellitus	Rabbit antithymocyte globulins	Tacrolimus/azathioprine/steroid
14	Kidney and pancreas	Chronic	Cadaver	58	M	27	Diabetes mellitus	Rabbit antithymocyte globulins	Tacrolimus/mycophenolate mofetil

* All patients were born in France. HEV denotes hepatitis E virus.
† Resolving indicates clearance of HEV RNA from serum and stools, and chronic indicates persisting elevated liver-enzyme levels and detectable RNA in the serum or stools at least 6 months after the acute phase.
‡ Cadaveric donors had a heartbeat.

2 kidney and pancreas recipients) in whom acute HEV infection developed (Table 1). The acute hepatitis episode was asymptomatic in 7 of the 14 patients; these 7 patients were tested for HEV after liver-enzyme abnormalities were detected during routine biologic examinations that are performed every 3 to 4 months after organ transplantation. The seven other patients presented with fatigue, diffuse arthralgias, and myalgias that had evolved over a period of 1 to 2 weeks. One of the symptomatic patients also had marked weight loss (approximately 8 kg [18 lb] during the month before the presenting symptoms appeared) and was icteric. The symptoms disappeared within 2 weeks after diagnosis. No abnormalities were detected during physical examination of any other patient. No patients were febrile, and none had traveled outside France during the year before their hepatitis episode. Only two patients reported having been in contact with animals: one patient with chickens and rabbits and the other with birds. No patients had had an acute rejection episode after undergoing transplantation. Immunosuppressive therapy had remained unchanged in all patients for at least 6 months before their acute episode. Liver-enzyme levels were significantly higher than the levels 3 to 4 months before the diagnosis of HEV infection (Table 2).

DIAGNOSIS OF HEV INFECTION

At admission, classic causes of hepatitis were ruled out (Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). The ferritin level was 567 ng per milliliter (range, 110 to 2007; normal range, 30 to 380), and the ceruloplasmin level was 0.35 ng per milliliter (range, 0.24 to 0.47; normal range, 0.20 to 0.45). At diagnosis, HEV RNA was detected in the serum of all patients and in the stool of the three patients whose stool was examined. PCR-amplification products of the serum HEV of 12 patients were sequenced and analyzed. Phylogenetic analysis revealed that all the strains belonged to genotype 3 (GenBank accession numbers, EU220992 to EU221003) (Fig. 1 of the Supplementary Appendix). We tried but failed to sequence the strains of the remaining two patients. No correlation was found between HEV RNA concentration and either liver-enzyme levels or liver-activity scores at diagnosis.

LIVER HISTOLOGIC FINDINGS DURING THE ACUTE PHASE

In the acute phase, 9 of the 14 patients underwent a liver biopsy to evaluate the severity of the acute episode of hepatitis; the remaining 5 patients declined biopsy. In liver-transplant recipients, liver biopsy also was performed to detect acute rejection. The mean (±SD) Metavir activity and fibrosis scores were 1.3±1.0 and 0.9±0.6, respectively (for assessment of disease activity, a Metavir score of 0 indicates no activity, 1 mild activity, 2 moderate activity, and 3 severe activity; for assessment of fibrosis, a Metavir score of 0 indicates no fibrosis, 1 portal fibrosis without septa, 2 a few septa, 3 numerous septa without cirrhosis, and 4 cirrhosis). The dominant lesions were lobular, with inflammation but no ballooning, and with spotty necrosis that included acidophilic bodies. The portal tract was mildly or moderately expanded and included an inflammatory infiltrate composed mainly of lymphocytes. Mild piecemeal necrosis was observed in six patients.

COURSE OF HEV INFECTION

Immunosuppressive therapy and target immunosuppressive trough levels were not modified after the diagnosis of HEV infection (data not shown). HEV infection resolved in six patients (43%); serum and stool HEV RNA in these patients became undetectable within 6 months after diagnosis and remained undetectable until the last follow-up at a mean of 12 months (range, 5 to 36) (Table 2). However, in the eight other patients (57%), HEV infection evolved to chronic hepatitis, as indicated by persistently elevated liver-enzyme levels and detectable HEV RNA in the serum or stool for a mean of 15 months (range, 10 to 24) after the acute phase.

Among the patients with resolving HEV infection, the levels of aspartate aminotransferase and alanine aminotransferase returned to preinfection values within 1 month (five patients) or 3 months (one patient) after diagnosis. The levels of γ-glutamyltransferase and alkaline phosphate returned to baseline levels within 3 months after diagnosis. Among those with chronic HEV infection, liver-enzyme levels remained above the upper limit of normal at the last follow-up. In both groups, the total bilirubin levels rapidly returned to preinfection levels. In both groups, hematologic and re-

Table 2. Liver Function in Patients with HEV Infection.

Patient No.	Time of Measurement	Alanine Aminotransferase*	Aspartate Aminotransferase†	γ-Glutamyl-transferase‡	Bilirubin§	Liver Biopsy	
						Metavir activity score¶	*Metavir fibrosis score*‖
			units/liter		*mg/dl*		
1	Baseline	10	16	18	584		
	Diagnosis	69	37	40	584	0	1
	15-Mo follow-up	59	41	30	409	3	2
2**	Baseline	102	95	1164	584		
	Diagnosis	248	229	3482	2339		
	16-Mo follow-up	59	54	173	701	1	3
3	Baseline	49	23	35	584		
	Diagnosis	169	76	76	994	1	1
	17-Mo follow-up	85	47	35	701	1	1
4	Baseline	26	12	19	701		
	Diagnosis	166	47	167	760	1	1
	15-Mo follow-up	135	57	146	760	3	1
5	Baseline	41	26	73	584		
	Diagnosis	66	47	118	526	0	1
	5-Mo follow-up	52	35	148	584		
6	Baseline	26	25	26	608		
	Diagnosis	245	104	118	468		
	12-Mo follow-up	30	32	18	584		
7	Baseline	26	18	55	397		
	Diagnosis	874	436	669	701	1	0
	10-Mo follow-up	158	89	156	584		
8	Baseline	32	24	32	1286		
	Diagnosis	770	340	373	2514		
	36-Mo follow-up	22	22	19	1169		
9	Baseline	42	39	26	584		
	Diagnosis	310	160	92	643	2	2
	24-Mo follow-up	90	39	42	760	2	2
10	Baseline	37	30	26	584		
	Diagnosis	518	235	459	1286		
	36-Mo follow-up	28	27	109	1286		
11	Baseline	23	18	42	351		
	Diagnosis	255	154	1055	3041	3	1
	12-Mo follow-up	13	7	80	351		
12	Baseline	12	14	19	368		
	Diagnosis	298	71	216	818	2	1
	5-Mo follow-up	15	24	51	877		
13	Baseline	13	22	8	643		
	Diagnosis	156	115	47	935	2	0
	15-Mo follow-up	298	238	79	760		

Table 2. (Continued.)

Patient No.	Time of Measurement	Alanine Aminotransferase*	Aspartate Aminotransferase†	γ-Glutamyl-transferase‡	Bilirubin§	Liver Biopsy	
						Metavir activity score¶	*Metavir fibrosis score*‖
			units/liter		*mg/dl*		
14	Baseline	14	23	30	1169		
	Diagnosis	143	106	132	877		
	13-Mo follow-up	126	118	585	994	1	3
Median							
	Baseline	26	23	32	584		
	Diagnosis††	248	115	167	818		
	Follow-up‡‡	59	40	79.5	731		

* Normal values for alanine aminotransferase range from 5 to 34 units per liter.
† Normal values for aspartate aminotransferase range from 3 to 30 units per liter.
‡ Normal values for γ-glutamyltransferase range from 7 to 38 units per liter.
§ To convert values for bilirubin to micromoles per liter, multiply by 17.1. Normal values range from 2 to 21 mg per deciliter.
¶ For assessment of disease activity, a Metavir score of 0 indicates no activity, 1 mild activity, 2 moderate activity, and 3 severe activity.
‖ For assessment of fibrosis, a Metavir score of 0 indicates no fibrosis, 1 portal fibrosis without septa, 2 a few septa, 3 numerous septa without cirrhosis, and 4 cirrhosis.
** Patient 2 had substantial alcohol consumption before the acute phase.
†† The differences between values at baseline and at diagnosis are significant for alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase ($P=0.001$) and for bilirubin ($P=0.02$).
‡‡ The differences between values at diagnosis and at last follow-up (median, 15 months) are significant for alanine aminotransferase ($P=0.003$), aspartate aminotransferase ($P=0.02$), and γ-glutamyltransferase ($P=0.03$).

nal measurements remained unchanged during the follow-up as compared with preinfection levels (data not shown). HEV seroconversion was observed in four patients with resolving HEV infection (two at 1 month and one each at 3 and 6 months after diagnosis) and seven patients with chronic infection (one at 3 months, two at 6 months, two at 12 months, and one each at 13 and 15 months after diagnosis).

Only six of the eight patients with chronic infection underwent a second liver biopsy (one at 10 months, two at 12 months, and one each at 13, 15, and 18 months after the diagnosis of acute HEV infection). The two remaining patients declined liver biopsy. The mean Metavir activity and fibrosis scores of the six patients who underwent biopsy were 2.0±1.0 and 1.8±0.8, respectively. All biopsy specimens showed features of chronic viral hepatitis, characterized by fibrosis and portal hepatitis, with dense lymphocytic infiltrate and variable degrees of piecemeal necrosis. Lobular hepatitis was mild to moderate in all cases. In the four patients who underwent a liver biopsy during both the acute phase and the chronic phase, the Metavir activity scores progressed from 1.0±0.8 to 2.2±0.9 and the fibrosis scores from 1.2±0.5 to 1.5±0.5.

RESOLVING VERSUS CHRONIC HEV INFECTION

During the acute phase, there were no significant differences between the patients with resolving HEV infection and those with chronic infection in median serum HEV RNA concentrations (5.97 $\log_{10}$ copies of RNA per milliliter [range, 5.79 to 6.44] and 6.18 $\log_{10}$ copies per milliliter [range, 4.92 to 7.28], respectively). There also were no significant differences between the groups in peak liver-enzyme levels. Hepatitis developed later after transplantation in patients with resolving HEV infection than in those in whom the infection progressed. Patients in whom chronic hepatitis developed had significantly lower serum creatinine levels at baseline and significantly lower counts of leukocytes, total lymphocytes, platelets, and CD2, CD3, and CD4 lymphocytes (Table 3). The percentages of patients who received induction therapy at transplantation or who received calcineurin inhibitors, mycophenolate mofetil or sodium, or inhibitors of the mammalian target of rapamycin (mTOR) were similar in the two groups. The dosage and trough levels of immunosuppressive drugs, as well as the proportions of patients with anti–hepatitis A virus, anticytomegalovirus, or IgG antibodies to Epstein–Barr virus, were similar in the two groups (data not shown).

Table 3. Patients with Resolving HEV Infection and Those in Whom the Infection Evolved to Chronic Hepatitis.

Variable	Patients with Resolving Infection (N=6)	Patients with Chronic Infection (N=8)	P Value
	median (range)		
At diagnosis			
Time since transplantation — mo	78.5 (25–168)	37.5 (6.0–63.0)	0.03
Leukocyte count — $\times 10^{-3}/mm^3$	8.85 (6–9.66)	4.31 (2.19–7.20)	0.004
Lymphocyte count — $\times 10^{-3}/mm^3$			
Total	1.73 (1.12–2.33)	0.75 (0.63–1.04)	0.004
CD2+	1.59 (0.84–2.25)	0.66 (0.58–0.92)	<0.001
CD3+	1.54 (0.70–1.88)	0.61 (0.49–0.79)	0.01
CD4+	0.93 (0.49–1.07)	0.22 (0.16–0.40)	0.004
Platelet count — $\times 10^{-3}/mm^3$	261 (190–285)	155.5 (75.0–250.0)	0.01
Serum creatinine — mg/dl*	2.15 (1.31–2.84)	1.33 (1.08–1.89)	0.01
At last follow-up			
Aspartate aminotransferase — IU/liter	25.5 (7–35)	55.5 (39.0–238.0)	0.002
Alanine aminotransferase — IU/liter	25 (13–45)	108.0 (59.0–298.0)	0.002

* To convert values for creatinine to micromoles per liter, multiply by 88.4.

DISCUSSION

HEV infection is transmitted by the fecal–oral route and may be a zoonosis in industrialized countries. It has a mortality rate of about 1% in the general population and 30% in pregnant women.[13] HEV-induced acute hepatitis may be fulminant,[14] but we are not aware that any cases of chronic hepatitis have previously been reported. Recently, the diagnosis of many cases of acute HEV hepatitis in nonimmunocompromised patients in southwest France[15] prompted us to look systematically for HEV in recipients of solid-organ transplants who had unexplained hepatitis. Of the 14 patients with acute HEV infection whom we report on here, 8 underwent progression to chronic hepatitis. In addition, in this issue of the *Journal*, Gérolami et al. report a case of HEV-related cirrhosis in a kidney-transplant recipient.[16]

After all other causes of hepatitis had been ruled out, the serum of 14 patients, none of whom had traveled outside France in the previous year, was found to be positive for HEV RNA. We did not identify any source of contamination. The peak aminotransferase levels were lower than in nonimmunocompromised patients.[17,18] Histologic lesions (mainly spotty lobular necrosis) that are characteristic of classic acute viral hepatitis were seen; these lesions were less severe than those typically seen in nonimmunocompromised patients. These findings could be related to the immunosuppressive therapy in transplant recipients.

HEV infection resolved in 6 of the 14 patients within 6 months after the end of the acute phase. In contrast, HEV infection in eight patients evolved to chronic hepatitis, as indicated by persistently elevated liver-enzyme levels and detectable serum HEV RNA at a median of 15 months (range, 10 to 24) after the end of the acute phase. Liver biopsies performed at a median of 12.5 months (range, 10 to 18) after the acute phase revealed signs of chronic viral hepatitis. The histologic lesions — dense lymphocytic portal infiltrate with constant piecemeal necrosis — were similar to those observed in patients chronically infected with hepatitis C virus. None of the patients received any specific therapy; in particular, none received antiviral therapy. Immunosuppressive therapy was not modified after the diagnosis of HEV. In the absence of available therapeutic recommendations for patients infected with HEV, we only performed close monitoring of liver-enzyme levels.

There were no significant differences between patients with resolving HEV infection and those with chronic HEV infection in demographic or clinical features, including treatment with immunosuppressive agents before the acute phase. However, the immunologic status of the patients may have had a role in the evolution to chronic dis-

ease. In patients in whom the infection became chronic, the time from transplantation to the development of infection was significantly shorter — and consequently, the total lymphocyte counts and the CD2, CD3, and CD4 lymphocyte counts were significantly lower — than in patients in whom HEV infection resolved. Hence, the T-cell response seems to have a role in HEV clearance, as does the B-cell response.

HEV seroconversion occurred later in patients with chronic infection than in those with resolving infection. This difference may be related to the reduction in the humoral immune response caused by treatment with mycophenolate, inhibitors of mTOR, or both. These drugs are known to decrease the synthesis of antibodies[19,20] and to inhibit the cell-cycle progression and differentiation of human B lymphocytes.[21] The humoral immune response is necessary to clear HEV and to prevent hepatitis. Bryan et al. have shown that antibodies to the HEV capsid can be protective against hepatitis E.[22] Passive immunoprophylaxis studies in cynomolgus monkeys have confirmed that the antibody to the HEV capsid may prevent HEV infection in humans.[23] Recently an HEV recombinant protein vaccine was found to be effective in preventing HEV infection.[24]

Further studies are required to determine the incidence of chronic HEV infection in transplant recipients who live in areas where the disease is not endemic. Vaccination against HEV could be proposed to patients before or after organ transplantation. However, the efficacy of vaccination in these populations should be addressed.

In conclusion, our data suggest that HEV should be considered an etiologic agent of hepatitis in organ-transplant recipients. We have demonstrated that HEV infection can evolve to chronic hepatitis, at least in organ-transplant recipients. A longer follow-up is required to assess the outcome of HEV infection in organ-transplant recipients.

No potential conflict of interest relevant to this article was reported.

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Chronic Hepatitis E with Cirrhosis in a Kidney-Transplant Recipient

TO THE EDITOR: Hepatitis E virus (HEV) is an important cause of acute viral hepatitis worldwide.[1] Kamar et al. in this issue of the *Journal*[2] and others[3,4] have recently suggested that HEV infection might result in chronic hepatitis in immunocompromised patients. We report a rapidly progressing case of cirrhosis in a renal-transplant recipient with chronic HEV infection.

A 52-year-old man who had undergone kidney transplantation in March 2005 presented with increased aminotransferase levels in June 2006. Four months later, the alanine aminotransferase level reached 126 U per liter and thereafter plateaued at three times the upper limit of the normal range. Serologic testing for hepatitis C virus (HCV) and HCV RNA had been

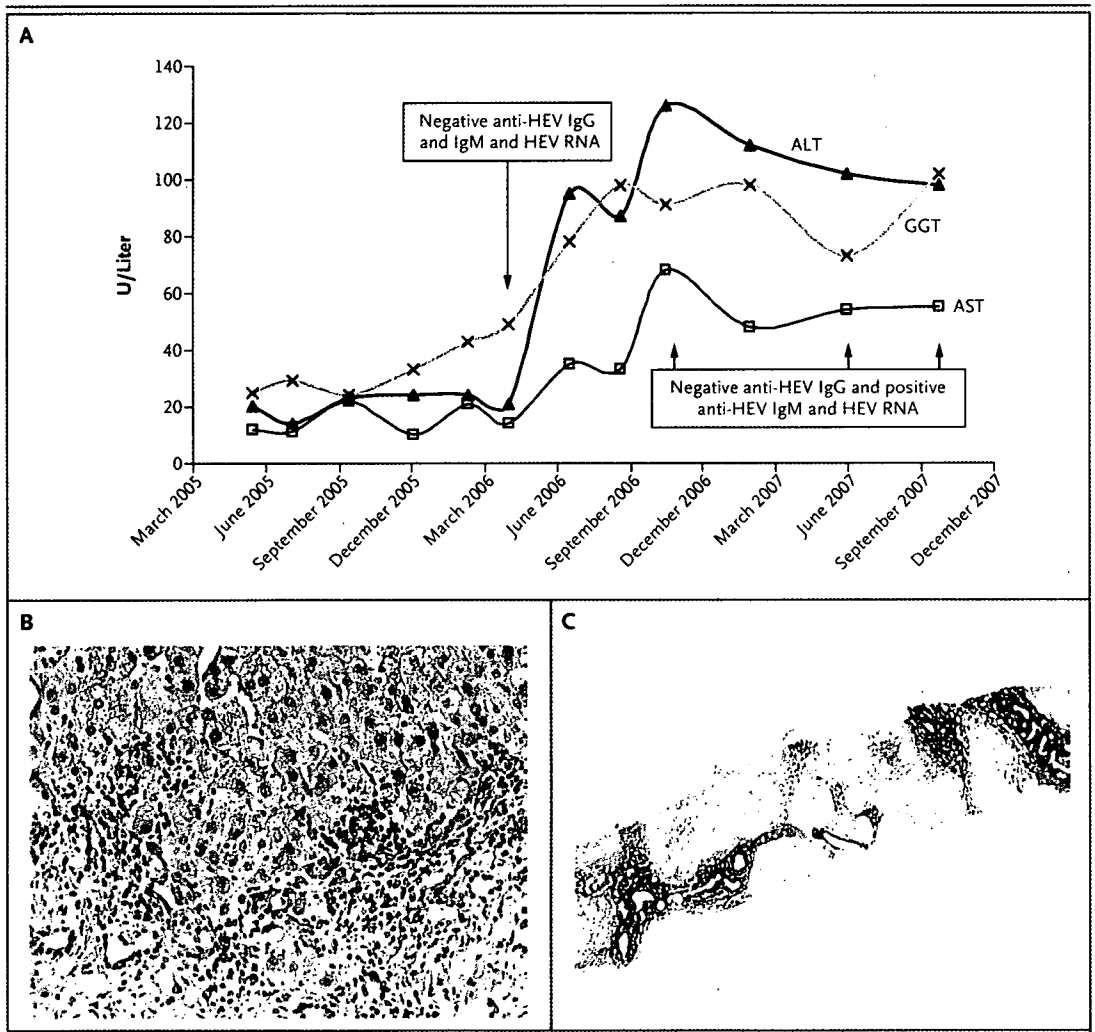

Figure 1. Results of Virologic Analysis and Liver Biopsy in a Patient with Chronic Hepatitis E Virus Infection.

Panel A shows changes in liver biologic markers alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) and virologic measures of HEV RNA and IgG and IgM anti-HEV antibodies in serum. HEV RNA titers remained stable from November 2006 to September 2007, and tests for IgG anti-HEV antibodies remained negative during the entire follow-up period. Panel B shows a liver-biopsy specimen, obtained in September 2007, with an inflamed portal tract and mononuclear cells extending beyond the limiting plate and surrounding individual or small clusters of hepatocytes (hematoxylin and eosin). Panel C shows Sirius red staining of collagen, indicating cirrhosis, with an advanced fibrosing phenomenon isolating parenchymal nodules.

negative at the time of transplantation and during follow-up. The results of serologic testing for hepatitis B virus (HBV) were consistent with past immunization, and HBV DNA was undetectable. The patient's alcohol consumption was lower than 10 g per day. Other causes of chronic hepatitis were ruled out.

Hepatitis E was diagnosed in June 2007 on the basis of positive results on IgM anti-HEV antibody testing (EIAGen kit, Adaltis) and HEV RNA detection (genotype 3f; GenBank accession number, EU116340).[5] The patient did not report any recent travel, and no potential route of HEV transmission other than consumption of pork was identified. Retrospective analysis showed that HEV RNA was undetectable in the patient's serum in April 2006, whereas it was repeatedly detected in available serum samples from November 2006 to September 2007 (Fig. 1A), when the diagnosis of active chronic hepatitis and cirrhosis was confirmed on liver biopsy (Fig. 1B and 1C).

HEV-related cirrhosis appears to be a novel observation. Other unusual features in this patient were a low peak alanine aminotransferase level (no higher than 126 U per liter) and the absence of IgG anti-HEV antibody seroconversion. The unusual course might be explained to a great extent by the patient's immunosuppressed state. A few cases of protracted HEV infection and even HEV-related chronic active hepatitis have recently been described in patients who received solid-organ transplants.[2-4] Our observation further suggests that chronic HEV infection may induce rapid and severe liver disease.

Persistently negative results of IgG anti-HEV antibody testing have previously been observed in the context of immunosuppression, despite evidence of HEV infection, as assessed by HEV RNA detection in blood.[6] The present case highlights the need to diagnose HEV infection on the basis of molecular testing rather than only serologic assays in such settings.

In conclusion, this case indicates that HEV infection may result in active chronic hepatitis and rapid progression to cirrhosis in organ-transplant recipients. Further studies are needed to assess the actual incidence, prevalence, and clinical effect of autochthonous HEV infection in these patients.

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