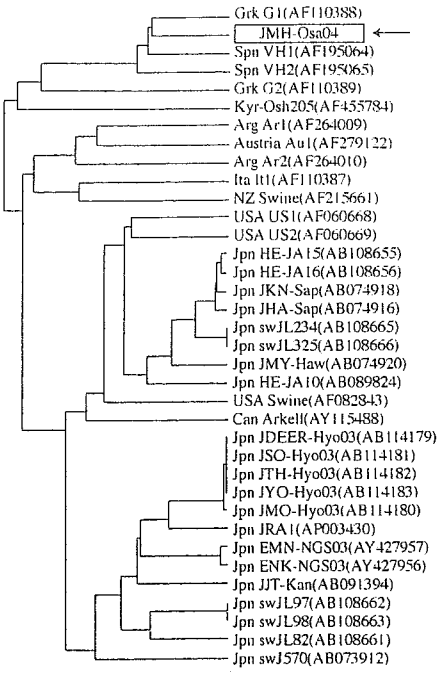

Fig. 2　Phylogenetic tree (UPGMA) of genotype III HEV isolates. Japanese isolates are shaded.

相当する領域）を増幅し塩基配列決定を行い（"JMH-Osa 04" と命名，Accession Number AB 189070），既報株塩基配列と比較した．JMH-Osa04 は genotype III に属していたが，意外なことに，他の日本株よりはギリシャ・スペインからの分離株の方に近似していた（Fig. 2）．

考案：疫学上の問題；患者は発病前にタイへ出張した（2. 23－3. 1）．そのタイ出張で HEV に感染したと仮定すると，潜伏期（仮に ALT のピークまでとして計算）は最長で 16 日，最短では 9 日である．前回のタイ出張（1. 16－1. 22）を起点にすれば 47－53 日である．E 型肝炎の潜伏期は一般に 6－7 週間とされるが，感染時点が特定可能であった兵庫のシカ刺摂取後 E 型肝炎事例[3]では 53 日以下，長崎のイノシシ BBQ 後 E 型肝炎事例[4]では 39 日と 43 日，室蘭の輸血後 E 型肝炎例[5]では 40 日であり，これらの例では初診時に既に HEV 抗体が陽性化していた．本例が 1 月のタイ出張で HEV に感染した可能性は残されているが，初診時には未だ HEV 抗体が出現していなかった所見に鑑みて，感染時期は 2 度のタイ出張の中間にあった可能性も考慮せねばならない．また，タイ国に於ける HEV が主に genotype I であることも，後者の可能性を支持している．

もし国内で感染したとすれば，本患者から採取される HEV は既報の日本土着株のどれかと近似しているのが自然であった．しかし，意外にも，本例由来 HEV 株 JMH-Osa 04 に近似する配列を持つ HEV は，日本からではなくギリシャとスペインから報告されていた．当該地への直近の渡航歴は本患者にはない．また同地からの客人との特別の接触もない．感染源は謎に包まれているが，今後 JMH-Osa04 に類似する株がリアルタイムあるいはレトロスペクティブに日本国内から発掘される可能性はゼロではないので，感染源の絞り込みも全く不可能ではないと考えられる．

診断学上の問題：本例は当初 HEV 抗体が IgM，IgG 共に陰性であり，他の肝炎ウイルスマーカーも陰性であった．本例の如く抗体陽性化が遅延する例はマイナーながらも存在するから，HAV，HBV，HCV が否定され且つ病歴より薬剤性肝障害や自己免疫性肝炎の可能性も否定的である場合には，高感度の検出系[2]を用いて HEV RNA の検出を試みるべきであろう．

索引用語：E 型肝炎，疫学，診断

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英文要旨

A Japanese patient with seronegative hepatitis E caused by a Greece/Spain-origin-like HEV after visiting Thailand

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This case of hepatitis E was interesting in the following points. 1) Although thought as an imported infection from Thailand, this case had shorter or longer incubation period for that, and had an HEV genotype which is rare in Thailand. 2) Domestic infection was thought then, but the HEV isolate from the patient was more homologous to Greece/Spain isolates than to Japanese strains. 3) Response of antibodies to HEV was delayed than in usual cases. Also noteworthy was that a highly increased level of the serum 2'-5' OAS suggested strongly that the hepatitis in this patient would be virus-origin. But for the finding, we would not have tried to test HEV RNA in the absence of antibodies to HEV.

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肝臓　46巻4号　224-225（2005）

＜短　報＞

京浜地区E型肝炎国内感染例10例の疫学的特徴とHEV分離株塩基配列

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緒言：北海道等の多発地域に較べれば，京浜地区（＝東京＋神奈川）はE型肝炎の発生が明らかに低率ではあるが，皆無ではない．我々は，過去7年間に京浜地区内の6病院で経験された10例の国内感染例について，疫学的特徴と分離株塩基配列の解析を試みた．

対象：1998—2004年の間に海外渡航歴なく発症しHEV RNA陽性によりE型肝炎と診断された計10名（東芝病院4例，東京逓信病院2例，帝京大学医学部溝口病院，一心病院，板橋中央総合病院，NTT東日本関東病院それぞれ1例）の日本人．いずれも散発性で非重症型の急性肝炎であった．

疫学的背景因子（Table 1）：(1) 男女比は7 vs 3．年齢は34—69 yrs（50.8±11.7）であった．(2) 職業は，1人（タクシー運転手）を除く男性の全員が会社員，女性の1人は郵便局員，1人はビル清掃のパート勤務，他の1人は無職（主婦）であった．(3) 飲酒嗜好は，量の多寡はあるものの，1名を除く全員に存在した．(4) 高リスク食品摂食歴が男性2人に認められた．即ち，タクシー運転手男性は発病1カ月前およびそれ以前にも頻回に，生ブタレバーを好んで食べていた．1人の会社員男性は，単身赴任の自炊生活の中でブタ肉のシャブシャブを頻回に食していた．

HEV RNAの検出と解析：10名中8名は独立した2つのRT-PCR法[1,2]の両者でHEV RNA陽性であったが，他の2名は高感度PCR法[2]でのみ陽性であった．従って，前者8名のHEVについては，ORF 1内の326塩基（日本土着HEV株のプロトタイプであるJRA 1株のnt 124-449に相当する領域）およびその上流の69塩基（同じくnt 42-110に相当）を増幅し塩基配列決定を行ったが，後者2名については69塩基のみを配列決定した．Fig. 1に示す如く，1例を除き全例がgenotype IIIに属していた．そのうちの2つの株（JKK-Tok 98とJRA 1-Tok 00）は極めて高い近縁性を示した．他の株も所謂『本州型genotype III』のクラスターに属していた．Genotype IVに属した1例には近縁の既報株が存在しなかった．

考案：中高年の特に男性に多いとされる本邦のE型肝炎の特徴の一つは本調査でも再現された（男女比は7対3，年齢は女性1名を除き全員40歳以上）．

本調査に於ける注目事の一つは飲酒癖（10名中9名に存在）である．飲酒がE型肝炎発病リスクの一つかもしれない可能性は次の3点に由来すると考える．(1) タクシー運転手と単身赴任生活会社員に於いて見られた如く，飲酒癖のある者は往々にして高リスク食品を生か生に近い状態で食べたがる．(2) 飲酒には酩酊が伴い，酩酊は衛生観念を低下させ，経口感染様式を取る病原体に対して一過性無防備状態を現出せしめる．(3) 飲酒はHCV感染後のviral clearanceを低下せしめる[3]との報告から，飲酒によるウイルス宿主反応の修飾の可能性が推定され，本来なら不顕性感染である筈のHEV感染が顕性感染に転じてしまう可能性も考えられ得る．

飲酒癖のなかった唯一の患者には，ビル清掃係という職業歴が存在した．ネパールのドブネズミからHEV RNAが検出されたとする報告[4]や日本棲息野生ネズミのHEV抗体陽性率に関する報告[5]に鑑みて，ネズミあるいはその糞便に接触する機会の多い職業は，相対的にHEV感染リスクも高い可能性がある．

京浜地区はヒト及びモノ（食品・食材を含む）の集散地である故に，HEVに関しても国内国外の様々な系統の株が流入しているだろうと考えられたが，その予想は裏切られた．本調査対象に於けるHEVのmajor genotypeはIII型であった．しかもそのIII型株の全てが『非北海道型のIII型クラスター』の中に集族していた（Fig. 1 a）．そのうちの少なくとも2株が相互に非常に近縁であったことは，感染源が同一系統であって且つその系統が土着化している可能性を示唆した．

HEVのreservoirとして，ブタ，イノシシ，シカなどが注目されている．特にブタは広く食用に供され，北海道では，食用ブタレバーの1.9%にgenotype III型，IV型のHEV RNAが検出されたとの報告も存在する[6]．IV型は，北海道の散発例から多く検出されており，ブタレバーとの関連が推定されているが，IV型ウイルスが検出された症例8においても，ブタレバー刺身の摂取歴が存在し，感染経路を考える上で興味深い．

京浜地区からは他にも数例のE型肝炎例が研究会等で既に報告されている．今回の調査結果からも，未発掘の過去例あるいは見落とされ続けているリアルタイム例が多数存在すると予想される．感染経路を特定し感染予防対策を立てる為には，症例情報の更なる集積が必要である．

索引用語：E型肝炎，疫学，東京，神奈川

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[1]東芝病院消化器内科，[2]東京逓信病院消化器科，[3]帝京大学溝口病院第4内科，[4]一心病院内科，[5]板橋中央総合病院消化器内科，[6]NTT東日本関東病院消化器内科，[7]東芝病院研究部，* Corresponding author: masahiro1.arai@po.toshiba.co.jp

＜受付日2004年10月21日＞＜採択日2005年2月9日＞

Table 1 Ten patients from Tokyo-Kanagawa area with sporadic hepatitis E

Case	Hospital*	Age-sex	Onset	Nadir PT%	Occupation	Alcohol	Notes	HEV RNA**	Isolate name
1	(1)	57-M	Feb-98	84%	Corporate worker	+		+ve/+ve	JKK-Tok 98
2	(3)	44-M	Nov-98	100%	Corporate worker	+		+ve/+ve	JJT-Kan
3	(1)	52-M	Jun-99	71%	Corporate worker	+		+ve/−ve	JTF-Tok 99
4	(1)	62-M	Nov-00	106%	Corporate worker	+		+ve/−ve	JRA 1
5	(1)	40-M	Dec 01	95%	Corporate worker	+		+ve/+ve	JJT-Tok 01
6	(2)	34-F	Mar-02	91%	Corporate worker	+		−ve/+ve	JMS-Tok 02
7	(4)	69-F	Apr-03	65%	Part-time worker	−	Engaged in building sanitation	+ve/−ve	JSS-Tok 03
8	(5)	44-M	Jun-03	89%	Taxi driver	+	Likes to eat *Sashimi* of pork liver	+ve/+ve	JYK-Tok 03
9	(6)	42-M	Feb-04	100%	Corporate worker	+	Likes to eat *Shabu-shabu* of pork	−ve/+ve	JKS-Tok 04
10	(2)	64-F	Jun-04	99%	House wife	+		−ve/+ve	JJH-Tok 04

* See footnotes of this page. ** HEV RNA was positive by both of the two PCR methods [1] in "+ve/+ve", while by only the high-sensitivity PCR method [2] in "−ve/+ve".

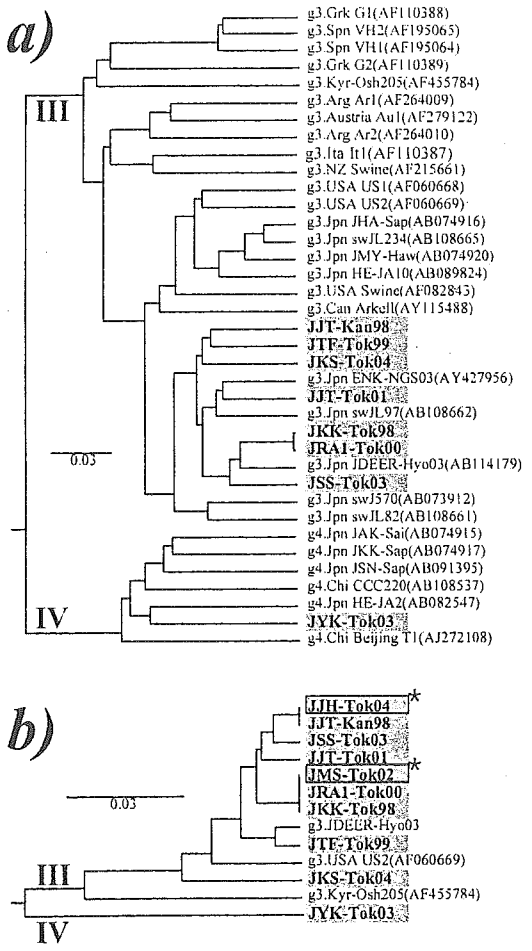

Fig. 1 Phylogenetic trees (UPGMA) based on 326 nt [1] (*a*) and 69 nt [2] (*b*) within ORF 1. Tokyo/Kanagawa-derived isolates are shaded. * Two isolates were unavailable for the 326-nt sequence. Accession numbers for the shaded isolates are AB 091394, 189926-8, 193016-26, and AP 003430.

308−18. 3) Piasecki BA, Lewis JD, Reddy KR, et al. Hepatology 2004；40：892−9 4) He J, Innis BL, Shrestha MP, et al. J Clin Microbiol. 2002；40：4493−8 5) Hirano M, Ding H, Li T-C, et al. Hepatol Res 2003；27：1−5 6) Yazaki Y, Mizuo H, Takahashi M, et al. J Gen Virol 2003；84：2351−7

英文要旨

Epidemiological and virological characteristics of 10 cases of sporadic acute hepatitis E from Tokyo and Kanagawa

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A total of 10 Japanese patients with acute sporadic hepatitis E in Tokyo and Kanagawa area from 1998 to 2004 were analyzed for epidemiological and viro-genetic characteristics of their HEV infections. Our findings therefrom corroborated the previous ones on the middle-aged male predominance. Noteworthy was that all were alcohol drinkers except for one female patient. Two of the drinkers had a fondness for eating uncooked or undercooked pork meat or liver. The one and only non-drinker among the subjects was engaged in the job of building-sanitation. Molecular analyses indicated that most of the HEV isolates from these patients segregated to a cluster within genotype III, suggesting these strains (if not all) might be autochthonous in the Tokyo and Kanagawa area.

Kanzo 2005；46：224−225

＜症例報告＞

富山県からは初報告例となる散発性E型急性肝炎の1例

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工藤　浩[1]　平野　克治[1]　矢田　豊[1]　安村　敏[2]
峯村　正実[1]　高原　照美[1]　高橋　和明[3]　安倍　夏生[3]
三代　俊治[3]　杉山　敏郎[1]

要　旨：近年本邦におけるE型急性肝炎は，渡航歴のない国内発症例が増加してきており，そのHEV株がそれぞれの地域に特有の土着株であることが明らかになってきた．今回，渡航歴のない感染経路不明の散発性E型肝炎の1例を経験した．症例は50歳男性．海外渡航歴，輸血歴，性交渉，最近の生肉の摂取歴はなかった．2004年6月発熱および全身倦怠感が出現．市販の感冒薬を服用するも軽快せず，近医を受診，著明な肝機能障害を指摘され当科紹介入院となった．メシル酸ガベキサート・プロスタグランジンE1で加療し，肝炎は沈静化，第22病日に退院となった．IgG，IgM-HEV抗体陽性およびHEV-RNA陽性により急性E型肝炎と診断した．HEVはgenotype IIIで既報日本株に一致ないし酷似するものがなかった．

HEVは日本国内に広く定着し感染経路として生の獣肉が有力であるが，多くの症例で感染経路が明らかになっておらず，genotype解析等による解明が望まれる．

索引用語：　E型急性肝炎　　E型肝炎ウイルス　　感染経路

はじめに

E型急性肝炎は，E型肝炎ウイルス（HEV）の感染によって引き起こされる急性肝炎で，アジア，アフリカ，中米などの発展途上国に散発的に発生し，ときに汚染された飲料水などを介して大規模な流行を引き起こす．本邦をはじめとした先進国においては，輸入感染症として認識されてきたが，近年，渡航歴のない国内発症例が報告されるようになり，さらに，そのHEV株がそれぞれの地域に特有の土着株であることが明らかになってきた．今回，渡航歴のない感染経路不明の散発性E型肝炎の1例を経験したため報告する．

症　例

患者：50歳，男性．

主訴：発熱・全身倦怠感・食思不振．

家族歴：父（69歳）C型肝硬変，肝細胞癌にて死去．姉（40歳頃）急性肝炎にて入院歴あり．

既往歴：41歳より高血圧・高脂血症・高尿酸血症のため，近医Aにてバルニジピン・アトルバスタチン・アロプリロールを服薬中であり，最近1年間での薬剤変更なし．薬剤アレルギー・肝機能障害の既往なし，入院歴なし，手術歴なし，輸血歴なし，海外渡航歴なし，性交渉なし．

生活歴：富山県出身．飲酒歴；なし．喫煙歴；なし．職業；印刷会社営業．自宅の井戸水を愛飲していた．

現病歴：2004年6月8日，発熱・全身倦怠感が出現．同日から市販の風邪薬（新ルルA錠，エスタック，カコナール）を内服．6月12日から食欲不振，13日からは褐色尿も出現し以後持続していた．6月14日，近医Bを受診し，総ビリルビン6.54 mg/dl，直接ビリルビン4.30 mg/dl，AST 4557 IU/l，ALT 5253 IU/l，ALP 704 IU/l，γ-GTP 889 IU/l，LDH 2979 IU/lと著明な肝機能障害を指摘され，6月15日当科を紹介受診し，即日入院となった．検診は毎年受けていたが高血圧以外は異常なかった．なお，1995年から近医Aより高血圧，高脂血症，高尿酸血症の薬を処方されていた．同院では2004年2月に採血しているがその際に

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＜受付日2005年2月24日＞＜採択日2005年9月30日＞

Table 1　Laboratory data on admission

⟨CBC and blood chemistry⟩		CRE	1 mg/dl	HBV	
WBC	6210/μl	Na	139 mEq/l	HBsAg	(−)
RBC	531×10⁴/μl	K	4.1 mEq/l	anti-HBs	(−)
Hb	16.9 g/dl	Cl	100 mEq/l	anti-HBc	(−)
Plt	12.4×10⁴/μl	Ca	9.4 mg/dl	IgM-anti-HBc	(−)
TP	7.1 g/dl	Fe	362 μg/dl	HCV	
Alb	3.9 g/dl	PT%	66%	anti-HCV	(−)
AMY	75 IU/l	PT-INR	1.38	HCV-RNA	(−)
AST	6375 IU/l	STS	(−)	EB virus	
ALT	7460 IU/l	ANA	(−)	IgM-anti-VCA	(−)
ALP	735 IU/l	IgG	1231 mg/dl	IgG-anti-VCA	(−)
γGTP	729 IU/l	IgA	145.8 mg/dl	EB EBNA	(−)
LDH	3770 IU/l	IgM	455 mg/dl	CMV	
T-Bil	7.3 mg/dl			IgG-anti-CMV	(−)
D-Bil	5.1 mg/dl	⟨viral markers⟩		IgM-anti-CMV	(−)
CPK	100 mg/dl	HAV		HEV	
NH₃	79 μg/dl	IgG-anti-HA	(−)	IgG-anti-HE	(+) (CI：35)
UA	8.1 mg/dl	IgM-anti-HA	(−)	IgM-anti-HE	(+) (CI＞200)
BUN	26 mg/dl			HEV-RNA	(+)

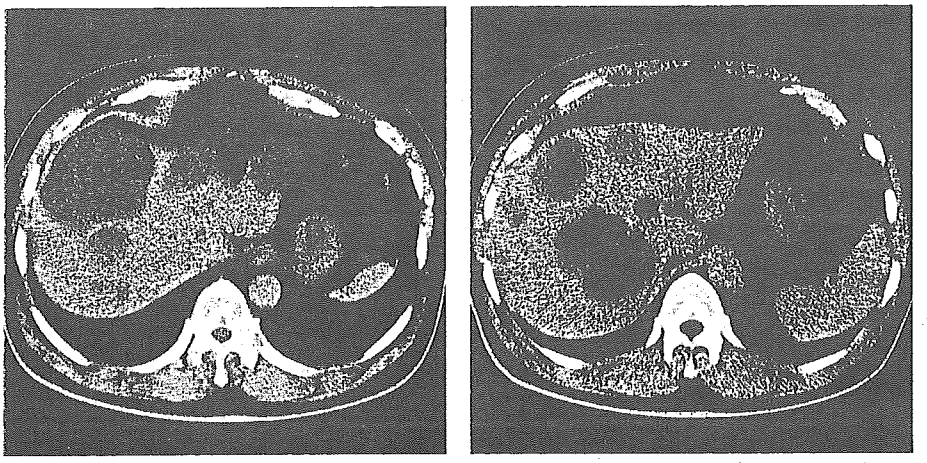

Fig. 1　Abdominal CT：Multiple liver cysts and mild liver atrophy are shown.

異常は指摘されていない．

入院時現症：身長 169.7 cm，体重 78.1 kg，血圧 116/68 mmHg，脈拍 82/分(整)，体温 38.4℃，皮膚・結膜に黄疸あり，リンパ節腫脹なし，腹部は軟平で右肋骨弓下に肝を 2 横指触知，脾腫なし，四肢に浮腫なし，羽ばたき振戦なし，神経学的異常は認められず．

入院時検査所見(Table 1)：トランスアミナーゼを主とした肝胆道系酵素の著明な上昇，直接型優位の高ビリルビン血症を認め，プロトロンビン時間(PT)は延長していた．肝炎ウイルスでは A，B，C 型肝炎感染の所見はなく，EB ウイルス・サイトメガロウイルス感染症は否定された．

腹部超音波検査：最大径で 86 mm の多発性肝嚢胞が認められ，全体的に肝は萎縮していた．

腹部 CT(Fig. 1)：軽度の肝萎縮を認め，多発性肝嚢胞が確認されたが，その他の異常所見は認めなかった．

入院後経過(Fig. 2)：エコー所見より肝萎縮が否定できず，またプロトロンビン時間も延長していたことから，重症化を予防するために入院第 2 日目よりメシル酸ガベキサート(1500 mg/day)・プロスタグランジン E1 (250 μg/day)投与を開始した．高度な肝細胞障害の原

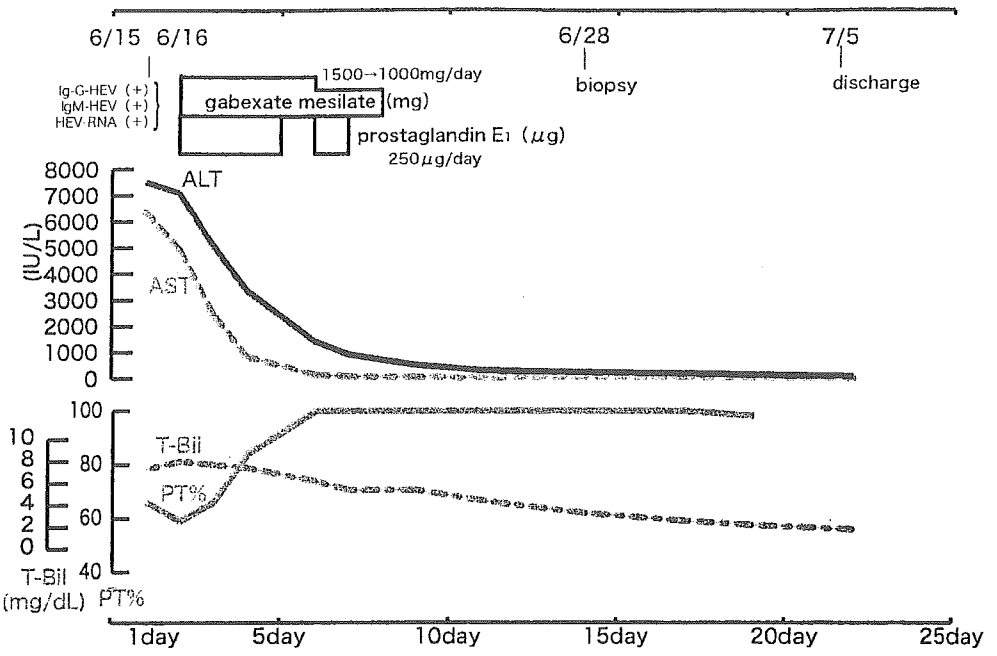

Fig. 2　Clinical course

因として，A型，B型，C型肝炎は否定され，自己免疫性肝炎も否定的であった．薬剤性肝障害については，カコナールを初めて内服したが，他に薬剤の服用歴は聴取できなかった．2004年6月25日，IgG-HEV抗体陽性(CI：35)，IgM-HEV抗体陽性(CI＞200)，HEV-RNA陽性(RT-PCR法)の結果より，急性E型肝炎と診断した．6月25日の時点でAST 43 IU/*l*，ALT 270 IU/*l*，T-Bil 4.4 mg/d*l*と肝炎は沈静化に向かっており，外泊後も肝機能の増悪は認められず，7月5日，AST 19 IU/*l*，ALT 54 IU/*l*，T-bil 1.8 mg/d*l*，PT%＞100であり，退院となった．

肝生検所見(Fig. 3)：6月28日実施．肝小葉構造は保たれており，門脈域に小円形細胞の浸潤がみられたが軽度であった．実質内に巣状壊死像，肝細胞の大小不同，および2核，3核の細胞を認め，急性肝炎の像に一致した．

HEVゲノム解析(RT-PCR法によりHEVのORF1領域の326塩基長の配列の解析を行い，UPGMA法で作図した[1])(Fig. 4)：患者より分離されたHEVのgenotypeはIII型で，既報日本株に一致ないし酷似するものがなく，JHK-Toy04と命名した．既報のHEV株の中では，日本固有株であるJJT-Kan株の塩基配列と最も高い一致率(92.9%)を示した．

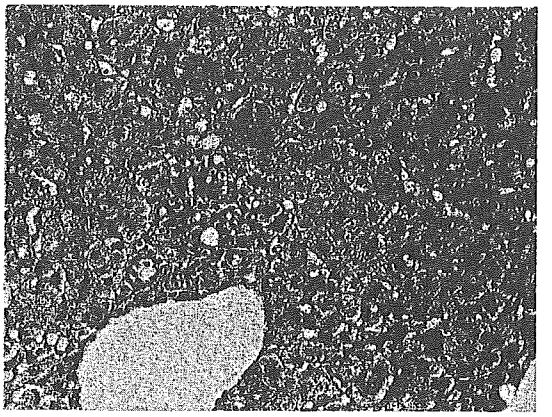

Fig. 3　Histological findings of the liver biopsy specimen：Mild infiltration of small round cells is observed in the portal area, and spotty necrosis is shown in the liver parenchyma. (Hematoxylin-eosin, ×100)

患者は自宅の井戸水を愛飲しており感染源として疑ったが，1000倍濃縮井戸水をサンプルとしたRT-PCR法でHEV-RNAは陰性であった．また，同居している母親は井戸水はほとんど摂取していなかったが，IgM，IgG-HEV抗体はともに陰性であった．

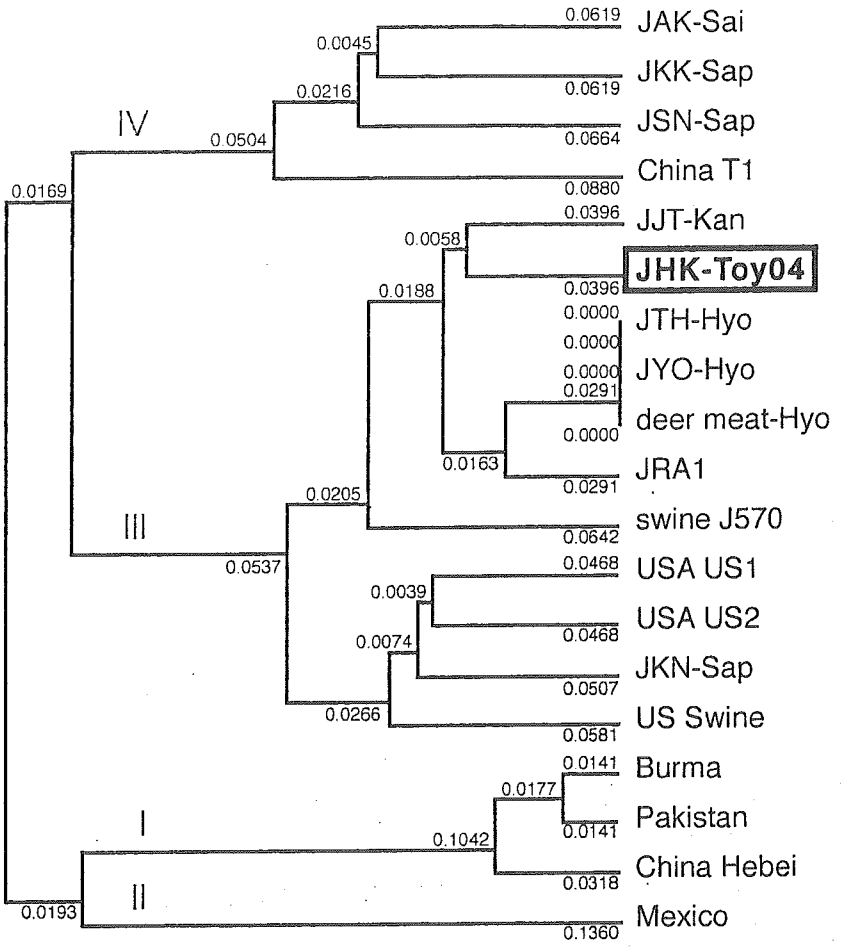

Fig. 4 Phylogenetic tree (UPGMA method) for the HEV isolate (shown within a box) based on a 326-nt region from open-reading frame 1

考　察

かつて輸入感染症としての発症が多かったE型肝炎だが，最近は国内感染例の報告が増えてきており，2003年は約8割が国内感染例であった[2]．

本症例は，海外渡航歴がなく国内感染例と考えられる．自宅の井戸水を愛飲していたが，1000倍濃縮井戸水をサンプルとしたPCR法によってもHEV-RNAは陰性であり，また同居の母親のIgM，IgG-HEV抗体も陰性であった．感染の原因として報告のある生肉摂取や輸血などの既往もなく，感染経路は不明であった．

2004年11月現在までに雑誌，会議録に報告された国内感染例（IgM-HEV抗体もしくはHEV-RNAが証明され，かつ国内感染と考えられる症例）は，我々の調べた限り147症例ある．そのうち感染経路が判明したのは鹿肉の4例[3]，猪の生肉8例[4]，猪のレバー2例[5]，豚のレバー9例[6]と輸血2例[7]のみである．疑わしい感染源があるものでも生の魚介類4例[8]，ペット（ネコ）2例[9,10]，豚ホルモン焼1例[11]，性的接触1例[12]の8例のみであり，他の約8割は全く不明である．過去の症例では感染経路に言及していない報告も多く，8割のすべての感染経路が不明ではないのかもしれない．一方，1999年4月から2004年第47週までの感染症発生動向調査[2]でも，推定感染地域が国内とされている56例のうち，猪8例（肉4，肝臓3，心臓1），豚9例（生肉2，肝臓5，腸2，横隔膜1，胃1），鹿6例（生肉4，その他2），魚介類（カキ）1例の他は不明であり，やはり多

くの症例で感染経路は判明していない．

国内感染においては，上記の如く人獣共通感染症の一つであると考えられる．実際，鹿，猪，豚の生肉による感染の証明の他，北海道で市販されていた生の豚レバーの一部からHEV-RNAが検出され[5]，これらは感染経路としてほぼ間違いないと思われる．しかし最近になって輸血による感染が2例報告され[7]，本症例を含めて生肉の摂取歴のない症例も多くみられるため，多様な感染経路の可能性も考えられる．

また，健常人のHEV-IgG抗体保有率が5.4%もあったという報告があり[2]，不顕性感染者が気づかずに輸血，もしくはヒトーヒト間を含めた未知の感染経路を介して蔓延している可能性も考えられる．

E型肝炎は大半の症例ではA型肝炎に類似し，一過性の経過をとることが多いが，稀に劇症化する．特に妊婦において死亡率が高いと考えられていたが，最近の報告では否定的な意見がある[14]．今後，我が国でも早急な国内の感染実態把握と感染ルートの解明が望まれる．

結　語

富山県では初報告例であり，北陸地区でも2例目となる散発性E型急性肝炎の1例を経験した．E型急性肝炎はもはや日本土着の疾患であるが，その感染経路は未だ十分には解明されていない．今後，原因不明の急性肝炎の診断の際にはE型急性肝炎の可能性を常に考慮すべきであり，その感染経路を明らかにすることが重要である．

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A domestic case of acute sporadic hepatitis E first identified in Toyama prefecture

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Recently, sporadic acute hepatitis E patients who had no history of travel to endemic areas were increased in Japan. It became clear that these hepatitis cases were caused by Japan-indigenous HEV strains of each local area. We experienced a case of sporadic acute hepatitis E. The patient was a 50-year-old male who did not have history of travel, blood transfusion, sexual intercourse and ingestion of uncooked meat. He had fever and general malaise. He consulted a doctor and was pointed out marked liver dysfunction. Then, he was introduced and admitted to our hospital. We detected HEV-RNA and diagnosed him as acute hepatitis E. The HEV isolate belongs to genotype III, and have never been determined previously. Hepatitis E virus is distributed broadly in Japan, but the routes of infection are not clarified in the most cases. Further studies were required to make clear the routes of HEV infection.

Kanzo 2005；46：647－652

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Case Report

A Patient with Clinical Features of Acute Hepatitis E Viral Infection and Autoimmune Hepatitis

FUTOSHI NAGASAKI, YOSHIYUKI UENO, YUTAKA MANO, TAKEHIKO IGARASHI, KAICHIRO YAHAGI, HIROFUMI NIITSUMA, HIROAKI OKAMOTO[1] and TOORU SHIMOSEGAWA

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NAGASAKI, F., UENO, Y., MANO, Y., IGARASHI, T., YAHAGI, K., NIITSUMA, H., OKAMOTO, H. and SHIMOSEGAWA, T. *A Patient with Clinical Features of Acute Hepatitis E Viral Infection and Autoimmune Hepatitis.* Tohoku J. Exp. Med., 2005, **206** (2), 173-179 —— Hepatitis E virus (HEV) is one of the major causative agents of acute hepatitis in many developing countries. Recent intensive examination has revealed the existence of non-imported cases in industrialized countries. The patient was a 25-year-old Japanese female with acute hepatitis. Laboratory test demonstrated positive anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA) and high level of serum immunoglobulin G (IgG). The patient was negative for serum markers of hepatitis A, B or C virus infection. She demonstrated a clinical course similar to severe autoimmune hepatitis, including response to prednisolone therapy. After a few years, with the availability of tests for the serum antibodies to HEV, we examined the frozen stocked sera of the patient and found her exact diagnosis was acute hepatitis E. Although we could not detect HEV-RNA, which is positive only in limited period of acute phase, serum IgA and IgG antibodies to HEV were positive and the titer of IgA and IgG antibodies were declined with the time course. In conclusion, we must take into consideration of HEV infection for the diagnosis of acute cryptogenic hepatitis including autoimmune hepatitis. Further studies are feasible to understand the pathogenesis of liver injuries induced by HEV infections. ———— acute hepatitis; hepatitis E virus; autoimmune hepatitis; viral hepatitis

Hepatitis E virus (HEV) that has a single and positive-strand RNA genome of approximately 7,200 nucleotides is one of the major causative agents of acute hepatitis in many developing countries in Asia, Africa and Central America. HEV is transmitted via fecal-oral route (Balayan et al. 1983; Reyes et al. 1990; Hino et al. 1991; Tam et al. 1991; Zaaijer et al. 1993; Scharschmidt 1995; Purcell and Emerson 2001; Emerson and Purcell 2003). However, the availability of recent intensive examination has revealed the existences of some non-imported cases even in industrialized

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countries. Thus, it is now believed that the virus is much more diverse and widespread than expected. Up to now, 4 major genotypes have been identified (Schlauder and Mushahwar 2001).

HEV infection has scarcely been reported in Japan, and most of the cases observed so far have been recognized as imported ones (Hino et al. 1991; Ishikawa et al. 1995). However, more recently, several sporadic cases without history of traveling to endemic area of HEV have been reported (Takahashi et al. 2001; Suzuki et al. 2002; Takahashi et al. 2002a; Ohnishi et al. 2003; Yazaki et al. 2003).

In this report, we present a patient with features of acute hepatitis E infection, who had never been abroad and demonstrated a clinical course similar to severe autoimmune hepatitis (AIH).

Patient

The patient was a 25-year-old Japanese housewife. Her previous medical history revealed nothing particular events such as blood transfusion or operations except for artificial abortion. She had an occasional alcohol intake, but no history of traveling abroad and no contact with foreign travelers. She did not receive any drug medication or intravenous injection.

Present illness

She felt deteriorating abdominal distension at December 9th, 2000. Her local physician pointed out the presence of ascites by abdominal ultrasound sonography (US). Next day, she was referred to a gynecologist, although there was not any gynecological abnormality. She also felt abdominal pain at December 14th, and visited another local hospital. Laboratory tests revealed anemia (Hemoglobin [Hb] 8.0 mg/100 ml), thrombocytopenia (Platelet [Plt] 71 $\times 10^3/\mu l$), elevated liver enzymes (asparate aminotranferase [AST] 222 IU/l, alanine aminotransferase [ALT] 230 IU/l) and elevated total bilirubin (T.Bil) 6.6 mg/100 ml. Moreover, splenomegaly was detected by computed tomography (CT) scan. Therefore, bone marrow aspiration was performed, and the presence of hematological disease was ruled out. Thereafter, she was referred to our hospital, and admitted on the December 15th, 2000.

Physical findings at administration

Physical examination revealed: height 153 cm; body weight 52.9 kg; blood pressure 124/80 mmHg; body temperature 37.7°C; and clear consciousness. The bulber conjunctiva was icteric. No peripheral edema, vascular spider, palmar erythema, and flapping tremor were observed.

Laboratory findings

She was admitted on the late Friday night, thus we could not perform routine laboratory tests. The result of initial tests revealed liver dysfunction, coagulopathy, anemia and thrombocytopenia (Table 1). Her routine laboratory test on the 4th hospital day is shown on the Table 2. Of note, anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) were positive, although anti-mitochondria antibody (AMA) was negative. Serum markers of hepatitis A, B or C virus were all negative.

Clinical course

Prior to obtaining entire laboratory tests, we temporally diagnosed that the patient had an acute hepatic failure, and started to transfuse fresh frozen plasma and albumin. Abdominal CT did not show space occupying lesions or the presence of chronic liver disease except for mild splenomegaly, huge amount of ascites and pleural effusion.

On the 7th hospital day, we serologically

TABLE 1. *Laboratory findings on admission*

WBC	9,200/μl	RBC	241 $\times 10^4/\mu l$
Hb	8.5 g/100 ml	Plt	88 $\times 10^3/\mu l$
T.Bil	9.3 mg/100 ml	AST	230 IU/l
ALT	235 IU/l	ALP	409 IU/l
LDH	423 IU/l		
CRP	0.4 mg/100 ml	BUN	10 mg/100 ml
Cr	0.5 mg/100 ml	PT	31%

WBC, white blood cell; CRP, C-reactive protein; Cr, Creatine; RBC, red blood cell; ALP, alkaline phosphatase; BUN, blood urea nitrogen; PT, prothrombin time.

TABLE 2. *Laboratory findings on 4th hospital day*

WBC	5,100 /μl	RBC	206 × 10^4/μl
Hb	7.0 g/100 ml	Plt	60 × 10^3 /μl
PT	43%	Hepaplastin test	43%
T.Bil	6.4 mg/100 ml	Direct Bil	3.6 mg/100 ml
AST	111 IU/l	ALT	116 IU/l
ALP	318 IU/l	GGTP	25 IU/l
LDH	368 IU/l		
CRP	4.1 mg/100 ml		
BUN	11 mg/100 ml	Cr	0.5 mg/100 ml
Total protein	7.1 g/100 ml	Albumin	2.8 g/100 ml
IgM-HAAb	negative		
HBs-Ag	negative	IgM-HBcAb	negative
HCV-Ab	negative		
HIV-Ab	negative		
ANA	× 80	ASMA	≧ ×160
AMA	negative		
IgG	3,585 mg/100 ml	IgA	294 mg/100 ml
IgM	511 mg/100 ml		

WBC, white blood cell; PT, prothrombin time; AST, asparate aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehidrogenase; CRP, C-reactive protein; BUN, blood urea nitrogen; ANA, anti nuclear antibody; AMA, anti mitochondria antibody; RBC, red blood cell; Plt, platelet; ALT, alanine aminotransferase; GGTP, gamma glutamil transpeptidase; Cr, creatine; ASMA, anti-smooth muscle antibody.

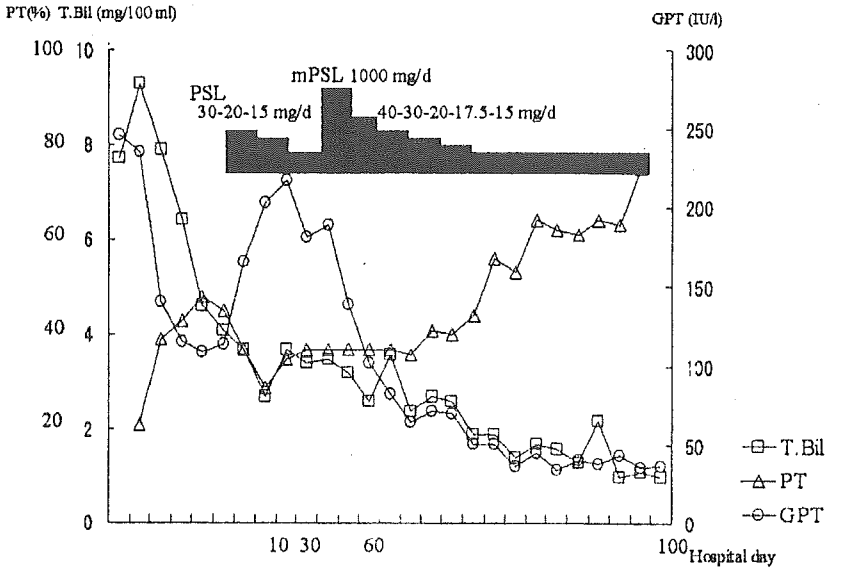

Fig. 1. Clinical course of the patient. The patient recovered after administration of corticosteroid.

made diagnosis to the case as acute onset type AIH, and started the administration of prednisone (PSL) 30 mg/day (Fig. 1). However, she showed minimal response to the therapy. Therefore, we administrated methyl-PSL 1g/day for three days, which was followed by PSL 40 mg/day and tapered over weekly. Her general condition as well as clinical data had improved, and finally she discharged on March 26th, 2001. During this admission, the unexpected illness of her family prevented further extensive examinations including liver biopsy.

Finally the patient underwent the laparoscopic liver biopsy at 8 months after the onset, when PSL had been already withdrawn and laboratory tests showed normal liver function. Pathological findings of the specimens showed inflammatory changes in the portal vein area, and the presence of bridging necrosis. It was compatible with the recovery phase of acute severe hepatitis (Figs. 2 and 3).

We administrated PSL for 8 months according to these data, and could withdraw it ultimately. It has been 1.5 years since the withdrawal of PSL, and her transaminase, serum IgG level and ANA are all within normal limit without any medication. At the last visit to our department (Oct 15th, 2002), her laboratory examination demonstrated normal liver function (ALT 15 IU/l, AST 15 IU/l), normal serum immunoglobulins

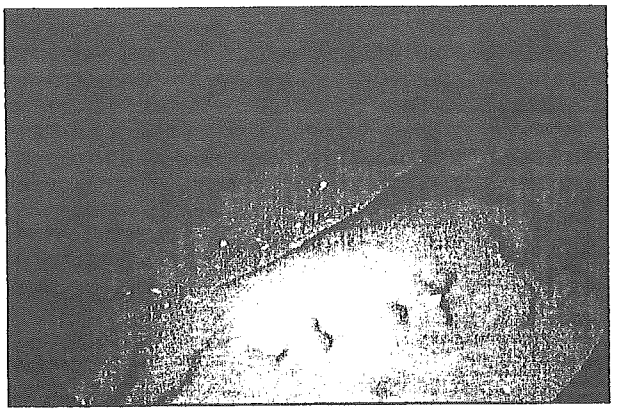

Fig. 2. Macroscopic pathological findings. Laparoscopy was performed on August 8th, 2001. Uneven liver surface due to severe and massive inflammation was apparent. This morphological view clearly ruled out the presence of cirrhosis.

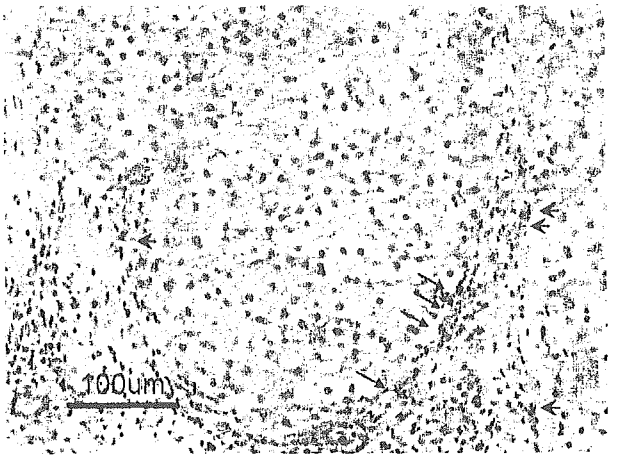

Fig. 3. Microscopic pathological findings. The specimen did not demonstrate classical features of AIH, such as infiltration of plasma cells (arrow heads) or presence of interface hepatitis (arrows). This biopsy was compatible with the recovery phase of severe acute inflammation. (H&E, × 20)

TABLE 3. *Titer of anti-HEV assay (ELISA)*

Date	IgM-HEV	IgG-HEV	IgA-HEV	HEV-RNA
2000.12.15	0.253 (−)	> 3.000 (+)	0.413 (+)	negative
2001. 3.12	0.186 (−)	> 3.000 (+)	0.327 (−)	negative
2003. 4. 8	0.142 (−)	0.827 (+)	0.072 (−)	negative

The specificity of the anti-HEV IgG and anti-HEV IgA assays was verified by absorption by the same recombinant ORF2 protein that was sued as the antigen probe or a mock protein obtained from the pupae of silkworm infected with non-recombinant baculovirus. The details were described in the text.

(IgG 1,289 mg/100 ml, IgA 191 mg/100 ml, IgM 212 mg/100 ml) and negative ANA (< 20).

Recently we evaluated the possibility of HEV infection in this case. Enzyme-linked immunosorbent assays (ELISAs) and RT-PCR were performed with the serial stocked serum samples as previously described (Okamoto et al. 2001; Mizuo et al. 2002). The specificity of the anti-HEV IgG and anti-HEV IgA assays was verified by absorption by the same recombinant ORF2 protein that was used as the antigen probe or a mock protein obtained from the pupae of silkworm infected with non-recombinant baculovirus. Briefly, when the OD value of the tested sample decreased to less than 30% of the original value after absorption with the recombinant ORF2 protein and remained greater than 70% of the original value after absorption with a mock protein, the sample was considered to be positive for anti-HEV. Although we could not detect HEV-RNA from them, IgA and IgG antibodies to HEV were detectable from the serum obtained at admission. The titer of IgA and IgG type anti-HEV antibodies decreased with time course (Table 3). Taken together, we have concluded that her possible diagnosis is acute hepatitis E.

Discussion

In industrialized countries, although anti-HEV has been detected in 4 to 36% of healthy individuals (Tam et al. 1991; Hsieh et al. 1999; Pina et al. 2000; Meng et al. 2002), sporadic cases of hepatitis E which were not associated with traveling to endemic area have rarely been reported (Schlauder et al. 1998; Erker et al. 1999; Hsieh et al. 1999; Schlauder et al. 1999; Zanetti et al. 1999; Li et al. 2000; Wu et al. 2000; Takahashi et al. 2002a).

Since HEV infection was not considered endemic in Japan, we did not examine it at the admission of this case. All the markers of hepatitis A, B, and C including other viral markers, such as Epstein-Barr virus, cytomegalovirus, and Varicella zoster virus were negative. Serum examination of autoantibodies revealed that ANA and ASMA were positive, and the titers of serum IgG and IgM levels were elevated. Other possible causes for hepatic failure (e.g., alcohol, drug-induced liver injury, etc.) were effectively ruled out.

From these data, we first diagnosed her clinically as an autoimmune hepatitis of acute onset form. When we looked over her clinical course, her initial response to PSL was not satisfactory, although subsequent corticosteroid pulse therapy was successful. We could successfully taper PSL without an exacerbation and finally discontinued it at 20 months after the administration. In classical AIH, the discontinuation of PSL is very difficult. The patient did not demonstrate any sign of a relapse after the cessation of PSL. In addition, her class II human leukocyte antigen (HLA) was DR6 and DR9, which is different from known major types in Japan (DR4 and DR8). Neither macroscopic nor microscopic pathological findings were compatible with classical AIH, but this might be due to the timing of performing liver biopsy (i.e., recovery phase of sever acute inflammation). Moreover, to the best of our knowledge, there are no established relationship between specific HLA haplotype and disease susceptibility of HEV infection as observed in chronic hepatitis C (Kondo et al. 2003).

In the recent study conducted in Japan, 11 (12.6%) of 87 patients who had previously been diagnosed as sporadic acute hepatitis of non-ABC etiology were found to be infected with HEV. The seroprevalence of antibodies against HEV in healthy individuals was reported to range from 1.9 to 14.1% in Japan (Li et al. 2000; Mizuo et al. 2002).

A genotype III strain of HEV has been isolated from a Japanese patient with acute hepatitis who had never been abroad. Also, several sporadic hepatitis E case has been reported (Takahashi et al. 2001; Suzuki et al. 2002; Takahashi et al. 2002b; Ohnishi et al. 2003; Yazaki et al. 2003).

These findings indicate that HEV infection may be endemic in Japan. We have considered possible involvement of HEV infection in the group of patients who had been diagnosed as acute hepatitis of unknown etiology in our hospital. Thus we examined the stocked sera obtained at the time of admission from these patients for HEV serological markers. We tested IgA, IgM

and IgG class antibodies to HEV by ELISAs and HEV-RNA by RT-PCR. Concerning the present case, we could not detect HEV-RNA in the any of stocked serum, although IgA, and IgG type antibodies to HEV were detected and their titers reduced with the clinical course. Therefore, we concluded that her diagnosis was acute hepatitis E. We assumed that positivity of ANA, ASMA and elevation of serum IgG level was due to the non-specific reaction with viral infection or possibly specific reaction with some type of HEV infection. We could also raise the possibility that the acute infection with HEV could induce polyclonal immunoglobulinemia as observed in the current case, although the mechanism of this phenomenon is unclear.

In general, hepatitis type E is diagnosed by serological tests: i) detection of IgM type anti-HEV, ii) elevated titer of IgG type anti-HEV, or iii) positive viral RNA by RT-PCR. Since HEV is known to poorly tolerate the freeze and thaw (Bradley 1990), it cannot be detected if the serum is stocked under inappropriate condition. As a consequence, the prevalence of HEV infection could be understimated. IgA type anti-HEV antibody can be utilized as an additional confirmatory antibody for recent HEV infection (Chau et al. 1993; Tokita et al. 2003), and this case demonstrated positive reaction for it in an examination of stocked sera at admission. Also, although judged as negative, the titer of IgM type anti-HEV was weakly reactive on admission and was decreased after time course (Table 3).

HEV infection causes severe hepatitis during pregnancy with a mortality rate up to 58%. HEV infection during pregnancy has been reported to take a severe course in developing countries (Scharschmidt 1995; Purcell and Emerson 2001; Khuroo and Kamili 2003). In addition, zoonotic transmission as well as food-borne transmission of HEV is reported in Japan (Suzuki et al. 2002; Tei et al. 2003; Yazaki et al. 2003). Furthermore, the risk factors for acute HEV infection includes male with higher age, and residence in Northern part of Japan (Okamoto et al. 2003). Although this patient lived in Northern part of Japan, she had no known other risk factors. The infectious route and the cause of her severe clinical course are still unknown. Further studies regarding the role of HEV genotype and other possible factors are feasible to understand the pathogenesis.

In conclusion, we must take acute hepatitis type E into consideration for the diagnosis of cryptogenic acute hepatitis, including ones previously diagnosed as AIH of acute onset type like this case. Further studies are feasible to understand the clinical feature of HEV infection, especially the association with autoimmune hepatitis.

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A case of acute hepatitis with positive autoantibodies who actually had hepatitis E virus infection

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Abstract

Hepatitis E virus (HEV) is one of the major causative agents of acute hepatitis in many developing countries. On the other hand, recent intensive investigation has revealed the existence of non-imported cases in industrialized countries. We encountered a sporadic patient with hepatitis E in 1999, who had had no recent travel abroad. He was a 67-year-old Japanese, and his laboratory data were negative for serum markers of hepatitis A, B and C virus infection and positive anti-nuclear antibody, anti-smooth muscle antibody and high level of serum immunoglobulin G. He scored as probable autoimmune hepatitis (AIH) with the scoring system by the international AIH group. He was given a diagnosis of acute cryptogenic hepatitis including acute onset AIH in those days, but the recent retrospective examination with frozen stocked serum revealed his exact diagnosis. In conclusion, we must take HEV infection into consideration for the diagnosis of cryptogenic acute hepatitis even in the developed countries, and some patients with hepatitis E could demonstrate positive for autoantibodies similar to clinical features of AIH. This case demonstrated the needs for further studies about clinical feature of acute hepatitis E virus infection.

Keywords: HEV; Acute hepatitis; Autoimmune hepatitis; Cryptogenic hepatitis

1. Introduction

Hepatitis E virus (HEV) is one of the major causative agents of acute hepatitis in many developing countries [1]. However, the availability of recent intensive investigation has revealed the existence of some non-imported cases even in the industrialized countries. It has been recently revealed that the virus is much more diverse and widespread than expected, and four major genotypes are identified up to now [2].

Patients with hepatitis E have been scarcely reported in Japan, and most of them observed so far were recognized as imported ones [3,4]. However, several sporadic cases without history of traveling to endemic area have been reported recently [5–10]. Thus, the clinical manifestation of acute hepatitis E in Japan has not been established.

In this report, we present a patient with acute hepatitis E who had not been abroad prior to the diagnosis, and demonstrated clinical features similar to autoimmune hepatitis (AIH).

2. Case report

A 67-year-old Japanese man, who was an office worker, was referred and admitted to our hospital on September 15, 1999.

He felt general fatigue, abdominal discomfort and nausea on September 7, 1999, and visited a local physician 1 week later. He was pointed out jaundice and his laboratory tests revealed elevated levels of liver enzymes (asparate

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Table 1
Laboratory findings on admission of 67-year-old man

T.Bil	3.2 mg/dl	PT	86%
D.Bil	2.4 mg/dl	HPT	61%
AST	2850 IU/l	WBC	4800 μl^{-1}
ALT	5180 IU/l	RBC	483 × 104 μl^{-1}
ALP	548 IU/l	Hb	15.6 g/dl
γGTP	513 IU/l	Plt	20.0 × 104 μl^{-1}
LDH	984 IU/l	ANA	×80
CRP	2.0 mg/dl	ASMA	×80
BUN	8.0 mg/dl	AMA	–
Cr	0.8 mg/dl	IgG	2178 mg/dl
TP	7.6 g/dl	IgA	294 mg/dl
Alb	4.1 g/dl	IgM	399 mg/dl

aminotranferase [AST] 6730 IU/l, alanine aminotransferase [ALT] 7810 IU/l]. His previous medical history revealed nothing particular events such as blood transfusion or operations. As for an alcohol intake, he had 30–50 g/day every day. He had no recent history of travel abroad, neither contact with foreigners nor animal exposure, but he had been to Hokkaido many times on business, where HEV infection has been found to be endemic in Japan. He had not received any drug medications or intravenous injection. None of his family members had suffered from acute hepatitis. Physical examination on admission revealed: blood pressure 130/80 mmHg, body temperature 36.3 °C and clear consciousness. The bulber conjunctiva were slightly icteric. No peripheral edema, vascular spider, palmar erythema and flapping tremor were observed.

His laboratory tests on admission revealed serum AST 2850 IU/l, ALT 5180 IU/l and total bilirubin 3.2 mg/dl, and serum markers of hepatitis A, B, C virus, EB virus, cytomegalovirus and herpes zoster virus were negative. The serum assay for these viruses were established elsewhere. The results of the initial tests revealed anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) were positive along with high level immunoglobulin G (IgG) and immunoglobulin M (IgM), but anti-mitochondria antibody (AMA) was negative as shown in Table 1. Abdominal ultrasound sonography (US) and computed tomography (CT) showed just mild fatty liver change.

At first, we clinically gave him a diagnoses of acute cryptogenic hepatitis and probable AIH based on international AIH score (point: 12, before treatment). We considered administration of prednisolone (PSL), but his general condition as well as his laboratory data showed spontaneous and rapid recovery as shown in Fig. 1. On the 7th hospital day, we administrated liver biopsy. The pathology of the specimens showed inflammatory changes namely in the portal area and regenerating change of the hepatocytes. It was just compatible with the recovery phase of acute hepatitis. Finally, he was discharged on October 6, 1999. Although his ANA and serum IgG levels were elevated even after 4 years (Table 2), his laboratory data and general condition improved spontaneously and rapidly without registration of PSL and showed no relapse in 5 years, minimally [11,12]. It was far from typical

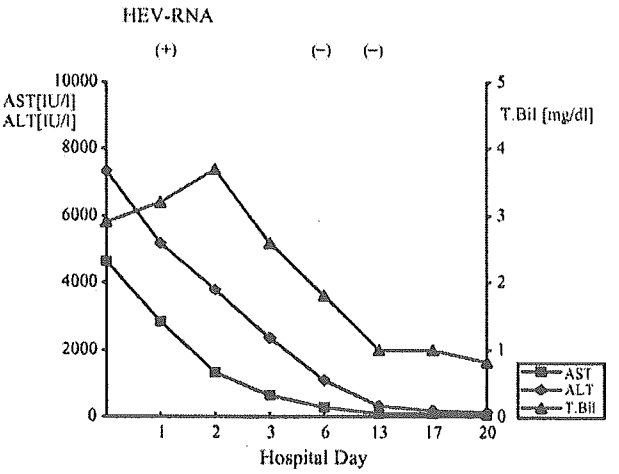

Fig. 1. Clinical course of 67-year-old patient. The patient demonstrated HEV viremia on admission, which has dissolved after 6th hospital day.

Table 2
Transition of serum IgG levels and ANA titer

	Year 1999		Year 2003	
	16 September	18 October	15 November	28 October
Serum IgG (mg/dl)	2178	1629	2060	2057
Serum IgA (mg/dl)	265	249	258	258
Serum IgM (mg/dl)	339	249	218	202
ANA (titer)	40	Not tested	20	20

clinical features of patients with AIH including acute onset type.

Later, he was further evaluated for the HEV infection. Enzyme-linked immunosorbent assays (ELISAs) and RT-PCR were performed with frozen stocked sera sample as previously described [13,14].

HEV-RNA (genotype IV) and immunoglobulin A (IgA), IgM and IgG class antibodies against HEV were detectable in his serum (Table 3). Although we have tried to identify possible source of infection with this case, he had no confident experience with eating raw material from wild animals including reindeer, seal, wild boar and deer. Moreover, he had

Table 3
Transition of the titer of anti-HEV and transaminases

	Year 1999			Year 2003
	15 September	20 September	27 September	28 October
IgM class anti-HEV	1.702	1.606	1.449	0.172
IgG class anti-HEV	>3.000	>3.000	>3.000	2.41
IgA class anti-HEV	>3.000	>3.000	>3.000	0.001
AST (IU/l)	2850	249	109	23
ALT (IU/l)	5180	1097	295	26

no memory that he had eaten raw material from either pork or beef. However, he had been to Hokkaido, the endemic area of HEV infection in Japan and HEV genotype IV is most prevalent in that area. Finally, we gave him a diagnosis of acute hepatitis E. The transition of his laboratory showed the gradual reduction of the titers of IgA, IgM and IgG class antibodies against HEV, but they remained positive for long time even after remission of hepatitis (shown in Table 3).

3. Discussions

In industrialized countries, although anti-HEV antibody has been detected in 4–36% of healthy individuals [15–17], limited numbers of sporadic cases of hepatitis E without traveling to endemic area have been reported [15,18–24]. Similarly, HEV infection was not considered to be endemic in Japan, so we did not routinely check HEV markers as the first line medical examination of cases with acute cryptogenic hepatitis.

Recent study conducted in Japan revealed that 11 (12.6%) of 87 patients who had previously been given a diagnosis of sporadic acute hepatitis of non-A, B and C etiology were infected with HEV. The sero-prevalence of antibodies against HEV in healthy individuals was reported to range from 1.9 to 14.1% in Japan [7,8]. These findings indicate that HEV infection may be endemic in Japan, so we evaluated the possible involvement of HEV infection by serological markers of a patient who had been given a diagnosis of acute hepatitis of unknown etiology.

In general, hepatitis E is diagnosed by serological tests: (i) detection of IgM type anti-HEV, (ii) elevated titer of IgG type anti-HEV and (iii) positive viral RNA by RT-PCR. We tested IgA in addition to IgM, IgG class antibodies against HEV by ELISAs and HEV-RNA by RT-PCR with his stocked sera. IgA class anti-HEV antibody can be utilized as additional confirmatory antibody for recent HEV infection [25,26]. Our examination revealed HEV-RNA (genotype IV), and IgM, IgG and IgA class antibodies against HEV were all positive. It is notable that genotype IV is more prevalent in Hokkaido than in Honshu. The patient's several histories of traveling to Hokkaido supported that he could be infected with HEV in that endemic area with this genotype. The results turned out that his exact diagnosis was acute hepatitis E. We had difficulty with his diagnosis in those days, although current investigation resolved our doubt. Given these data, we have registered the obtained sequence to DDBJ/EMBL/GeneBank (accession number AB206467).

As for other serological findings, he showed positive several autoantibodies such as ANA and ASMA and high IgG similar to clinical features of AIH. His serological findings imply two possibilities: (i) some patients with viral hepatitis can demonstrate clinical features of AIH [27], giving the hypothesis that HEV infection also could show clinical features similar to AIH, and (ii) some patients with AIH can be induced by a viral infection including hepatitis A [28,29], suggesting he had originally autoimmune factor and it was activated with HEV infection. In other words, HEV might trigger the development of AIH.

The facts below stand for the former idea. First, the patient was 67-year-old and had never been pointed out liver dysfunction not only in previous annual health checkup but also in that after the remission of acute hepatitis. In Japan, the feature of distribution of patients with AIH is the dominance of middle-aged women and acute onset AIH is rare [11]. Furthermore, the interface hepatitis and centrilobular necrosis are common in both acute-onset and classical AIH [30], but the pathology of the specimens did not show clinical features like that.

In general, infection with a particular microbe can indicate a particular autoimmune disease. It derives from the structural similarity between viral T cell epitopes and self-peptides or the result as a by-product of the immune response to microbial infection [31,32]. We assumed from the facts that positive for ANA, ASMA and elevation of serum IgG and IgM levels was due to the non-specific reaction with viral infection or possibly specific reaction with some type of HEV infection. Although HEV infection is known to induce IgM and IgG humoral immune responses, and HEV antigen is reported to induce serum IgG and fecal IgA in the animal models [33,34], the clinical features of the patients with HEV in both developed and developing countries are not in common. Further studies are required to solve the question.

In Japan, the risk factors for acute HEV infection are reported: male with higher age, and residence in northern part [35]. He agrees with the risk factors. He was a resident in Miyagi Prefecture, the northeastern area of Japan. Nevertheless, his infectious route was still unknown. He had taken kinds of fish and meat in Hokkaido, the most endemic area of HEV infection in Japan, including in the raw with alcohol intake. His wife was also examined about the possibilities of her past HEV infection in 2004, but we could not detect any class antibody against HEV. We considered him to be infected from foods in Hokkaido from these facts, but further investigation, especially inquiry regarding taste for foods, is needed.

In conclusion, we must take acute hepatitis type E into consideration for a diagnosis of acute cryptogenic hepatitis also in industrialized countries, and some cases with hepatitis E can show clinical features similar to AIH. It is also desirable to establish the easier and more accurate clinical diagnostic method for HEV infection. Further study is feasible to understand the clinical features of HEV infection, especially the association with AIH.

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