医薬品
医薬部外品　研究報告 調査報告書
化粧品

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
				2004.10.20	該当なし	

一般的名称	人赤血球濃厚液	研究報告の公表状況	日本輸血学会誌, 2004;50(5):726-729	公表国 日本
販売名(企業名)	赤血球M・A・P「日赤」(日本赤十字社) 照射赤血球M・A・P「日赤」(日本赤十字社)			

研究報告の概要

シングルドナー由来の血小板輸血後に *Morganella morganii*（*M. morganii*）による敗血症性ショックを呈した7ヶ月の男児の症例について報告する。患児の先天的心疾患に対して、動脈管閉鎖術ならびに右室流出路形成術を施行した。しかし心不全、呼吸器不全とも改善しなかったため、6ヶ月後に二回目の手術を施行した。術後20日目に患児が播種性血管内凝固による血小板減少症を呈したため、シングルドナー由来の血小板製剤を輸血した。輸血開始1時間後に悪寒および発疹が出現し、2時間後には高熱、血圧低下、頻拍をきたしたため、輸血を中止した。男児血液および血小板製剤の細菌培養が行われ、3日後に血液、血小板製剤の両者から *M. morganii* が検出された。セフタジジム投与後、発熱はおさまり血漿CRP値が低下したことから、血小板製剤の *M. morganii* 汚染が強く疑われた。*M. morganii* による輸血後感染症が強く示唆された報告は、今回が最初であると考えられる。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「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
M. morganii による輸血後感染症が強く示唆されたとの報告である。本菌による感染症はまれである。 本症例については、副作用感染症例報告として報告済みである。尚、同時に採血された血漿から菌は検出されなかった。	日本赤十字社は、輸血用血液への細菌の混入防止を目的とした初流血除去及び混入した感染性因子を不活化する技術導入を検討している。

Japanese Journal of Transfusion Medicine, Vol. 50. No. 5　50(5)：726—729, 2004

症　例

血小板輸血後に敗血症性ショックを呈し，*Morganella morganii* 菌による輸血後感染症が強く示唆された1例

石田　明[1)]　上村　知恵[1)]　橋詰　賢一[2)]　饗庭　了[2)]
加藤木利行[2)]　四津　良平[2)]　半田　誠[1)]
[1)]慶應義塾大学医学部輸血・細胞療法部
[2)]同　心臓血管外科

（平成16年5月11日受付）
（平成16年6月14日受理）

A CASE OF SEPTIC SHOCK CAUSED BY *MORGANELLA MORGANII* AFTER SINGLE DONOR-DERIVED PLATELET TRANSFUSION

Akaru Ishida[1)], Tomoe Uemura[1)], Ken-ichi Hashizume[2)], Ryo Aiba[2)], Toshiyuki Katogi[2)], Ryohei Yozu[2)] and Makoto Handa[1)]
[1)]Department of Transfusion Medicine and Cell Therapy,
[2)]Department of Cardio-vascular-surgery, Faculty of Medicine, Keio University

We report a baby with septic shock caused by *Morganella morganii*（*M. morganii*）after a single donor-derived platelet transfusion. A 7-month old boy was admitted to Keio University Hospital and operated on to repair a hereditary cardiac defect. The cardiac failure and respiratory failure did not improve, and a second operation was performed about six months after the first. Twenty days post-operation, he received a single donor-derived platelet transfusion due to thrombocytopenia caused by disseminated intravascular coagulation. Chill and skin rash appeared one hour after the starting of transfusion, followed by a high-grade fever, hypotension and tachycardia at two hours, at which time the transfusion was stopped. Bacterial culture of the patient's blood and platelet concentrate were performed. Three days later, *M. morganii* was detected from both samples. Following the administration of ceftazidime, the fever gradually decreased and plasma CRP levels decreased, leading to the strong suspicion of *M. morganii* contamination of the platelet concentrate. To our knowledge, this is the first case reported of bacteria-contaminated blood transfusion by *M. morganii*. Outcome in this patient would not have been successful of the bacterial contamination of blood products had not been suspected.

Key words：bacteria, infection, *Morganella morganii*, blood product

はじめに

輸血後細菌感染症の発症頻度は決して高くないものの，一定の頻度で起こり得る致死的合併症であり，正しい知識と適切な対応策が不可欠である．

今回我々は，血小板輸血後に敗血症性ショックを呈し，*Morganella morganii*（*M. morganii*）菌による輸血後細菌感染症が強く示唆された症例を経験した．*M. morganii* 菌による輸血後細菌感染症は過去に報告がなく，また本例は適切な対応によって病態の改善が得られた貴重な症例と考えられたの

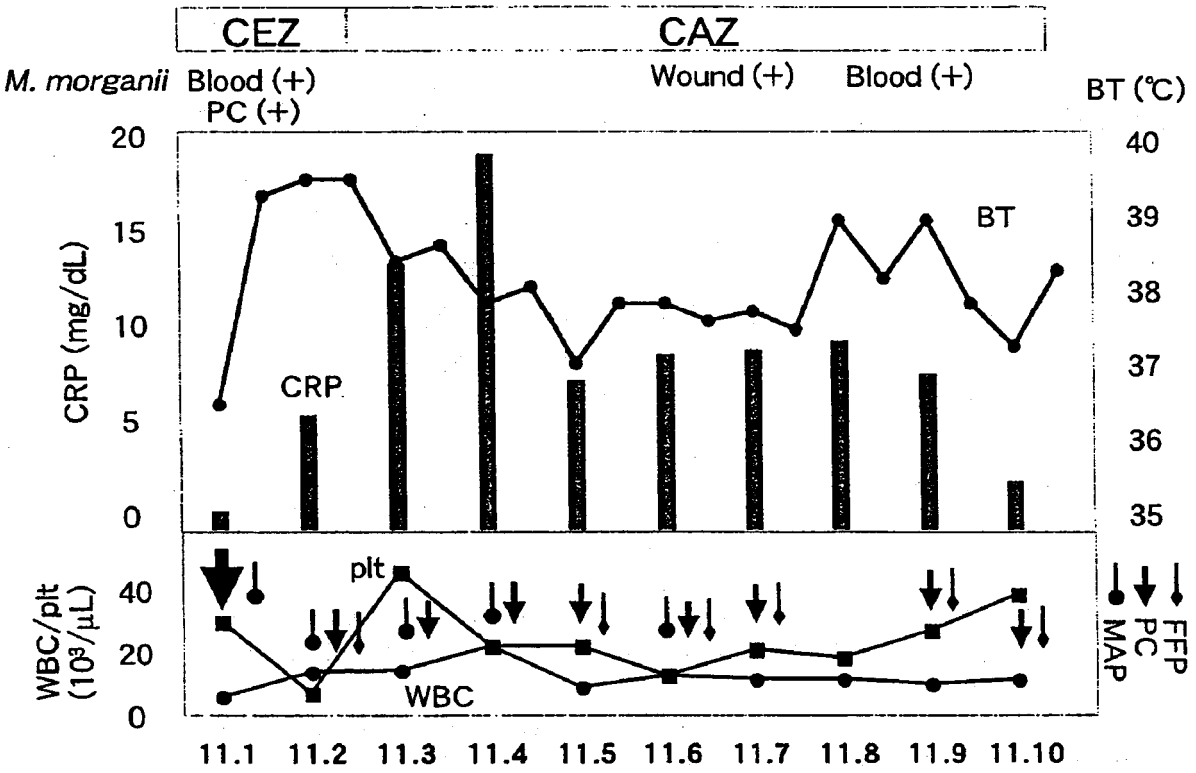

図　Fever developed and plasma CPR levels increased after platelet transfusion. *M. morganii* were detected just after the transfusion from both the patient's blood and the platelet concentrates used. *M. morganii* had not been detected before this. The patient improved two days after the transfusion, when ceftazidime was started.

で，ここに報告する．

症　例

症例は7カ月の男児．平成10年3月3日に近医で出生，出生時体重は2,568g，Apgar scoreは8点，出産は妊娠39週4日目の自然分娩であった．出生時よりチアノーゼを認め，心エコーでファロー四徴，肺動脈弁閉鎖症，大動脈管開存症と診断，プロスタグランジン E_2 療法などの保存的治療が無効なため，手術目的で4月1日に当院転入となった．入院同日に動脈管閉鎖術ならびに右室流出路形成術を施行したが心不全は改善せず，同年10月14日に右室流出路拡大術を施行した．同28日頃より播種性血管内凝固症候群（disseminated intravascular coagulation syndrome；DIC）が出現し，11月1日に血小板数が3.1万/μLに低下したため，血小板製剤（platelet concentrates；PC）を輸血した．製剤は成分採血由来10単位の濃厚血小板「日赤」であり，輸血時に白血球除去フィルター（セパセルPLX-10A-W）を使用した．

輸血開始の時点で体温36.5℃，血圧90/50，脈拍116/分，輸血開始1時間後に顔面と体幹部の紅斑様発疹に気付くも，体温36.8℃，血圧120/60，脈拍125/分と安定していたため，輸血速度を遅くして経過観察した．輸血開始2時間後に紅斑が全身に広がって悪寒と戦慄が出現，体温38.5℃，血圧80/40，脈拍170/分となったため，輸血を中止した（輸血総量35mL）．残りの製剤は無菌的に保冷庫に保存した．輸血中止1時間後，体温38.1℃，血圧75/40，脈拍172/分と改善しないため，昇圧剤投与などの対症的治療を開始し，患者自身の血液（動脈血）培養検査を提出した．抗生物質は術後から予防投与中のCefazolinを継続投与した．同日，一連の経過を主治医と当輸血・細胞療法部で相談し，製剤の一部を細菌培養検査に提出した．出庫時と回収時の2回行った製剤の肉眼的観察では，いずれも外観異常は確認出来なかった．翌々日（同3

日)に，患者血液と血小板製剤の両者で多数の *M. morganii* 菌が検出され，直ちに同菌に感受性がある Ceftazidime の投与を開始した．本患者から同菌が検出されたのはこの時が最初であった．

WBC と CRP は輸血後上昇したが，同 4 日の 22,000/μL，17.98mg/dL をピークに改善傾向を示した．*M. morganii* 菌はさらに同 7 日に手術創部から，同 9 日に動脈血液から検出されたが，以後全て陰性化した．DIC は一時増悪傾向にあり，口腔内，上気道～気管内から粘膜出血が続いたため，濃厚赤血球 MAP，PC，新鮮凍結血漿（fresh frozen plasma；FFP)を輸血した．これらの輸血に伴う合併症はみられなかった．同 10 日に右半身痙攣が出現し，CT で左側頭葉の梗塞巣と硬膜下血腫の所見が確認された．輸血後経過を図に示す．

翌平成 11 年 2 月に *Escherichia Coli* による腹膜炎を併発し，敗血症性ショックのため 2 月 12 日に死亡した．

平成 10 年 11 月 2 日に採取した本患者血液を日本赤十字血液センターに提出し，抗 human leukocyte antigen（HLA）抗体を lymphocyte cytotoxicity test (LCT 法) で，抗 human platelet antigen (HPA) 抗体を mixed passive hemoagglutination test（MPHA 法）で，抗血漿蛋白抗体をオクタロニー法と enzyme-linked immunosorbent assay (ELISA 法)で行ったが，いずれも陰性であった．また本患者に投与した血小板製剤と同一献血者由来の FFP 製剤を用いた，塗沫検査，細菌培養検査，エンドスペシーによるエンドトキシンテストも全て陰性であった．

考　察

本例は血小板輸血後に敗血症性ショックを呈し，血液培養と輸血製剤培養の両者で *M. morganii* 菌が検出された 1 例である．血小板輸血を開始後早期に全身性の発疹様紅斑，悪寒，戦慄を伴う 38℃ 台の発熱が出現し，血圧低下，脈拍増加を認めた．患者血液と血小板製剤から同時に *M. morganii* 菌が検出され，その後さらに術創部と血液から同菌が検出された．

米国の輸血副作用報告システム[1]を用いて解析した BaCon study は，輸血後細菌感染症の現状を提供する，非常に信頼性の高い調査研究である[2]．報告によれば，輸血後細菌感染症の発症頻度はシングルドナー由来血小板製剤 100 万単位当たり 9.98 とされている．国内情報では，赤十字血液センターの医薬情報部が実施している輸血副作用調査が唯一である[3]．この 1998 年から 2001 年までの 4 年間の集計では，輸血後細菌感染疑いは 40 例，うち 27 例で患者検体から細菌が検出された．ただし，同一献血者由来の FFP 製剤から同一菌が検出されたのはわずか 3 例しかない．一方日本赤十字血液センターが行った血小板製剤の無菌試験では，10,750 回に 1 回陽性（陽性率 0.01％）であった[4]．本例は BaCon study の診断基準を全て満たしており，輸血後感染症が強く示唆された．

M. morganii 菌は腸内細菌科 Morganella 属の通性嫌気性グラム陰性桿菌である．鞭毛を有して運動性を示すことが特徴であり，健常人の便から検出されるが，ヒトで菌血症を起こすことは稀である[5]．重症感染症の報告は，新生児敗血症[6][7]，新生児脳膿瘍[8]，造血器腫瘍に合併した髄膜炎[9]等の免疫不全患者に限られ，輸血後感染症の報告はない．

ま と め

アフェレーシス血小板製剤の輸血後に発症し，輸血後細菌感染症の可能性が強く示唆された症例を経験した．本例は血小板輸血後の経過ならびに動脈血液培養と輸血血小板製剤培養の結果から，輸血後 *M. morganii* 感染症に伴う敗血症性ショックを起こしたものと推察された．

追記：2004 年の Transfusion Medicine に献血者由来 *M. morganii* 菌による致死的敗血症例の症例報告が掲載されたので追記致します．

謝辞：本報告に際し，輸血副作用検査にご協力いただきました日本赤十字血液センターに深謝致します．

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販売名(企業名)	赤血球M・A・P「日赤」(日本赤十字社) 照射赤血球M・A・P「日赤」(日本赤十字社)			

研究報告の概要

デング熱を呈したボストン地区の医療従事者の症例を報告する。医療従事者には最近米国北東部以外への旅行歴はなかったが、ペルーから最近帰国した発熱患者の血液をシリンジから培養ボトルに移す際に、医療従事者の顔、眼、鼻、口に血液が飛び散った。血清学的検査により、ペルーから帰国した患者、医療従事者とも急性デングウイルス感染症が確認された。デング熱は熱帯、亜熱帯地域で主にみられる感染蚊を介したウイルス感染症であると考えられており、本症例は粘膜・皮膚を介してデングウイルスが伝播したと推察される最初の報告である。

報告企業の意見	今後の対応
本症例は粘膜・皮膚を介してデングウイルスが伝播したと推察される最初の報告である。なお、東南アジア諸国におけるデング熱の大流行については、本年 3 月に情報を入手し、報告している。	日本赤十字社では問診時に海外渡航歴の有無を確認し、帰国後 4 週間は献血不適とし、デング熱の既往を認めた場合には、治癒後１ヶ月が経過するまでは献血不適としている。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「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

(17)

BRIEF REPORT

Transmission of Dengue Virus without a Mosquito Vector: Nosocomial Mucocutaneous Transmission and Other Routes of Transmission

Lin H. Chen[1,2,3] and Mary E. Wilson[1,3]

[1]Harvard Medical School, and [2]Travel Medicine Center and [3]Division of Infectious Diseases, Mount Auburn Hospital, Cambridge, Massachusetts

We report a case of dengue fever in a Boston-area health care worker with no recent history of travel but with mucocutaneous exposure to infected blood from a febrile traveler who had recently returned from Peru. Serologic tests confirmed acute dengue virus infection in both the traveler and the health care worker. We believe that this is the first documented case of dengue virus transmission via the mucocutaneous route. We present case reports and review other ways that dengue virus has been transmitted without a mosquito vector.

Dengue fever, a mosquito-borne viral infection caused by 4 antigenically distinct dengue virus serotypes in the family *Flaviviridae*, is widespread in tropical and subtropical regions. Infection is characterized by the abrupt onset of fever, myalgia, fatigue, and headache. Diffuse erythema may be present early in the course of infection, and maculopapular eruption may be present later. Associated complications include dengue hemorrhagic fever and dengue shock syndrome, which are diagnosed on the basis of the presence of fever, thrombocytopenia, hemorrhage, and excessive vascular permeability. Laboratory findings commonly include leukopenia, thrombocytopenia, and abnormalities in the results of liver function tests.

We report a case of dengue fever in a health care worker with no recent history of travel outside of the northeastern United States. The source of her infection was a traveler who had recently returned from Peru; the presumed mechanism of transmission was mucocutaneous exposure that occurred during medical care. We describe both cases of dengue fever and review the ways that dengue virus can be transmitted without mosquito vectors.

Case reports. Patient 1, a 48-year-old female traveler, presented in November 2002 with a 5-day history of fever, myalgia, and headache. She had recently returned from Iquitos, Peru (on a trip that lasted from 1 through 10 November), where she worked as a nurse on a medical mission and traveled through the Amazon jungles. She stayed in a hotel that had unscreened, open windows. The patient had received hepatitis A virus, hepatitis B virus, and oral typhoid vaccines prior to travel, and she took mefloquine hydrochloride for malaria prophylaxis. She had received yellow fever vaccine in 1997.

At examination, the patient's temperature was 37.9°C. Abnormal findings included marked erythroderma, especially on the patient's back, and a maculopapular rash along her hairline. She had generalized erythema and a faint maculopapular confluent rash on her arms, legs, and back. Laboratory results obtained on 18 November (i.e., day 2 of illness) are summarized in table 1, along with the results of subsequent studies.

Patient 2, a 37-year-old health care worker, was seen on 19 December 2002 for residual fatigue, myalgia, headache, and low-grade fever, which occurred after an acute illness that began on 28 November 2002 and that included eye pain, nosebleeds, and decreased appetite. Ten days prior to the onset of her symptoms, the patient had contact with blood from patient 1. While patient 2 was transferring blood from a syringe to a blood culture bottle, the needle dislodged from the syringe, and she felt blood splash onto her face, including her eye, nose, and mouth. She had a history of 2 previous occupational needlestick exposures (in 1995 and 1999) and had been vaccinated against hepatitis B virus in 1995. Results of tests for HIV were negative after those incidents. Her only international travel was to the Bahamas 20 years before the exposure occurred; she denied recent travel to Texas or Florida.

Serum samples obtained from both patients were submitted to the Dengue Branch of the Centers for Disease Control and Prevention (CDC) in Puerto Rico. No virus was isolated from patient 1 on day 6 of illness, but dengue virus IgM titers were positive, and IgG titers were positive at 1:163,840. The convalescent-phase serum sample (obtained on day 23 after the onset of illness) was IgM positive. IgG titers were positive at 1:655,360, which is consistent with a secondary flavivirus infection. A serum sample from patient 2 (obtained on day 8 of

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Reprints or correspondence: Dr. Lin H. Chen, Div. of Infectious Diseases, Mount Auburn Hospital, 330 Mount Auburn St., Cambridge, MA (lchen@hms.harvard.edu).

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Table 1. Pertinent laboratory values and findings for 2 patients infected with dengue virus in 2002, by date of illness.

	Patient 1					Patient 2	
Variable	18 Nov	20 Nov	22 Nov	26 Nov	10 Dec	5 Dec	19 Dec
Day of illness	2	4	6	10	24	8	22
Laboratory values							
WBC count[a], × 10^3 cells/mm^3	**2.97**	...	**1.92**	5.47	5.46	**2.63**	5.22
Hematocrit[b], %	37.7	...	**44**	**43**	34.8	**44.6**	39.1
Platelet count[c], × 10^3 platelets/mm^3	255	...	**121**	332	437	**110**	209
ALP level[d], U/L	52	...	61	59	**48**	131	129
ALT level[e], U/L	**107**	...	**108**	**91**	35	**88**	55
AST level[f], U/L	**227**	...	**104**	**65**	21	**75**	36
Findings of serologic tests							
Dengue virus							
Isolation	...	...	−	...	...	...	...
IgM	...	−	+	...	+	+	+
IgG	...	+	+[g]	...	+[h]	−	+[i]
Neutralization antibodies	...	...	...	...	**Serotypes 2 and 3**	...	**Serotype 3**

NOTE. Abnormal values or findings are in bold. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; −, negative finding; +, positive finding.

[a] Normal range, 4.0–10.8 × 10^3 cells/mm^3.
[b] Normal range, 34%–40%.
[c] Normal range, 150–350 × 10^3 platelets/mm^3.
[d] Normal range, 50–136 U/L.
[e] Normal range, 30–65 U/L.
[f] Normal range, 15–37 U/L.
[g] Titer of 1:163,840.
[h] Titer of 1:655,360.
[i] Titer of 1:2560.

illness) was IgM positive and IgG negative. Virus isolation was not attempted. A convalescent-phase serum sample from patient 2 (obtained on day 22 of illness) was positive for IgM and IgG at titers of 1:2560. Neutralization antibody tests showed antibodies against dengue serotype 2 and dengue serotype 3 in patient 1 and antibodies against dengue serotype 3 in patient 2 (figure 1).

Discussion. The usual mosquito vectors for dengue virus are *Aedes aegypti* and, less frequently, *Aedes albopictus*. Vector control programs initiated after World War II eliminated *A. aegypti* from most parts of the Americas, but, after the cessation of the programs in the 1960s, *A. aegypti* reinfestation occurred in most countries, including their urban areas. Dengue has become widespread in the Americas, and its incidence has been increasing [1].

Although dengue epidemics occurred in the United States decades ago, most of the recent cases of dengue have occurred among international travelers. Autochthonous transmission can occur in areas that have competent vectors, such as Texas and Florida. In 2001–2002, local transmission of dengue virus in Hawaii resulted in >100 cases of infection [2].

The diagnosis of dengue is confirmed by isolating the virus from serum either by inoculating live mosquitoes or by performing cell cultures [3, 4]. Although these methods are specific, the sensitivity may be as low as 50%, and the procedures take at least 1 week to perform. Viremia typically begins 2–3 days before the onset of symptoms, and it continues for 4–5 days during acute illness [4]. Hence, there is a limited period during which the virus can be isolated. Among Thai children, viral RNA levels peaked 2 days before defervescence [5]. PCR detects viral RNA [5, 6], can be performed more rapidly than can virus isolation but can detect viral RNA only during the period of viremia, and has a sensitivity similar to that of viral culture.

Because of the drawbacks of culture and PCR, testing paired acute-phase and convalescent-phase serum samples by use of ELISA has become the primary technique for the diagnosis of dengue [7, 8]. Detection of IgM in acute-phase serum samples usually supports the diagnosis of dengue, although IgM may be undetectable during the early stages of the infection. A 4-fold increase in the levels of antibodies in specimens obtained from the acute phase to the convalescent phase strongly supports the diagnosis of acute dengue virus infection. However, dengue virus antibodies cross-react with those of many other flaviviruses, including West Nile virus, Japanese encephalitis, and yellow fever viruses. Acute or past infections with other flaviviruses, or vaccination against them (in the case of yellow fever virus or Japanese encephalitis), can complicate the interpretation of dengue serologic findings.

For patient 1 (the traveler), the results of ELISA performed

Table 2. Details of published reports of dengue virus transmission without a mosquito vector.

Route of exposure	Case report	Reference
Needlestick	A nurse sustained a needlestick while drawing blood from a febrile traveler who had returned from the Ivory Coast. The injury occurred on day 8 of illness, and the nurse developed fever and myalgia 8 days after the event. Both patients were positive for dengue virus IgM, serotype 2.	deWazieres [11]
Needlestick	A medical student pricked a finger while drawing blood from a febrile traveler who had returned from India and Sri Lanka. The incident occurred on day 5 of illness, and the medical student became ill 6 days after the event. For the patient and the medical student, results of tests for dengue virus IgG and IgM were positive.	Langgartner [12]
Needlestick	A health care worker who pricked her finger while drawing blood from a febrile traveler who had returned from Thailand became ill 6 days after the incident. Dengue virus serotype 2 was isolated from the traveler. Results of serologic testing for the health care worker were consistent with acute flavivirus infection.	Hirsch [13]
Needlestick	A nurse sustained a needlestick while drawing blood from a febrile traveler who had returned from Cambodia. The nurse developed headache, myalgia, and arthralgia 4 days after the incident. For the patient, results of tests for dengue virus IgG were positive; fpr the nurse, results of serial tests for dengue virus IgMshowed seroconversion consistent with acute infection.	Bauer [14]
Bone marrow transplantation	A 6-year-old child from Puerto Rico developed fever 4 days after bone marrow transplantation and died 7 days later. Dengue virus serotype 4 was isolated from the child's blood and tissues. The donor became febrile 2 days after the marrow was harvested, and results of tests for dengue virus IgM were positive when performed 3 weeks later, with serotype 4 being the most likely serotype.	Rigau-Perez [15]
Intrapartum or vertical	Six days after birth, a newborn had a positive result of PCR for dengue virus serotype 2. His mother had a denguelike illness 1 day before a cesarean procedure was performed, and results of a test performed 5 days after delivery were positive for dengue virus IgM.	Rigau-Perez [15]
Intrapartum or vertical	Two mothers had acute dengue virus infection develop 4 and 8 days before delivery, respectively. One newborn was ill at birth, had an intracerebral hemorrhage, and died 6 days after birth. Dengue virus serotype 2 was isolated from the infant, and dengue virus IgM was detected in the mother's blood. A newborn from the second mother was thrombocytopenic at birth. Dengue virus serotype 2 virus was isolated from the mother's blood, and dengue virus IgM was detected in the newborn's blood.	Chye [16]
Intrapartum or vertical	A 39-year-old pregnant woman presented with a 3-day history of fever and with thrombocytopenia 5 days before childbirth, and a diagnosis of dengue hemorrhagic fever was established 2 days after presentation. An infant was delivered by cesarean section. Samples of maternal blood were positive for dengue virus IgM. Cord blood and the newborn's blood were PCR positive for dengue virus serotype 2.	Kerdpanich [17]
Intrapartum or vertical	A 27-year-old woman delivered an infant prematurely at 33 weeks' gestation. She developed fever and headache 10 h later, which lasted for 4 days, and she was dengue virus IgM positive and IgG negative. The newborn developed thrombocytopenia and leukopenia on day 9 but recovered. The infant subsequently was found to be positive for dengue virus IgM.	Boussemart [18]
Intrapartum or vertical	A newborn became febrile 6 days after birth by cesarean section, and dengue virus serotype 2 was isolated from the newborn. His mother had fever for 2 days prior to surgery and experienced hemorrhage postoperatively. She was later determined to have acute dengue infection.	Thaithumyanon [19]

on the acute-phase serum samples were dengue virus IgG positive, which could be attributed to past flavivirus infection or to immunization against yellow fever [4]. Although no virus was isolated from the serum samples obtained on day 6 of illness, a serum sample obtained on day 4 was IgM negative but became IgM positive on day 6, which is consistent with previous reports on the timing of seroconversion [9]. In addition, convalescent-phase serum samples tested positive for both IgM and IgG, with a 4-fold increase in IgG titers, strongly supporting the diagnosis of acute dengue virus infection.

For patient 2 (the health care worker), the diagnosis was more straightforward because of the absence of past exposure to flaviviruses. Although transmission of West Nile virus has been occurring in the northeastern United States since 1999, the December onset of illness for patient 2 occurred after the transmission season ended in Boston. The results of ELISA were positive for dengue virus IgM on day 7, strongly suggesting the diagnosis of acute dengue virus infection. Although the 2 women were linked epidemiologically, positive results of viral cultures with genetically identical isolates from both would have been required for absolute proof of linked infections.

Analysis of neutralizing antibodies against dengue viruses

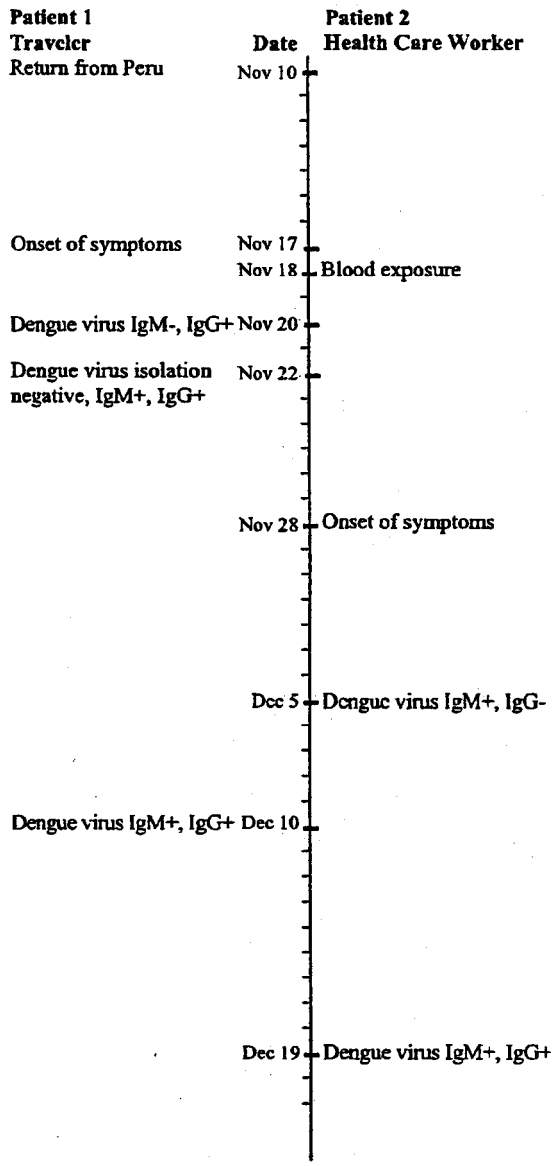

Figure 1. Sequence of events in 2 cases of dengue virus infection that occurred in 2002; 1 case involved a traveler, and 1 case involved a health care worker who had mucocutaneous exposure to the traveler's blood.

identified serotypes 2 and 3 in patient 1 and serotype 3 in patient 2. The plaque reduction neutralization test uses reference viruses (expressed as plaque-forming units), which are mixed and incubated with diluted test sera in cell culture. Antibodies that neutralize specific serotypes of the virus reduce the number of plaques formed [10]; therefore, the specific dengue serotype can often be determined.

Although rarely documented, dengue virus transmission without a mosquito vector has been reported. The routes of transmission include needlestick injuries, bone marrow transplantation, and intrapartum and vertical transmission (table 2). A brief report on ProMed-mail described 2 suspected cases of dengue fever aquired through blood transfusion in Hong Kong; in both cases, the donor developed symptoms consistent with dengue 1 day after giving blood and tested positive for dengue infection [20].

Dengue virus presumably infected patient 2 via blood contact with mucous membranes. This is biologically plausible, given the well-documented nosocomial spread of multiple viruses (i.e., hepatitis B virus, hepatitis C virus, and HIV) after mucocutaneous contact with blood [21]. The mean volume of blood delivered via a needlestick injury with a 22-gauge needle attached to a syringe containing 2 mL of blood has been found to be only 1.40 μL, yet transmission of many infections, including dengue, has occurred [22]. The amount of blood associated with mucocutaneous transmission of pathogens has not been defined. Because the level of viremia can reach 10^9 RNA copies per milliliter of blood in acute dengue virus infections, it is plausible that blood splashed on broken skin or on a mucous membrane could deliver a sufficient amount of virus to cause infection [5].

Nosocomial transmission, including mucocutaneous transmission, may occur in areas of endemicity but is unlikely to be recognized in areas in which dengue virus circulates widely. Hemorrhage, a feature of dengue hemorrhagic fever, may increase the risk of nosocomial transmission. Assessing the magnitude of nosocomial dengue virus transmission in areas of endemicity is difficult because all health care workers are also potentially exposed to infective mosquitoes. It is not surprising that nosocomial transmission of dengue virus has been identified primarily in areas of nonendemicity, in settings in which no other exposures to the virus are plausible.

West Nile virus is transmissible via breastfeeding, as well as through blood transfusions, organ transplantations, stem cell transplantations, intrauterine exposure, and needlestick injuries [23–27]. It is possible that dengue virus could be transmitted also through breast milk, although no documented cases have been reported.

Health care workers have frequent exposures to blood. One recently published survey found that 43% of physicians, 38.5% of registered nurses, 26.4% of licensed practical nurses, and 24.5% of medical technologists reported at least 1 mucocutaneous blood exposure within the previous 3 months [28]. Adherence to standard precautions was not ideal, and the underreporting of incidents was common. Phlebotomy equipment that operates as a closed system could minimize the number of blood-splash and needlestick exposures.

In summary, health care workers should be aware that nosocomial transmission of dengue virus can occur by mucocutaneous exposures, as well as by needlestick exposures. This

may be especially relevant to health care workers who care for patients with dengue with hemorrhage in resource-poor areas in which gloves and access to good infection-control measures are limited.

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研究報告の概要

単核食細胞系の致死的な感染症である内臓リューシュマニア症（VL；カラ・アザール）は、感染したサシチョウバエに刺されることで伝播する。VLの病原体である*Leishmania* spp.が末梢血中で寄生虫血症状態を引き起こすことが報告されているが、輸血を介した感染報告は稀である。今回、特発性血小板減少性紫斑病と診断され、ステロイド、免疫グロブリンによる治療を受け、血小板製剤を6回輸血されていた6歳の男児において、血小板輸血を介した感染が疑われるリューシュマニア感染症例がインドから報告された。本症例により、VL流行地域における輸血の安全性にかかわる問題が浮き彫りとなった。

報告企業の意見	今後の対応
内臓リューシュマニア症（VL；カラ・アザール）流行地域であるインドにおいて、輸血によるリューシュマニア感染が疑われた症例の報告であるが、確実に輸血感染であるとするにはエビデンスが不十分である。	日本赤十字社は、既にリューシュマニア流行地域への渡航歴およびリューシュマニア症の既往歴に対する問診マニュアルを改訂して問診を強化している。今後も、リューシュマニア感染症について情報収集に努める。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「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

Transfusion Medicine, 2004, 14, 319–321

CASE REPORT

The first probable case of platelet transfusion-transmitted visceral leishmaniasis

P. Mathur and J. C. Samantaray *Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India*

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SUMMARY. Visceral leishmaniasis (VL; kala-azar), a life-threatening infection of the mononuclear phagocytic system, is transmitted by the bite of infected sand flies. Though peripheral parasitaemia is documented for *Leishmania* spp. causing VL, reports of transfusion-transmitted infections are rare. A case of probable platelet transfusion-acquired VL is reported from India and issues related to transfusion safety in endemic areas are discussed.

Key words: India, platelet transfusion, visceral leishmaniasis.

Visceral leishmaniasis (VL; kala-azar) caused by protozoa of the genus *Leishmania* is a systemic illness of the mononuclear phagocyte system. More than 90% of the world's cases of VL occur in India, Sudan, Bangladesh and Nepal (Bora, 1999). In India, the disease is geographically restricted to a few states in eastern part of the country, the state of Bihar alone accounting for nearly 95% of the country's burden (Bora, 1999). The disease is transmitted by the bite of phlebotomine sand flies. Reports of leishmaniasis transmitted through blood transfusion are rare, although the parasite is known to circulate in the blood (Chulay *et al.*, 1985; Grogl *et al.*, 1993). We report a case of probable platelet transfusion-transmitted kala-azar from India. The diagnosis was delayed because the patient had never travelled to an endemic area and the clue was given by a simple laboratory test.

CASE REPORT

A 6-year-old boy from Delhi presented with complaints of easy bruising and recurrent bleeding from nose for 4 years along with fever and abdominal distension since the past 8 months. He was investigated 4 years back at a private hospital and was diagnosed as a case of idiopathic thrombocytopenic purpura. He was treated with steroids, immunoglobulins and repeated platelet transfusions (six times) over a period of 2–3 years. The platelet packs were purchased from private blood banks. The episodes of bleeding reduced, but he started developing high-grade fever and abdominal distension. Investigations done at this time in a private hospital revealed pancytopenia. A bone marrow examination done to rule out malignancy showed features suggestive of a reactive marrow and was negative for parasites. He was referred to our hospital due to persistent high-grade fever and splenomegaly. The child had never travelled to the eastern parts of India, endemic for VL.

On examination, the child was febrile and had pallor. There was no petechiae or skin pigmentation. Per abdomen, he had splenomegaly (8 cm below left costal margin) and hepatomegaly (3 cm below right costal margin). The cardiovascular and central nervous systems were normal.

Laboratory investigations revealed pancytopenia [haemoglobin 9 g dL^{-1}, total leucocyte count 2000 mm^{-3} (44% neutrophils and 56% lymphocytes) and platelets 56 000 mm^{-3}], hypergammaglobulinaemia and hypoalbuminaemia (total protein 8·9 g dL^{-1}, albumin 2·6 g dL^{-1} and globulin 6·3 g dL^{-1}; normal laboratory values 6·6–8·7, 4–5·5 and 3·8–4 g dL^{-1}, respectively). The level liver enzymes were raised (alanine transaminase 250 IU mL^{-1}, aspartate transminase 127 IU mL^{-1} and alkaline phosphatase 590 IU mL^{-1}; laboratory normal values: up to 50,

Correspondence: Dr J. C. Samantaray, Department of Microbiology, All India Institute of Medical Sciences, New Delhi 110029, India.
Tel.: +91 11 26594795; fax: +91 11 26588641;
e-mail: jsamataray@hotmail.com

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50 and 80–280 IU mL^{-1}, respectively). The urine and blood cultures were sterile, and peripheral smears, quantitative buffy coat assay (QBC™, BD Biosciences, Sparks, NV, USA) and lactate dehydrogenase antigen were negative for malarial parasite. The widal test and HIV serology was also negative. Because of the reversed albumin/globulin ratio, an aldehyde test was done, which was positive. The test depends on an increase of serum gamma globulins. Kala-azar patients usually have raised total serum proteins with hypergammaglobulinaemia (due to non-specific production of immunoglobulin G as a result of polyclonal proliferation) and hypoalbuminaemia. For aldehyde test, 1–2 mL of serum was taken in a test tube, and to it, 1–2 drops of 40% formaldehyde was added. A positive result is indicated by gellification and egg white opacification within 20 min (Faust *et al.*, 1970). Based on the above evidences, a bone marrow aspiration was repeated at our hospital, which revealed the presence of 1–10 amastigotes of *Leishmania donovani*/100 oil immersion fields (2+) (World Health Organization, 1984). Enzyme-linked immunosorbent assay for *Leishmania* antibodies was also positive (Ridascreen®, R-Biopharm, Dolivost, Germany). An immunochromatographic test for the detection of anti-rK39 antibodies against *L. donovani* complex was done subsequently using Kala-azar Detect® test (InBios International, Seattle, WA, USA) and was found to be positive. This test is specific for VL caused by members of *L. donovani* complex (Berado *et al.*, 1996; Houghton *et al.*, 1998). The child was treated with intravenous sodium stibogluconate (20 mg kg^{-1} day^{-1} for 28 days) and became afebrile within a few days of starting treatment. A bone marrow aspiration was repeated at the completion of treatment, which was negative for LD bodies. The child's haemoglobin, leucocyte count and platelet counts had improved, the spleen size had reduced and the albumin/globulin ratio was 1:1.

DISCUSSION

Despite accounting for a large percentage of the world's burden of VL, reports of transfusion-transmitted VL are rare from India (Singh *et al.*, 1996). Due to its transmission by sand fly bites, the distribution of the disease is restricted. *Leishmania amastigotes* parasitize the mononuclear phagocytes, less commonly the polymorphs, and it has been shown that viable parasites circulate in the blood (Chulay *et al.*, 1985).

A survey of English literature showed that only 10 cases of transfusion-transmitted kala-azar have been reported (Grogl *et al.*, 1993; Mauny *et al.*, 1993; Cumins *et al.*, 1995; Singh *et al.*, 1996). However, the true magnitude of transfusion-transmitted VL may be much higher than that currently reported, because in endemic areas, it is difficult to prove the mode of transmission in the face of concomitant sand fly bites (Grogl *et al.*, 1993). All the reported cases have been from non-endemic areas, the recipients being either infants or otherwise immunocompromised patients who had received multiple transfusions. Even in the few reported cases of transfusion-transmitted VL, the donors have not been identified.

Indigenous cases of VL have not been reported in and around Delhi, where infected sand flies do not exist. Due to unemployment and poor socioeconomic conditions, there is an increasing migration of people from endemic areas to metropolitan cities. Due to a paucity of blood supply, private blood banks accept blood from professional donors, many of whom are from endemic areas (Singh *et al.*, 1996).

The child in this report was born in Delhi, and both he and his mother had never stayed or travelled to endemic states. This makes congenital transmission or acquisition through sand fly bites unlikely. The child had also never received whole blood, bone marrow or any other organ transplantation. Because the child was transfused only with the platelet component on multiple occasions and the platelets were purchased from private blood banks, which entertain professional donors, it is postulated that he acquired the infection through platelet transfusions.

It has been shown that *Leishmania* can easily survive and is infective in the platelet fraction of blood up to 5 days at 24 °C, the recommended storage period for platelet transfusion (Grogl *et al.*, 1993). It was found in the same study that mononuclear cell contamination of red blood cell or platelet packs results in sufficient numbers of infected monocytes to contaminate these blood products with viable *Leishmania* (Grogl *et al.*, 1993). However, platelet transfusion-acquired leishmaniasis has not been reported till date.

The current blood bank screening techniques are unlikely to screen out the presence of *Leishmania*. Because blood product recipients include critically ill or immunocompromised patients, some authors have suggested the screening of blood donors in endemic areas for *Leishmania* spp. (Giger *et al.*, 2002). However, considering the additional costs involved in such exercise, it may be more appropriate to ascertain the incidence of *Leishmania* parasitaemia in asymptomatic people from endemic areas, before implementing mass screening. The diagnosis of VL is easily overlooked in non-endemic areas (Cohen *et al.*,

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1991). Therefore, clinicians in these areas must keep in mind all infectious agents as differential in cases of pyrexia of unknown origin. The initial bone marrow aspirate was reported negative for this patient, which emphasizes that microscopy of bone marrow smears has limited sensitivity and some of the cases of VL may be missed. Therefore, simple investigations like aldehyde test and serum albumin/globulin ratio may give a clue to the diagnosis in these cases.

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