ACKNOWLEDGMENT

The authors thank Rohan Walsh and Andrew Norden for bringing two of the patients to their attention.

Received May 1, 2006. Accepted in final form February 15, 2007.

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医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 6. 30	該当なし	
一般的名称	(製造承認書に記載なし)		研究報告の公表状況	H. Ikeda, H. Sakata, K. Matsubayashi, E. Tokushima, S. Tanaka, S. Sato, T. Kato. International Society of Blood Transfusion 17th Regional Congress, Europe; 2007 Jun. 23-27; Madrid.	公表国 日本	
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)					

研究報告の概要

○献血者のHEVスクリーニング

背景:本邦の主要なHEV伝播ルートは、動物食肉由来の食物感染である。最近我々は、輸血により伝播したE型肝炎症例を報告した。この症例の原因献血者は、動物由来食物ルートより感染したと考えられ無症状であった。

目的:1)献血者のHEVスクリーニングにより輸血伝播HEV感染を予防すること。2)HEV感染の自然史を明らかにすること。

方法:HEV-RNAの検出と定量はTaqMan real-time RT-PCR法により実施し、HEV-RNAを in vitroで転写したcDNA テンプレートを定量のスタンダードとして用いた。HEV 遺伝子型は、ORF1配列を基にダイレクトシークエンス法および系統樹解析により判定した。遺伝子組み換えHEVウイルス様粒子や市販のキットを用いたin-house ELISAにより、抗HEV抗体を検出するELISA法を実施した。

結果:2005年1月～2006年8月に北海道において献血者のHEVスクリーニングを行った。388,119名のうち、男性33名(1/7,120)、女性22名(1/6,962)がHEV-RNA陽性で、genotype 3が優勢であった(G3/G4=51/4)。55名中40名は献血時のHEV抗体陰性であり、後に陽性となった。フォローアップ検査では、一部のHEV陽性献血者のALT値が67～333 IU/Lまで上昇したが自覚症状のある献血者はいなかった。HEV-RNAは最長37日間検出され、最短で献血の6日後に検出されなくなった。IgM抗体は最短51日で検出されるようになった(献血後237日以上存在した)。55人分の献血血液のうち7製剤が輸血された。2製剤は2名の患者にHEV感染を発症させ、別の2製剤は2名に輸血されたがHEVを発症させず、3製剤では患者が輸血後30日以内に死亡したため不明であった。献血者の感染ルートは明らかではないが、献血者の多くに過去60日以内の動物内臓肉摂食歴があり、そうした肉ではHEV汚染が時々報告されているため、動物由来食物感染による可能性が高い。

結論:献血者の7000人に1人の割合でHEV-RNAが検出された。HEVキャリアの一部にALT値上昇が認められたが、ほとんどが無症状でHEV抗体陰性であった。HEVウイルス血症は、献血後最長で37日間検出された。HEV陽性献血者由来の輸血を受けた患者7名のうち、少なくとも2名が感染した(1名は顕性、もう1名は不顕性)。献血者の感染ルートは不明だが、動物食肉由来の食物感染が示唆されている。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
北海道の献血者のHEVスクリーニングを行ったところ、献血者の7000人に1人の割合でHEV-RNAが検出され、HEV陽性献血者由来の輸血を受けた患者7名のうち、少なくとも2名が感染した。献血者の感染ルートは明らかではないが、動物由来食物感染が示唆されたとの報告である。	日本赤十字社では、厚生労働科学研究「E型肝炎の感染経路・宿主域・遺伝的多様性・感染防止・診断治療に関する研究班」と共同して、献血者におけるHEV感染の疫学調査を行っている。北海道における輸血HEV感染報告を受け、試験的に北海道では研究的NATを行うなど安全対策を実施している。また、輸血による肝炎ウイルス感染防止のため、血液中のALT値61IU/L以上の血液を輸血用から排除している。今後もHEV感染の実態に関する情報の収集及び安全対策に努める。

(1)

Poster Session
6.2 Blood safety - transfusion transmitted disease (TTD) - hepatitis

P203

HEV SCREENING FOR BLOOD DONORS

Ikeda H, Sakata H, Matsubayashi K, Tokushima E, Tanaka S, Sato S, Kato, T
Hokkaido Red Cross Blood Center, Sapporo, Japan

Background: Zoonotic food-borne infection is a major transmission route of HEV in Japan. Recently, we reported a transfusion-transmitted hepatitis E case (Ikeda H et al., Transfusion 2005; 45: SP207), where the causative donor was apparently infected by zoonotic food-borne route and remained asymptomatic.
Aims: 1)To prevent transfusion-transmitted HEV infection by screening blood donors for HEV.
2) To clarify natural history of HEV infection.
Methods: HEV-RNA detection and quantitation was carried out by TaqMan real-time RT-PCR using in vitro-transcribed RNA from HEV cDNA template as quantitation standards. HEV genotype was determined by PCR direct sequencing and phylogenetic analysis base on ORF1 sequences.
ELISA for anti HEV was carried out with in-house ELISA using recombinant HEV virus-like particles(Li TC et al., J Med Virol 2000;62:327–33.) and/or commercial kit (Cosmic Corporation. Co., Ltd., Japan)
Results: Blood donors were screened for HEV-RNA from January 2005 to April 2006. Of 388, 119 donations, 33 males (1/7120) and 22 females (1/6962)were HEV-RNA(+). Genotype 3 was predominant(G3 /G4 = 51/4). Of 55 HEV-RNA(+)donors, 40 were seronegative at donation and eventually seroconverted. Follow-up studies revealed that no HEV(+)donor had subjective symptom, although ALT levels went up to 67–333 IU/L in some of them. HEV-RNAs were detected in 37 days at the longest or undetected in 6 days at the earliest after the donations. Their IgM antiHEV became detectable in 51 days at earliest or lasted more than 237 days after the donations.
Of 55 donations, seven were used for transfusion; two caused HEV infection in two patients; two did not cause infection in two patients; three were unknown because patients died before 30 days after transfusion. Although their infection routes were not very clear, zoonotic food-borne route was likely, because most of them had history of ingesting animal meat derived from internal organs in the past 60 days and such meat was reported to be sometimes contaminated with HEV (Kato M, et al., Kanzo 2004; 45:688).
Conclusion: HEV-RNA was detected in our blood donors at the rate of about 1/7000. HEV carriers were mostly asymptomatic and seronegative, although high ALT level was observed in some. HEV viremia was detected in 37 days at the longest after donation. Of seven patients who were transfused with HEV positive blood, at least two were infected (one symptomatic and the other asymptomatic). Although their infection route was not clear, zoonotic food borne infection was suggestive.

Print ISSN: 0042-9007
Online ISSN: 1423-0410

別紙様式第2-1

No. 38

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 6. 30	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	手稲渓仁会病院消化器病センター 松居剛志. 第43回日本肝臓学会総会; 2007 May 31-Jun. 1; 東京.	公表国 日本
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			

研究報告の概要

○輸血後E型肝炎の2例

背景と目的:近年、本邦におけるHEVの感染経路や、その臨床像が明らかになりつつある。今回、発症前からのウイルス血症推移、肝炎発症と沈静化までの経過を観察しえた輸血後E型急性肝炎(AH-E)2例を経験したので報告する。

症例1:60歳代、男性。2003年9月NH Lymphomaと診断され、治療中、血小板減少に対し照射濃厚血小板(Ir-PC)を輸血。後日、輸血されたIr-PCがHEV陽性であることが判明し、同年10月AH-E発症の可能性が高いと考えられ、精査加療目的で当院へ転院となる。輸血21日目にHEV RNA(genotype 4)を検出、対数増殖期を経て44日目に7.2log copies/mlとピークを示した。ALTは21日目に正常上限を越え59日目に673IU/Lまで上昇した。Genotype 4感染による肝炎の重症化を懸念し、IFNを使用したがウイルス血症、肝炎は改善せず、PSL(プレドニゾロン)30mg内服によりALTは低下、その後抗HEV IgGの出現と同期し87日目にウイルス血症も改善した。

症例2:70歳代、男性。2005年8月、急性心筋梗塞治療中に投与されたIr-PCが後にHEV陽性と判明し、AH-E精査加療目的に当院へ転入となる。HEV RNA(genotype 3)は輸血後3日目に同定され、54日目に7.4log copies/mlとピークに達し、ALTは17日目に正常上限を越え65日目に972IU/Lまで上昇した。抗HEV IgM、IgGが60日目に陽性化後HEV、トランスアミナーゼは低下し、113日目にウイルス血症も改善した。

まとめ:HEVウイルス血症は10～22日の潜伏期間を経て発現、対数増殖後約50日前後にピークを示し、その直後にAST、ALT上昇と血中HEV抗体の出現を順次認めた。

結語:輸血後AH-E2例の全経過を追跡しえた。本例のように、発症前から血中ウイルス感染マーカーを生化学所見、経過と同時に観察したAH-E例は実験例を除くと未見であり、貴重な症例と考えられる。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
発症前からのウイルス血症の推移、肝炎発症から沈静化までの経過を観察しえた輸血後E型肝炎症例において、HEVウイルス血症は10～22日の潜伏期間を経て発現、対数増殖後約50日前後にピークを示し、その直後にAST、ALT上昇と血中HEV抗体の出現を認めたとの報告である。	日本赤十字社では、厚生労働科学研究「E型肝炎の感染経路・宿主域・遺伝的多様性・感染防止・診断治療に関する研究班」と共同して、献血者におけるHEV感染の疫学調査を行っている。北海道における輸血HEV感染報告を受け、試験的に北海道では研究的NATを行うなど安全対策を実施している。また、輸血による肝炎ウイルス感染防止のため、血液中のALT値61IU/L以上の血液を輸血用から排除している。今後もHEV感染の実態に関する情報の収集及び安全対策に努める。

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O-178　輸血後E型肝炎の2例

松居剛志[1], 姜　貞憲[1], 矢根　圭[1], 西森博幸[1], 桜井康雄[1], 辻　邦彦[1], 真口宏介[1], 坂田秀勝[2], 松林圭二[2], 加藤俊明[2], 池田久實[2]
手稲渓仁会病院消化器病センター[1], 北海道赤十字血液センター検査部[2]

【背景と目的】近年, 本邦におけるHEVの感染経路や, 臨床像が明らかになりつつある. 今回, 発症前からのviremia推移, 肝炎発症と沈静化までの経過を観察しえた輸血後AH-E 2例を経験したので報告する.
【症例1】60歳代, 男性. 2003年9月NHLymphomaと診断され, 治療中, 血小板減少に対しIr-PCの輸血をうけた. 後日, 輸血されたIr-PCがHEV陽性であることが判明し, 同年10月AH-E発症の可能性が高いと考えられ, 精査加療目的で当院へ転院となる. 輸血21日目にHEV RNA (genotype 4) を検出, 対数増殖期を経て44日目に7.2 log copies/mlとピークを示した. ALTは21日目に正常上限を越え59日目に673 UI/Lまで上昇した. Genotype 4感染による肝炎の重症化を懸念し, IFNを使用したがviremia, 肝炎は改善せず, PSL 30mg内服によりALTは低下, その後抗HEV IgGの出現と同期し87日目にviremiaも改善した.
【症例2】70歳代, 男性. 2005年8月, 急性心筋梗塞治療中に投与されたIr-PCが後にHEV陽性と判明し, AH-E精査加療目的に当院へ転入となる. HEV RNA (genotype 3) は輸血後3日目に同定され, 54日目に7.4 log copies/mlとピークに達し, ALTは17日目に正常上限を越え65日目に972 IU/Lまで上昇した. 抗HEV IgM, IgGが60日目に陽性化後HEV, トランスアミナーゼは低下し, 113日目にviremiaも改善した.
【まとめ】HEV viremiaは10~22日のvirus学的潜伏期間を経て出現し対数増殖後約50日前後にピークを示し, その直後にAST, ALT上昇と血中anti HEVの出現を順に認めた.
【結語】輸血後AH-E2例の全経過を追跡しえた. 本例のように, 発症前から血中virus感染markerを生化学所見, 経過と同時に観察したAH-E例は実験例を除くと未見であり, 貴重な症例と考えられる.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 8. 23	該当なし	

一般的名称	新鮮凍結人血漿	研究報告の公表状況		公表国
販売名(企業名)	新鮮凍結血漿「日赤」(日本赤十字社) 新鮮凍結血漿-LR「日赤」(日本赤十字社)		Novitsky V, Gaolathe T, Woldegabriel E, Makhema J, Essex M. Clin Infect Dis. 2007 Sep 1;45(5):e68-71. Epub 2007 Jul 20.	米国

研究報告の概要

○ボツワナにおける血清学検査陰性のHIV-1サブタイプC感染
ボツワナにおける急性HIV-1感染スクリーニング中に特定された抗体陰性のヒト免疫不全ウイルス1型(HIV-1)サブタイプC感染の最初の症例を報告する。HIV-1抗体検査の結果は、迅速検査、通常の酵素免疫測定法及びウエスタンブロットで、全て陰性であった。遺伝子組換えが生じていないHIV-1サブタイプC感染は、ウイルスのgag、pol及びenv遺伝子のジェノタイピングによって確定された。臨床的に安定した状態での患者の紹介からAIDS関連死までの期間は、およそ3ヵ月だった。本症例は、サブタイプCが優勢なアフリカ南部における血清学検査陰性HIV-1感染の発生率を調査することの重要性を示している。

使用上の注意記載状況・その他参考事項等

新鮮凍結血漿「日赤」
新鮮凍結血漿-LR「日赤」

血液を介するウイルス、
細菌、原虫等の感染
vCJD等の伝播のリスク

報告企業の意見	今後の対応
ボツワナにおいて、HIV-1抗体検査陰性でウイルス遺伝子検査により感染が確認されたHIV-1サブタイプC感染の最初の症例報告である。	日本赤十字社では、HIVについて20プールNATを含むスクリーニングを行い、陽性血液を排除している。国内外のHIV感染、AIDS発生の動向やHIV感染に関する新たな知見等について今後も情報の収集に努める。次世代NAT試薬についての評価、検査方法の改良に向けた開発・検討を進める。

BRIEF REPORT

A Seronegative Case of HIV-1 Subtype C Infection in Botswana

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We report the first case, to our knowledge, of antibody-negative human immunodeficiency virus type 1 (HIV-1) subtype C infection, which was identified during screening for acute HIV-1 infection in Botswana. Results of tests for HIV-1 antibodies were consistently negative, including rapid and regular enzyme-linked immunosorbent assay and Western blot. The nonrecombinant HIV-1 subtype C infection was confirmed by viral genotyping within the *gag*, *pol*, and *env* genes. The period between referral of the patient in a clinically stable condition and AIDS-related death was ~3 months. The reported case indicates the importance of studying the prevalence of seronegative HIV-1 infection in southern Africa, where subtype C predominates.

Routine HIV-1 testing by rapid or standard ELISA has become a commonly used health care practice. The high sensitivity of currently used licensed ELISA kits results in a relatively low frequency of false-negative results during HIV-1 testing. Testing during the seroconversion "window period" is the most recognized reason for a temporarily negative ELISA result; other reasons may include atypical virus or agammaglobulinemia. Although false-negative ELISA results can be confirmed by alternative methods that target viral RNA in plasma and/or cell-associated proviral DNA, the nucleic acid–based methods are not commonly used for routine HIV-1 testing.

Some patients may not develop antibodies after primary HIV infection, and a lack of adequate immune response may facilitate rapid progression of disease [1]. Rare cases of seronegative HIV-1 subtype B infection have been reported in Europe and North America [1–6]. Among non-B clades, HIV-1 subtype A infection was found in a persistently HIV-1–seronegative woman from Ivory Coast [7], subtype A2 virus was identified in an HIV-1–seronegative woman in Portugal [8], HIV-1 CRF01_AE (a circulating recombinant form of HIV-1 that is composed predominantly of subtype A and a unique envelope designated lineage E) was documented in 4 HIV-1–seronegative drug users in Thailand [9, 10], and a rare A/G recombinant was found in an HIV-1–seronegative woman from Ghana [11]. To date, no studies, to our knowledge, have reported cases of seronegative HIV-1 subtype C infection, which is the predominant HIV-1 subtype in the worldwide epidemic.

Here, we report a case of persistently antibody-negative HIV-1 subtype C infection in Botswana. A 46-year-old woman was referred to our study of primary HIV-1 subtype C infection in Botswana for HIV screening with 2 documented antibody-negative rapid ELISA tests performed elsewhere during the previous year. At the time of referral, she did not present with any opportunistic or chronic illnesses but had complaints of recent deterioration in general health and weight loss. The patient had received antifungal treatment for oral candidiasis and nonspecific oral ulcers at the local city-council clinic. No behavioral risk for HIV infection was identified by interview of the patient or review of medical records. She denied having any sexual relationships for >6 months prior to study entrance and reported no blood transfusions or injection drug use.

After receiving counseling and signing an informed consent form, the patient was tested for HIV-1 antibodies and viral RNA. The antibody tests, including rapid ELISA (Determine HIV-1/2, Abbott, and Uni-Gold HIV kit, Trinity Biotech) and regular ELISA (Murex HIV 1.2.0, Abbott, and Ortho HIV-1/2 Ab Capture, Ortho Diagnostics), yielded negative results. Viral RNA was detected in plasma by RT-PCR at >750,000 copies/mL. The tests were repeated, and the results remained the same. Western blot (HIV 2.2 Western Blot assay, Gene Labs Diagnostics) did not reveal any reactive bands. IgG and IgM levels were within the normal range (1410 mg/dL and 179 mg/dL, respectively), whereas the IgA level was elevated to 588 mg/dL. Her $CD4^+$ T cell count was 38 cells/mm^3, and her $CD8^+$ T cell count was 138 cells/mm^3. The patient was offered antiretroviral therapy but declined. Her viral load fluctuated from 451,000 copies/mL to >750,000 copies/mL over 2 months. Her $CD4^+$ cell count decreased to 19 cells/mm^3. The $CD4^+/CCR5^+$ T cell percentage was detected within the range of 10.3%–17.3%, and the $CD4^+/CXCR4^+$ T cell percentage dominated at ~95%.

Received 26 March 2007; accepted 8 May 2007; electronically published 20 July 2007.

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Clinical Infectious Diseases 2007;45:e68–71

1058-4838/2007/4505-00E4$15.00
DOI: 10.1086/520683

Esophageal candidiasis and severe oral herpes were treated with fluconazole and oral acyclovir. Eight days after the initiation of HAART (600 mg of efavirenz once daily and 150 mg of lamivudine plus 300 mg of zidovudine twice daily), the patient presented with inability to communicate and unusual behavior. Altered mental status and HIV encephalopathy were listed as probable clinical conditions. Cryptococcal meningitis and intracranial space-occupying lesions or infections were ruled out by analysis of CSF specimens and CT of the brain. The biochemical laboratory results are summarized in table 1. The patient died 4 days after admission. Encephalopathy or meningitis, HIV infection, and pulmonary tuberculosis were listed as the diseases or conditions leading to death. Immune reconstitution syndrome [12] or herpetic etiology of encephalopathy could not be ruled out. Postmortem examination was not available, and therefore, the cause of death could not be ascertained.

Previous reports of seronegative HIV-1 infections described patients who progressed to AIDS rapidly [1]. Rapid progression was also observed in the current case. Routine identification of antibody-negative HIV infections may be associated with substantial logistical challenges. Nevertheless, initiation of HAART in patients identified to be seronegative who have high plasma viral loads apparently should not be deferred.

It is known that high levels of circulating immune complexes can be found during the late stage of HIV infection. Formation of immune complexes in the sera of patients with AIDS and AIDS-related complex may be responsible for failure to detect free HIV antibodies in some patients [13, 14]. Therefore, we cannot exclude formation of immune complexes as a potential reason for negative results of tests for HIV antibodies in the study patient. However, patients with detectable circulating immune complexes usually have increased levels of each immunoglobulin class [15]. Consequently, the normal levels of IgG and IgM, as well as the results of seronegative tests performed within the year prior to referral, might argue against immune complexes being the main cause of the HIV antibody–negative status of the patient in the current study.

Table 1. Clinical values for a patient presenting with HIV-1 antibody–seronegative AIDS.

Test or variable	Result or value	Reference value
HIV PCR	Positive	...
Rapid plasma regain	Nonreactive	...
Hemoglobin level, g/dL	10.1	12–15
Corpuscular volume, mean fL	78.5	83–99
Neutrophils, %	90.7	40–80
Absolute neutrophil count, $\times 10^9$ neutrophils/L	6.27	2–7
Lymphocytes, %	3.6	20–40
Eosinophils, %	0.0	1–6
Platelet count, $\times 10^9$ platelets/L	280	150–400
Sodium level, mmol/L	126.47	135–145
Potassium level, mmol/L	3.31	3.5–3.1
Chloride level, mmol/L	91.31	95–108
Urea level, mmol/L	6.34	2.0–7.0
Serum creatinine level, μmol/L	77.23	53–97
CSF sample examination		
Glucose level, mmol/L	3.40	2.25–4.55
Total protein level, g/L	1.90	0.10–0.45
Macroscopic examination	Clear, no xanthochromia, no clot	...
Microscopic examination	India ink–negative; no WBCs or yeast cells seen	...
Cryptococcal antigen test	Negative	...
Culture	No growth	...
$CD4^+$ cell count, cells/μL	23.32	700–1000
Viral load, copies/mL	>750,000	...
HIV ELISA	Negative	...
Alkaline phosphatase level	Not determined	...
AST level, U/L	74.86	10–34
ALT level, U/L	16.13	11–44
Hepatitis B virus surface antigen test	Negative	...

NOTE. ALT, alanine aminotransferase; AST, aspartate aminotransferase.